Canadian Spontaneous Coronary Artery Dissection Cohort Study

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Declaration of interest

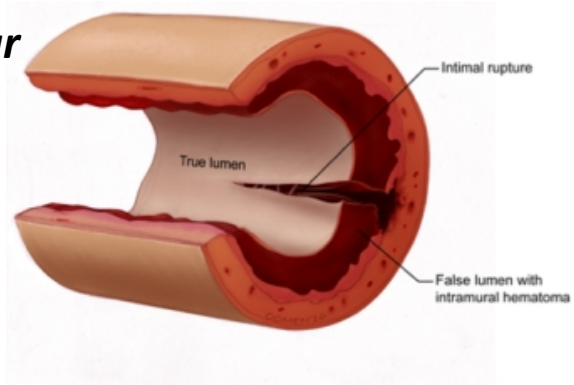
- Research contracts (Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, National Institutes of Health, Abbott Vascular, Boston Scientific, AstraZeneca, Servier)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Abbott Vascular, Boston Scientific)

Spontaneous Coronary Artery Dissection (SCAD)

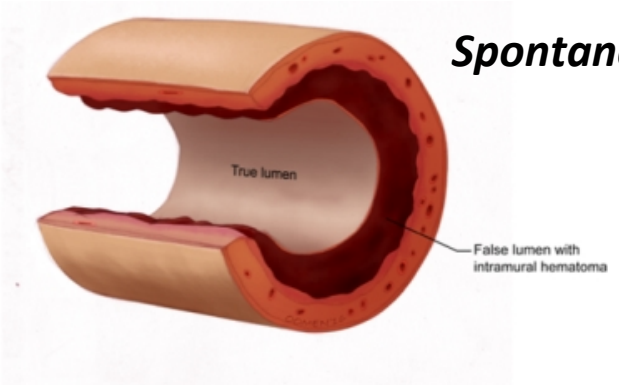
Definition:

- Non-traumatic, non-iatrogenic, non-atherosclerotic separation of the coronary arterial wall by intramural hemorrhage creating a false lumen, with or w/o an intimal tear
- Separation can occur between any arterial layers (intima, media or adventitia)
- Resulting intramural hematoma compresses the arterial lumen, compromising antegrade blood flow, and can cause myocardial ischemia or infarction

Intimal Tear



Spontaneous Bleed



Saw J, Mancini GBJ, Humphries K. JACC 2016;68:297-312.

SCAD

SCAD

- First reported in 1931
- Under-diagnosed (missed)
- Poorly/misunderstood
- Early myths: rare, young women, mostly peripartum, high fatality
- Unclear: management, predisposing/precipitating causes, outcomes

Case Series	Year	N	Age Mean ± SD	Women (%)	Peripartum (%)
Vanzetto	2009	23	46.0 ± 9.0	74%	0%
Mortensen	2009	22	49 ± 9	81%	10%
Ito	2011	23	46 ± 9	100%	30%
Alfonso	2012	27	53 ± 11	85%	4%
Lettieri	2015	134	52 ± 11	81%	N/A
Rogowski	2015	64	53.0 ± 11.2	94%	5%
Roura	2015	34	47.0 ± 12	94.1%	15%
Rashid	2016	21	53.3 ± 8.8	95.2%	0%
Nakashimi	2016	63	46.0 ± 10	94%	8%
Faden	2016	79	33 ± 5	100%	100%
McGrath-Cadell	2016	40	45 ± 10	95%	8%
Motreff	2017	55	50	100%	4%
Tweet	2018	323	35, 47	100%	16.7%
Saw	2018	327	52.5 ± 9.6	90.5%	2.4%

<1300 published cases

SCAD

CanSCAD: Study Design

Large prospective, multicenter, observational, natural history study

- ***Inclusion criteria:***
  A. New acute non-atherosclerotic SCAD event
  B. Documented SCAD on coronary angiogram confirmed by core laboratory

- ***Exclusion criteria:***
  A. Atherosclerotic coronary artery disease in other coronary arterial segments with diameter stenosis ≥50%

CanSCAD: Study Objectives

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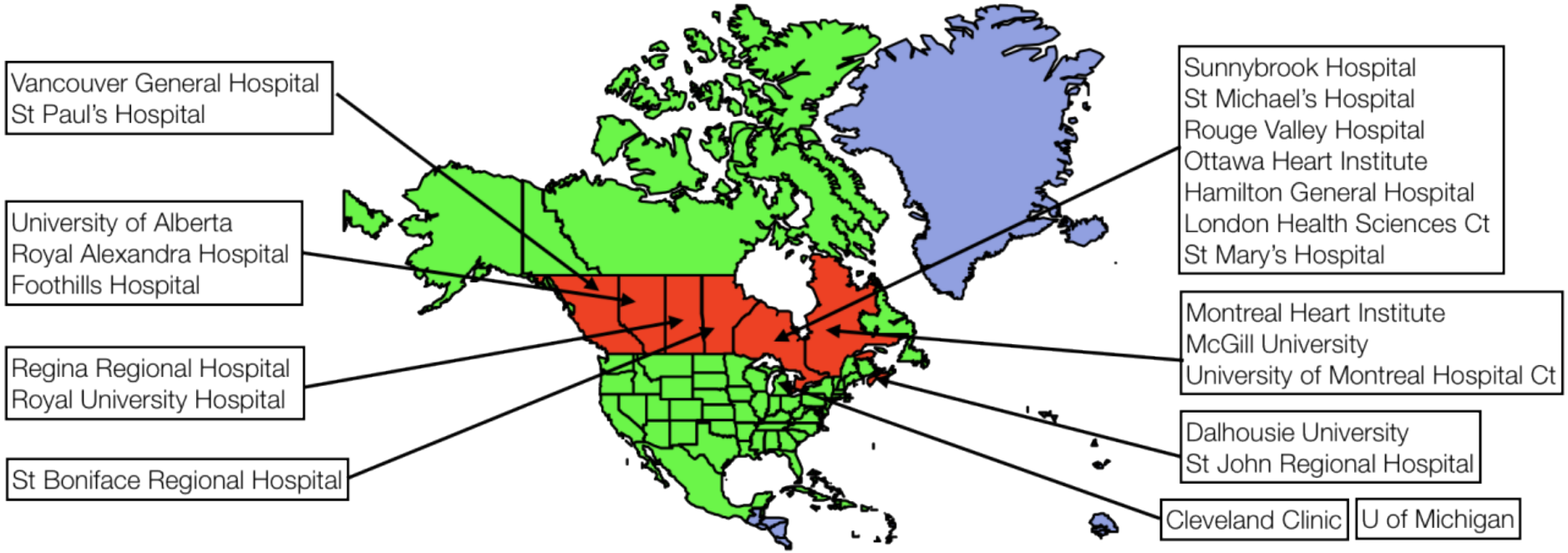
Primary Objectives:

- Describe the natural history of **Non-atherosclerotic SCAD**:
  A. Assess in-hospital and long-term cardiovascular outcomes
  B. Identify factors (e.g. predisposing conditions, precipitating stressors) associated with in-hospital and long-term cardiovascular outcomes

Secondary Objectives:

- Describe impact of conservative therapy and revascularization on outcomes
- Describe presenting angiographic patterns of SCAD

CanSCAD: Study Enrollment Sites (22)



CanSCAD: Study Methods

- Capture baseline: demographics, clinical characteristics, ECG, laboratory tests, management/medications/revascularization (at MD discretion), Seattle Angina Questionnaire (SAQ)
- Patients-reported questionnaires: predisposing conditions, precipitating stressors (emotional/physical), gynecologic/pregnancy history, hormonal therapy, symptoms, past medical history, and family history
- Coronary angiograms: reviewed by core laboratory (CIRCL) for SCAD, and classified according to Saw angiographic SCAD classification[1,2]
- FMD screening: recommended for renal, iliac, and cerebrovascular arteries (diagnosis with multifocal changes), with catheter or CT angiography

1. Saw J. Cathet Cardiovasc Interv 2014;84(7):1115-22.
2. Saw J, et al. JACC 2017 Aug;70(9):1148-58.

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CanSCAD: Follow-up, Outcome Definition

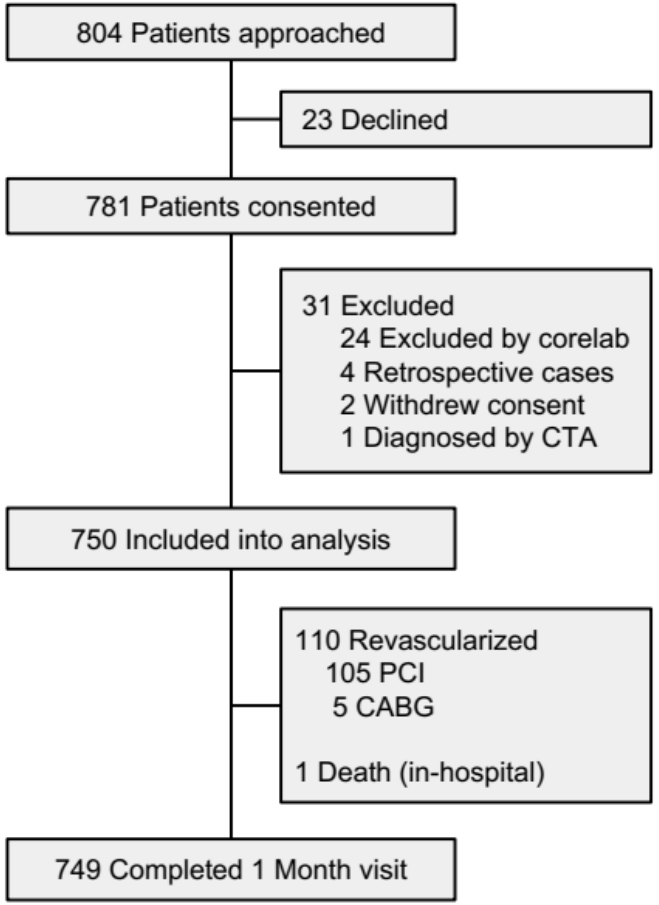
- Patients were followed in-hospital, and after discharge by telephone/office contact at 1, 6, 12 months, and annually for 3 years
- Seattle Angina Questionnaire (SAQ) was repeated at 6, 12, 24 and 36 months
- ***In-hospital Major Adverse Events (MAE):***
  - Composite of: all-cause mortality, stroke, recurrent MI, cardiogenic shock, CHF, cardiac arrest, repeat/unplanned revascularization, and cardiac transplantation
- ***30-day Major Adverse Cardiovascular Events (MACE):***
  - Composite of: all-cause mortality, stroke, recurrent MI, CHF, and revascularization

CanSCAD: Statistical Analysis

- Logistic regression analyses were performed to identify univariate and multivariable predictors of in-hospital and 30-day events
- Examined risk factors, predisposing conditions (e.g. FMD, CTD, peripartum), and precipitating stressors
- Variables significant in the univariate analyses, $p<0.20$, and clinically important factors (FMD, CTD) were included in multivariable models
- Multivariable models based on the female population only, which comprised 88.5% of the overall SCAD cohort

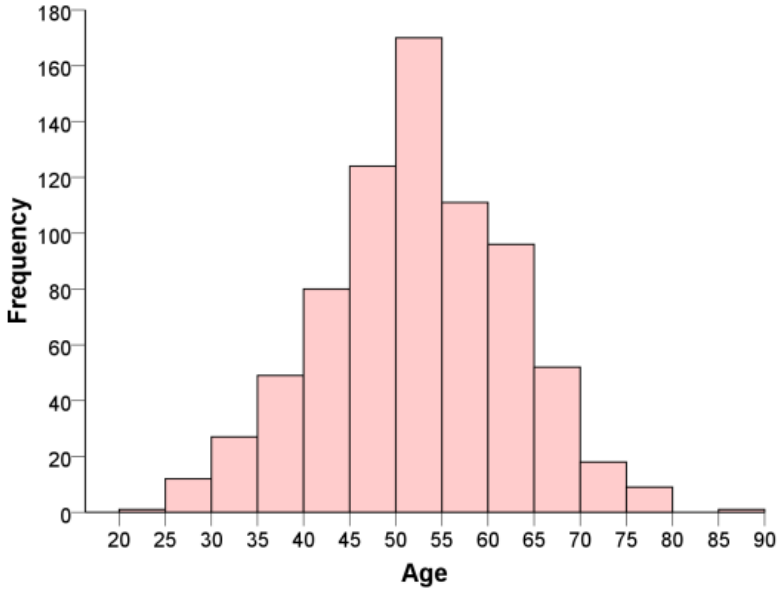
CanSCAD: Study Results

Prospectively enrolled 750 non-atherosclerotic SCAD patients from June2014 - June2018 from 22 centers (20 in Canada, 2 in United States)



Baseline Demographics

Mean ± SD, median (Q1, Q3), or n (%)	N=750
Age (years)	51.8 ± 10.2
Sex (female)	664 (88.5%)
Post-menopausal	365/664 (55.0%)
Weight (kg)	73.0 (63.0, 80.0)
Height (cm)	165 (160, 171)
BMI	26.4 (23.1, 31.2)
Race	
Caucasian	658 (87.7%)
East Asian	33 (4.4%)
South Asian	17 (2.3%)
African Canadian/American	12 (1.6%)
First Nation	10 (1.3%)
Other	20 (2.7%)
Medical History	
Diabetes mellitus	34 (4.5%)
Diabetes mellitus on medication	16 (2.1%)
Hypertension	241 (32.1%)
Dyslipidemia	152 (20.3%)
Current smoker	87 (11.6%)
Family History of premature CAD	285 (38.0%)
No cardiac risk factors*	254 (33.9%)
≥3 Cardiac risk factors*	71 (9.5%)
History of previous revascularization	13 (1.7%)
History of previous MI	63 (8.4%)
Confirmed cases of previous SCAD	42 (5.6%)
History of CVA	26 (3.5%)
History of heart failure	3 (0.4%)
Relevant Clinical History	
Tinnitus	100 (13.3%)
History of migraines	244 (32.5%)
History of depression	146 (19.5%)
On medication for depression	111 (14.8%)
History of anxiety	148 (19.7%)
On medication for anxiety	88 (11.7%)
Thyroid dysfunction	97 (12.9%)
Hypothyroid	85 (11.3%)



Age range 24-89yr
9.2% older than 65

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Hospital Presentation

median (Q1, Q3), or n (%)	N=750
Acute Coronary Syndrome	
STEMI	223 (29.7%)
NSTEMI	524 (69.9%)
Unstable angina	3 (0.4%)
Presenting main symptom	
Chest discomfort	686 (91.5%)
Back discomfort	15 (2.0%)
Shoulder or arm discomfort	10 (1.3%)
Dyspnea	7 (0.9%)
Arrhythmia	8 (1.1%)
Other	24 (3.2%)
Troponin Levels	
Elevated Troponin	732 (97.6%)
Troponin not elevated	3 (0.4%)
Troponin value not available	15 (2.0%)

median (Q1, Q3), or n (%)	N=750
ECG changes	
Normal ECG	170 (22.7%)
Non-specific changes	81 (10.8%)
T inversion	138 (18.4%)
ST depression	47 (6.3%)
ST elevation <1mm	85 (11.3%)
ST elevation >1mm	187 (24.9%)
Q waves	11 (1.5%)
LBBB	5 (0.7%)
Other	26 (3.5%)
Ventricular Tachycardia or Fibrillation	61 (8.1%)
Left ventricular function assessment	
Ejection fraction assessed	737 (98.2%)
Angiogram	491 (65.5%)
Echocardiogram	243 (32.4%)
Initial ejection fraction (%)	55 (50, 60)
Ejection fraction <50%	188/734 (25.6%)
Ejection fraction <35%	28/734 (3.8%)
Wall motion abnormality	
No abnormality	114 (15.2%)
Hypokinesis	359 (47.9%)
Akinesis	215 (28.7%)
Dyskinesis	43 (5.7%)
Not assessed	19 (2.5%)

Precipitating & Predisposing Factors

N (%)	N=750
Precipitating Stressors	
Emotional stress (rated high or severe)	377 (50.3%)
Perceived Stress Scale ≥20	288 (41.2%)
Unusually intense physical stress	216 (28.9%)
Isometric stress >50lb	74 (9.8%)
Cocaine/amphetamine use	2 (0.3%)
Valsalva-type stress	90 (12.0%)
No precipitating factor	252 (33.6%)
Predisposing Conditions	
Fibromuscular dysplasia	233 (31.1%)
Systemic inflammatory disease	35 (4.7%)
Connective tissue disorder	27 (3.6%)
Active hormonal therapy	75 (10.0%)
Peripartum	34 (4.5%)
Grand multigravida (≥5 pregnancies)	67 (8.9%)
Multiparous (≥4 births)	64 (8.5%)
Grand multiparity (≥5 births)	17 (2.3%)
Idiopathic (none of the above)	376 (50.1%)

Non-coronary FMD* Screen	N=750
Presence of non-coronary FMD	
FMD Present	233 (31.1%)
FMD possible (non-multifocal)	49 (6.5%)
No FMD on complete screen	129 (17.2%)
Incomplete screening	139 (18.5%)
FMD screen not done	200 (26.7%)
Territory of FMD involved	
Renal FMD	140/505 (27.7)
Femoral and/or iliac FMD	89/423 (21.0)
Cerebrovascular FMD	125/424 (29.5)
Cerebral aneurysm	30/424 (7.1)

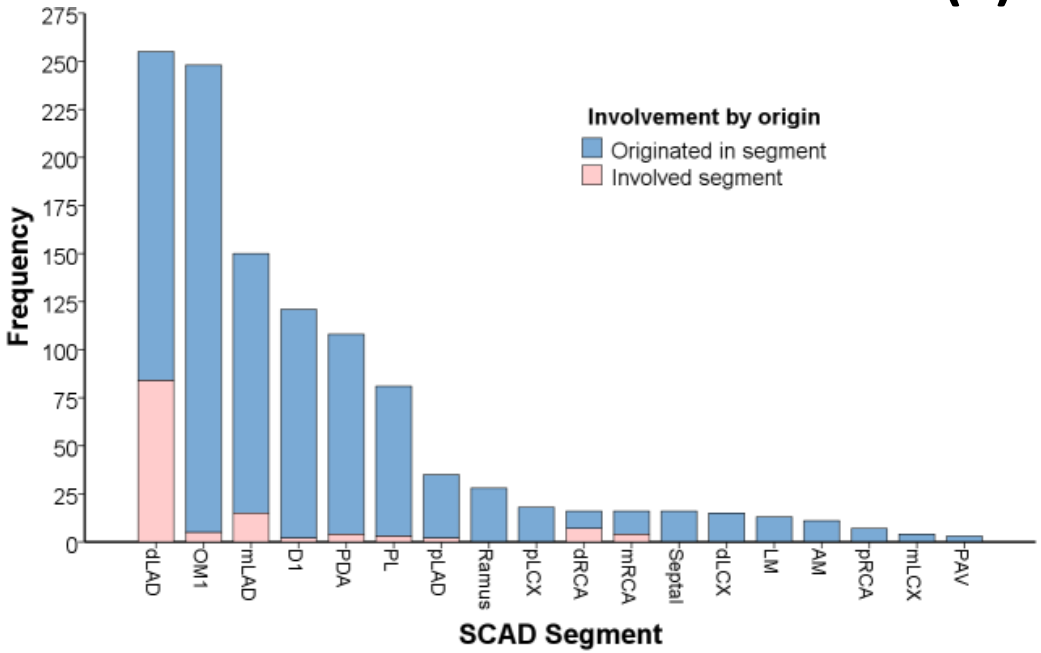
45.2%

*FMD: fibromuscular dysplasia

Angiographic Results (1)

N (%), mean ± SD	N=750
Radial approach catheterization	556 (74.1%)
Femoral approach catheterization	192 (25.6%)
OCT-confirmed SCAD	41 (5.5%)
IVUS-confirmed SCAD	16 (2.1%)
Number of non-contiguous SCAD arteries	
1	652 (86.9%)
2	88 (11.7%)
3	10 (1.3%)
Number of affected SCAD segments	
1	561 (74.8%)
2	147 (19.6%)
3	24 (3.2%)
4	16 (2.1%)
5	1 (0.1%)
6	1 (0.1%)
≥2 segments	189 (25.2%)
Dissected coronary arteries	
LM	11 (1.5%)
LAD	391 (52.1%)
LCX	283 (37.7%)
RCA	174 (23.2%)
LM or prox LAD or prox LCX or prox RCA	57 (7.6%)

7.6%



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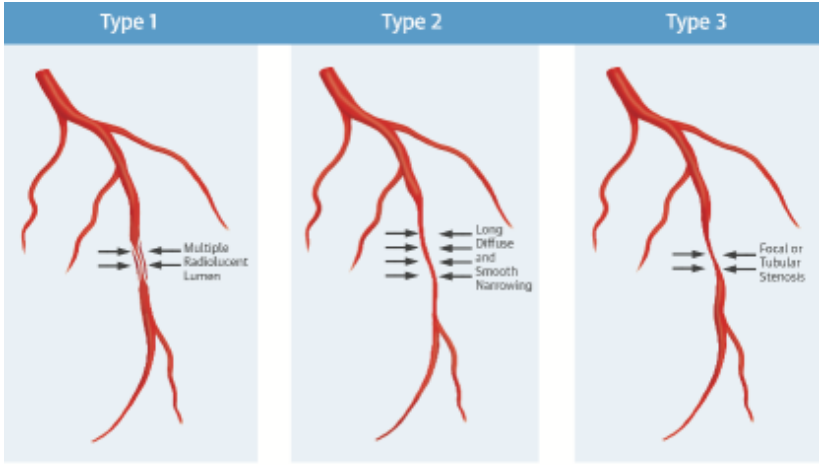
Angiographic Results (2)

N (%), mean ± SD	N=750
Angiographic SCAD type	N=1002 dissections
1	291 (29.0%)
2	603 (60.2%)
2A	343 (34.2%)
2B	260 (25.9%)
3	108 (10.8%)
Worst TIMI flow	
0	89 (8.9%)
1	185 (18.5%)
2	89 (8.9%)
3	639 (63.8%)
QCA Characteristics	
Total occlusion (Stenosis 100%)	307 (30.6%)
Vessel diameter (mm)	2.4 (2.0, 3.0)
Segment diameter stenosis (%)	79.0 (65.0, 100)
Segment length (mm)	33.2 (22.2, 48.9)



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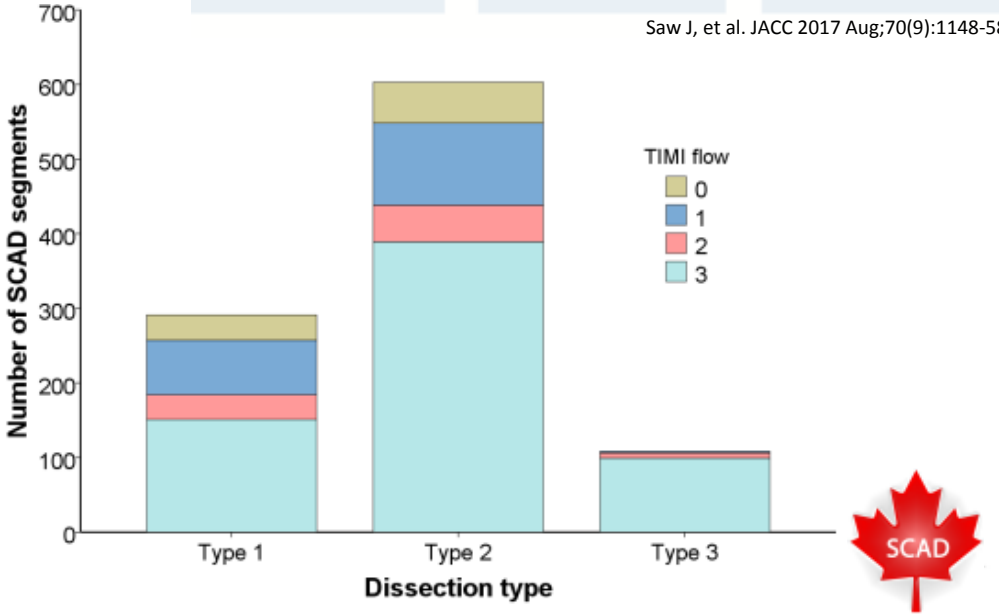

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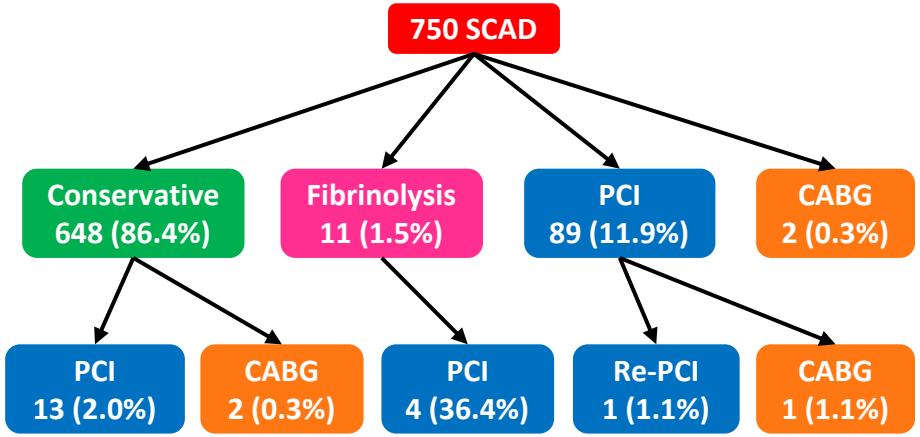
Revascularization:



PCI Strategy [n(%)]	N=750
Treatment strategy	
Conservative	632 (84.3%)
Fibrinolysis	11 (1.5%)
Revascularization (PCI or CABG)	110 (14.7%)
PCI	106 (14.1%)
CABG	5 (0.7%)
SCAD PCI Procedures & Outcomes	N=103
Wiring only	15 (14.6%)
Balloon angioplasty	21 (20.4%)
- Cutting balloon	5 (4.9%)
Stent placement	67 (65.0%)
Number of stents implanted	
1	21/67 (31.4%)
2	23/67 (34.1%)
3	15/67 (22.4%)
4 or more	8/67 (11.9%)

Rationale for revascularization [n(%)]	N=110
Ongoing chest pain	43 (39.1%)
Ongoing ischemia on ECG	38 (34.5%)
Dissection causing severe stenosis	35 (31.8%)
Proximal LAD, RCA, or LCX dissection	25 (22.7%)
Large artery (>3mm) dissection	16 (14.5%)
Iatrogenic catheter-induced dissection	10 (9.1%)
Left main dissection	9 (8.2%)
Ventricular arrhythmia	8 (7.3%)
Recurrent chest pain in-hospital	6 (5.5%)
Hemodynamic instability (shock)	6 (5.5%)
Multiple coronary dissections	6 (5.5%)

PCI Outcomes [n(%)]	N=750
Final TMI Flow	
0	16 (15.7%)
1	6 (5.9%)
2	13 (12.7%)
3	67 (65.7%)
PCI effect on TIMI flow	
Improved	59 (57.6%)
Unchanged	40 (38.8%)
Worse	4 (3.9%)
Propagation of SCAD during PCI	33 (32.0%)
Overall PCI success	
Successful	30 (29.1%)
Partial success	42 (40.8%)
Unsuccessful	31 (30.1%)

SCAD

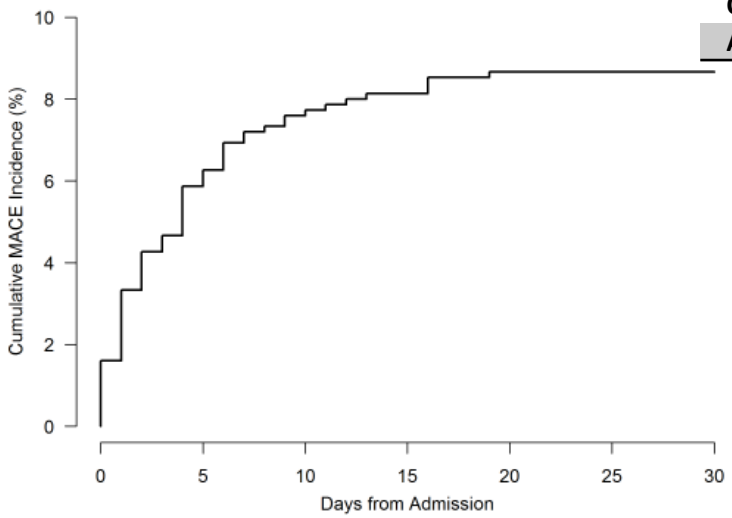
Medications: At Discharge & Follow-up

	Discharge N=749	Last follow-up N=749
ASA	702 (93.7)	668 (89.2)
Clopidogrel (or other ADP antagonist)	505 (67.4)	268 (35.8)
Beta-blocker	632 (84.8)	592 (79.0)
ACE inhibitor/ARB	430 (57.4)	361 (48.2)
Statin	413 (55.1)	300 (40.1)
Nitroglycerin	110 (14.7)	62 (8.3)
Calcium-channel blocker	78 (10.4)	72 (9.6)
Oral anticoagulant	19 (2.5)	41 (5.5)

In-hospital MAE & 30-day MACE

N (%)	N=750
Overall In-hospital MAE	66 (8.8%)
Death	1 (0.1%)
Recurrent MI	30 (4.0%)
- Extension of SCAD segment	15 (50%)
- Iatrogenic dissection	9 (30%)
- Other	6 (20%)
Severe ventricular arrhythmia	29 (3.9%)
- requiring ICD	6 (0.8%)
Cardiogenic shock	15 (2.0%)
- Use of Inotropes	9 (1.2%)
- IABP	6 (0.8%)
- LVAD	2 (0.3%)
- ECMO	2 (0.3%)
- LV rupture requiring surgery	1 (0.1%)
- Heart Transplant	0 (0%)
Unplanned revascularization	19 (2.5%)
Stroke/TIA	6 (0.8%)
Congestive heart failure	2 (0.3%)

Median hospital stay 4 days (3, 5)



N (%)	N=750
Total 30-day MACE	66 (8.8%)
Death	1 (0.1%)
Recurrent MI	46 (6.1%)
Unplanned revascularization	20 (2.7%)
Stroke/TIA	9 (1.2%)
Congestive heart failure	3 (0.4%)
Other complications w/in 30d	
Pericarditis	14 (1.9%)
New atrial fibrillation	7 (0.9%)
Cardiac emergency room visit	37 (4.9%)
Admission for chest pain	19 (2.5%)

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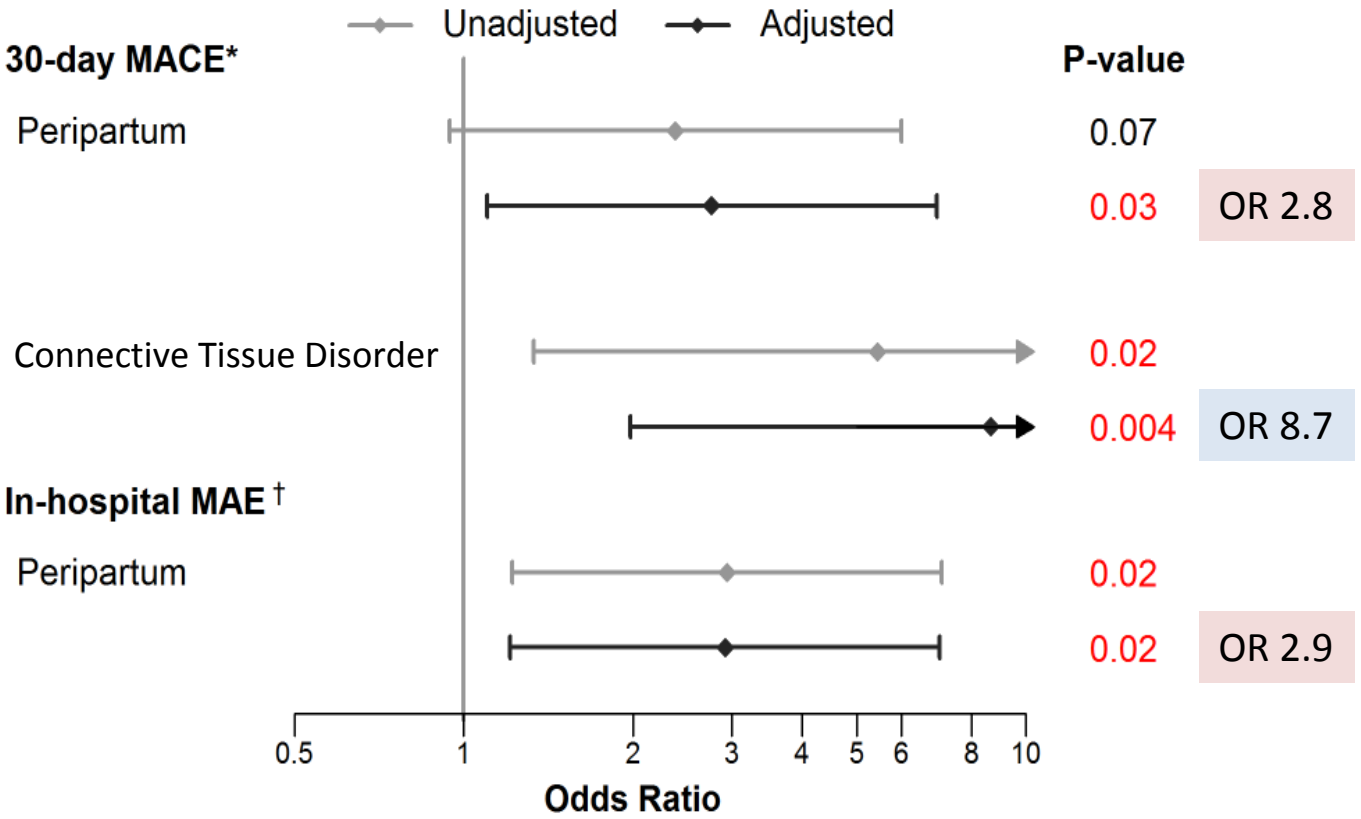
CanSCAD: Peripartum SCAD

	Peripartum^ n=34	Non-peripartum n=716	P value
Very high Trop >500x ULN	23.5%	11.6%	0.038
EF <50%	44.1%	24.7%	0.016
EF <35%	17.6%	3.1%	0.001
>2 dissected segments	41.2%	24.4%	0.041
Multi-vessel SCAD	26.5%	12.4%	0.032
LM dissection	5.9%	1.3%	0.085
LM, pLAD, pLCX, or pRCA	23.5%	6.8%	0.003
Iatrogenic dissection	8.8%	1.7%	0.027
In-hospital MAE	20.6%	8.2%	0.023
In-hospital high-risk events*	23.5%	6.8%	0.003
High HCG	45.5%	3.8%	<0.001
High CRP	92.9%	41.9%	<0.001

^3rd trimester or within 1yr delivery

*In-hospital high-risk events: death, cardiac arrest, cardiogenic shock, LVEF<35%, and/or left main dissection

Predictors: In-hospital MAE & 30-day MACE



* Adjusted model includes peripartum, connective tissue disease, and number of pregnancies
† Adjusted model includes peripartum, connective tissue disease, and history of smoking

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CanSCAD: Study Conclusion

- SCAD predominantly affected young to middle-aged women, and presented with MI
- Despite conservative therapy in the majority of patients, acute in-hospital and 30-day survival was good
- However, significant cardiovascular complications accrued within 30 days post-SCAD, including recurrent MI, unplanned revascularization, and stroke/TIA
- Peripartum SCAD was independent predictor of in-hospital MAE and 30-day MACE
- Connective tissue disorder was also independent predictor of 30-day MACE
- Longer-term follow-up of this large prospective cohort, and further investigations on pathophysiology, risk/predictors of recurrence, and management are warranted

CanSCAD: Steering Committee

- Principal Investigator: Jacqueline Saw
- Co-Investigators: GB John Mancini, Karin Humphries, Dennis Ko
- ClinicalTrials.gov: NCT02188069
- Primary Funding: Canadian Institutes of Health Research
- Secondary Funding: Abbott Vascular, AstraZeneca, St Jude Medical, Servier
- Managed by: University of British Columbia Research group (Study Manager: Andrew Starovoytov, MD)

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- BC Centre for Improved Cardiovascular Health: Karin Humphries (scientific director), Defen Peng, Yinshan Zhao, Melissa Pak
- Study Sites PI & team: Vancouver General Hospital (J.Saw), Hamilton General Hospital (T.Sheth), University of Ottawa (D.So), St. Boniface Hospital (K.Minhas), Royal Alexandra Hospital (N.Brass), Prairie Vascular Research Network (A.Lavoie), Queen Elizabeth Health Centre (H.Bishop), London Health Sciences (S.Lavi), Royal University Hospital (C.Pearce), St Mary's General Hospital (S.Renner), Sunnybrook Health Sciences Centre (M.Madan), University of Alberta (R.Welsh), St John Regional Hospital (S.Lutchmedial), Rouge Valley Health System (R.Vijayaraghavan), St Paul's Hospital (E.Aymong), Foothills Hospital (B.Har), Montreal Heart Institute (R.Ibrahim), Cleveland Clinic Foundation (H.Gornik), University of Michigan (S.Ganesh), St Michael's Hospital (C.Buller), University of Montreal Hospital Centre (A.Matteau), McGill University Health Centre (G.Martucci)

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EXTRA SLIDES

CanSCAD: PCI Outcome Definition

- Initial management strategy chosen following the acute SCAD angiogram (conservative, PCI or CABG), and indications for revascularization (if chosen) were recorded
- ***PCI outcomes were defined as:***

  A. Successful if angioplasty or stenting of the dissection accomplished final TIMI 3 flow with no residual dissection

  B. Partially successful if angioplasty or stenting resulted in residual dissection or stenosis ≤50% of lumen diameter, and with final TIMI 3 or improved flow

  C. Unsuccessful if angioplasty or stenting concluded with residual dissection or stenosis >50% of lumen diameter, or worsened TIMI flow compared to baseline, or extension of dissection requiring bail-out CABG.

In-hospital MAE & 30-day MACE

N (%)	N=750
Overall In-hospital MAE	66 (8.8%)
Death	1 (0.1%)
Recurrent MI	30 (4.0%)
- Extension of SCAD segment	15 (50%)
- Iatrogenic dissection	9 (30%)
- Other	6 (20%)
Severe ventricular arrhythmia	29 (3.9%)
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- ECMO	2 (0.3%)
- LV rupture requiring surgery	1 (0.1%)
- Heart Transplant	0 (0%)
Unplanned revascularization	19 (2.5%)
Stroke/TIA	6 (0.8%)
Congestive heart failure	2 (0.3%)

N (%)	N=750
Post-discharge 30-day MACE	19 (2.5%)
Death	0 (0%)
Recurrent MI	16 (2.1%)
- Extension of SCAD segment	8 (50%)
- Iatrogenic dissection	1 (6.3%)
- New de-novo SCAD	1 (6.3%)
- Other	6 (37.5%)
Unplanned revascularization	1 (0.1%)
Stroke/TIA	3 (0.4%)
Congestive heart failure	1 (0.1%)
Total 30-day MACE	66 (8.8%)
Death	1 (0.1%)
Recurrent MI	46 (6.1%)
Unplanned revascularization	20 (2.7%)
Stroke/TIA	9 (1.2%)
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Other complications w/in 30d	
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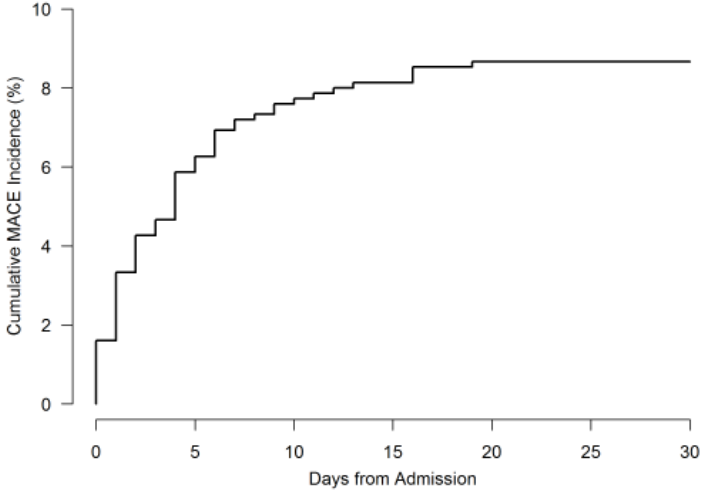
Median hospital stay 4 days (3, 5)



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CanSCAD: Predictors of MAE & MACE

Predictors of In-hospital major adverse events								
	Univariate				Multivariable			
	P value	Odds Ratio	Lower 95% CI	Upper 95% CI	P value	Odds Ratio	Lower 95% CI	Upper 95% CI
Age	0.1672	0.911	0.799	1.040				
History of smoking	0.0897	0.509	0.234	1.110				
Physical stress	0.1546	0.610	0.309	1.205				
Connective tissue disease	0.7996	1.312	0.161	10.673				
≥5 Pregnancies	0.1372	0.197	0.023	1.678				
Peripartum	0.0161	2.943	1.222	7.091	0.017	2.92	1.21	7.02

Predictors of 30-day major adverse cardiac events								
	Univariate				Multivariable			
	P value	Odds Ratio	Lower 95% CI	Upper 95% CI	P value	Odds Ratio	Lower 95% CI	Upper 95% CI
Age	0.167	0.982	0.956	1.008				
History of smoking	0.193	0.609	0.388	1.286				
Connective tissue disorder	0.019	5.455	1.328	22.412	0.004	8.67	1.98	38.08
≥5 Pregnancies	0.172	0.391	0.101	1.505				
Peripartum	0.066	2.382	0.944	6.015	0.031	2.76	1.10	6.95