

BIOGRAPHICAL SKETCH

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NAME: Stephen Fremes MD FRCSC

eRA COMMONS USER NAME (credential, e.g., agency login): SFREMES

POSITION TITLE: Cardiovascular Surgeon; Professor, University of Toronto

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---------------------------|----------------------------|-----------------|
| University of Toronto, Toronto, Ontario | BSc | 05/1975 | Arts & Sciences |
| University of Toronto, Toronto, Ontario | MD | 06/1979 | Medicine |
| University of Toronto, Toronto, Ontario | MSc | 07/1984 | Medical Science |
| University of Toronto, Toronto, Ontario | FRCSC | 06/1986 | General Surgery |
| University of Toronto, Toronto, Ontario | FRCSC | 06/1988 | CVT Surgery |
| University of Toronto, Toronto, Ontario | Fellowship | 06/1989 | Cardiac Surgery |

A. Personal Statement

I am a Staff Cardiac Surgeon at Sunnybrook HSC since 1989, a Professor of Surgery at the University of Toronto since 2001, and the inaugural Bernard Goldman Chair in Cardiovascular Surgery, with appointments at UofT in the School of Graduate Studies, Institute of Medical Science, and the Institute of Health Policy Management and Evaluation. I have had peer reviewed grant support for studies in cardiac surgery as a principal applicant or co-principal applicant for more than 30 years and have published more than 450 manuscripts in peer-reviewed journals including many in the highest impact medical journals such as *N Engl J Med*, *Lancet*, *JAMA*, *JACC*, *EHJ* and *Circulation*, with a Google Scholar h-index of 71. My program of research has focused on three main themes: 1) improving outcomes following CABG, 2) myocardial protection/cardiopulmonary bypass management, and 3) transcatheter aortic valve surgery. I have utilized a variety of methodologies in my research including multicenter clinical trials, observational studies (single center and health systems research), systematic reviews and meta-analyses, and health economics and modelling. I have also had extensive experience with Clinical Practice Guidelines including the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization. I am the NPI of the Canadian Institutes of Health Research (CIHR) funded international multi-centre Randomized comparison of the clinical Outcome of single versus Multiple Arterial grafts trial (ROMA NCT03217006) and Co-A of the NIH-funded ROMA-QOL and (ROMA:Cog) sub-studies. As the NPI of the CIHR funded ROMA trial and the Canadian lead for the ROMA: Women GCRFF application, I am uniquely qualified to be a MPI of the ROMA: Women NIH application.

- Desai ND, Cohen EA, Naylor CD, **Fremes SE**; Radial Artery Patency Study Investigators. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. *N Engl J Med*. 2004 Nov 25; 351(22):2302-9.
- Deb S, Cohen EA, Singh SK, Une D, Laupacis A, **Fremes SE**; RAPS Investigators. Radial artery and saphenous vein patency more than 5 years after coronary artery bypass surgery: results from RAPS (Radial Artery Patency Study). *J Am Coll Cardiol*. 2012 Jul 3; 60(1):28-35.
- Gaudino M, Benedetto U, **Fremes S**, et al. Association of Radial Artery Graft vs Saphenous Vein Graft With Long-term Cardiovascular Outcomes Among Patients Undergoing Coronary Artery Bypass Grafting: A Systematic Review and Meta-analysis. *JAMA*. 2020;324(2):179-187. doi:10.1001/jama.2020.8228
- Gaudino M, Alexander JH, Bakaeen FG, Ballman K, Barili F, Calafiore AM, Davierwala P, Goldman S, Kappetein P, Lorusso R, Mylotte D, Pagano D, Ruel M, Schwann T, Suma H, Taggart DP, Tranbaugh RF, **Fremes S**. Randomized comparison of the clinical outcome of single versus multiple arterial grafts: the ROMA trial-rationale and study protocol. *Eur J Cardiothoracic Surg*. 2017 Dec 1; 52(6):1031-1040.

B. Positions and Honors

Positions and Employment

| | |
|----------------|---|
| 2002 - present | Associate Member - Institute Health Policy, Management and Evaluation, School of Graduate Studies, University of Toronto, Toronto Ontario |
| 2001 - present | Professor, Surgery, University of Toronto, Toronto, Ontario |
| 1996 - present | Senior Scientist, Sunnybrook Health Sciences Centre, Toronto, Ontario |
| 1999 - 2013 | Head, Cardiovascular Surgery, SHSC, Toronto, Ontario |
| 1999 - 2009 | Adjunct Scientist, Cardiovascular Surgery, Institute for Clinical Evaluative Sciences, Toronto, Ontario |
| 1995 - 2002 | Research Director, Heart & Circulation Program, SHSC, Toronto, Ontario |
| 1993 - present | Membership, Institute of Medical Science, School of Graduate Studies, University of Toronto, Toronto, Ontario |
| 1989 - present | Staff Surgeon, Cardiovascular Surgery, SHSC, Toronto, Ontario |

Other Experience and Professional Membership

| | |
|----------------|--|
| 2022-present | Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy |
| 2019-2021 | Writing Committee member for Guideline for Coronary Artery Revascularization ACC/AHA/SCAI |
| 2018-2019 | Writing Committee member for Transcatheter Aortic Valve Implantation Canadian Cardiovascular Society |
| 2016-2017 | Writing Committee member for the Management of Heart Failure Canadian Cardiovascular Society |
| 2017 - present | Canadian Cardiovascular Society, Canadian TAVR Guidelines, Canada |
| 2016 – 2020 | Canadian Cardiovascular Society, Guidelines Committee, Canada |
| 2016 - present | The Journal of Thoracic and Cardiovascular Surgery, Associate Statistical Editor |
| 2015 - present | LEVO-CTS Steering Committee, Levosimendan in Cardio Thoracic Surgery |
| 2015 - present | The Journal of Thoracic and Cardiovascular Surgery, Associate Statistical Editor |
| 2014 - present | Canadian Journal of Cardiology, Associate Editor |
| 2012 – 2014 | Canadian Cardiovascular Society, Canadian CHF Guidelines, Canada |
| 2012 – 2016 | Society of Thoracic Surgeons Arterial Conduit Guidelines Committee |
| 2011 - present | National Heart, Lung and Blood Institute Member, ISCHEMIA Surgical Ctte |
| 2009 - present | American College of Chest Physicians, Member, Antithrombotic and Thrombolytic Therapy: ACCP Clinical Practice Guidelines, 9th Ed |
| 2009 - present | Member, CIHR Clinical Investigation D - Peer Review Committee |

Honors

| | |
|-------------|---|
| 2010 - 2020 | Dr. Bernard S. Goldman Chair in Cardiovascular Surgery, Sunnybrook HSC Centre |
| 2015 - 2016 | Charles H. Tator Surgeon-Scientist Mentoring Award, University of Toronto |
| 2005 - 2006 | Lister Prize, University of Toronto |
| 1993 - 1998 | Career Investigator Award, Heart and Stroke Foundation of Canada |
| 1992 - 1993 | George Armstrong Peters Prize, University of Toronto |
| 1988 - 1989 | Heart and Stroke Foundation of Canada - Fellowship |
| 1982 - 1984 | Heart and Stroke Foundation of Canada - Fellowship |

C. Contributions to Science

1. Arterial conduits for coronary artery bypass surgery

One of my key scientific contributions has been demonstrating that the radial artery has superior 1-year and late graft patency compared to the saphenous vein for non-LAD targets, and that radial graft patency is dependent on high grade proximal target vessel stenosis. I was the PI of the CIHR-sponsored multi-centre longitudinal studies (Radial Artery Patency Study (RAPS), and RAPS-5 Years comparing the angiographic patency of the radial artery and saphenous vein grafts at 1 year and more than 5 years following surgery. We also published on the patient and target vessel characteristics associated with 1-year graft patency. The

important findings were that the severity of target vessel stenosis and peripheral vascular disease were associated with radial failure and that female gender and target vessel size with saphenous vein occlusions graft occlusion. We also showed that the radial artery was effective in diabetic patients. The 1-year angiographic outcome in diabetic patients was published in *Circulation*, and the late findings in *JTCVS*. I participated in the STS Practice Guidelines of Arterial Conduits which summarized the evidence for the use of arterial grafts for coronary surgery. Importantly, the radial conduit was considered a Class IIa recommendation, Level of evidence B. I am currently a member of the AHA/ACC Revascularization Guidelines, for distribution 2021, in which the radial artery received a Class I recommendation, Level of Evidence A.

- Desai ND, Naylor CD, Kiss A, Cohen EA, Feder-Elituv R, Miwa S, Radhakrishnan S, Dubbin J, Schwartz L, **Fremes SE**, Radial Artery Patency Study Investigators *Circulation*. 2007 Feb 13; 115(6):684-91. Epub 2007 Feb 5.
- Deb S, Singh SK, Moussa F, Tsubota H, Une D, Kiss A, Tomlinson G, Afshar M, Sless R, Cohen EA, Radhakrishnan S, Dubbin J, Schwartz L, **Fremes SE**. Radial Artery Patency Study Investigators. The long-term impact of diabetes on graft patency after coronary artery bypass grafting surgery: a substudy of the multicenter Radial Artery Patency Study. *J Thorac Cardiovasc Surg*. 2014 Oct; 148(4):1246-53; discussion 1253. doi: 10.1016/j.jtcvs.2014.06.057. Epub 2014 Jul 17.
- Aldea GS, Bakaeen FG, Pal J, **Fremes S**, Head SJ, Sabik J, Rosengart T, Kappetein AP, Thourani VH, Firestone S, Mitchell JD; The Society of Thoracic Surgeons Clinical Practice Guidelines on Arterial Conduits for Coronary Artery Bypass Grafting. *Ann Thorac Surg*. 2016 Feb;101(2):801-9. doi: 10.1016/j.athoracsur.2015.09.100. Epub 2015 Dec 8. PMID: 26680310
- Gaudino M, Benedetto U, **Fremes S**, Biondi-Zoccai G, Sedrakyan A, Puskas JD, Angelini GD, Buxton B, Frati G, Hare DL, Hayward P, Nasso G, Moat N, Peric M, Yoo KJ, Speziale G, Girardi LN, Taggart DP; RADIAL Investigators. Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery. *N Engl J Med* 2018 May 31; 378(22):2069-2077.
- Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG, DiMaio JM, Don CW, **Fremes SE**, Gaudino MF, Goldberger ZD, Grant MC, Jaswal JB, Kurlansky PA, Mehran R, Metkus TS Jr, Nnacheta LC, Rao SV, Sellke FW, Sharma G, Yong CM, Zwischenberger BA. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022 Jan 18; 45(3): e4-e17.

2. Transcatheter aortic valve replacement (TAVR)

I was the senior author in a systematic review and meta-analysis comparing TAVR and surgical AVR in intermediate risk patients. There was no difference in 30-day and late mortality, while the rate of complications differed between TAVR and surgical AVR. Cost-effectiveness studies have been completed in intermediate risk patients comparing balloon expandable TAVR and surgical AVR, and comparing self-expanding TAVR and surgical AVR. TAVR with balloon expandable devices may be cost-effective for the treatment of severe aortic stenosis in patients with intermediate surgical risk. More recently, balloon expandable TAVR was found to be cost effective in low surgical risk patients. A population level study in the province of Ontario, Canada showed that TAVR v-in-v was a preferred strategy compared to redo surgery for failing bioprostheses in a propensity score matched study. Using discrete event simulation, transcatheter valve durability was found to be unlikely to affect survival in older low-risk patients, but may affect survival in young patients if durability was substantially less than surgical bioprostheses.

- Tam DY, Vo TX, Wijeyesundera HC, Ko DT, Rocha RV, Friedrich J, **Fremes SE**. Transcatheter vs surgical aortic valve replacement for aortic stenosis in low-intermediate risk patients: a meta-analysis. *Can J Cardiol*. 2017 Sep; 33(9):1171-1179.
- Tam DY, Azizi PM, **Fremes SE**, Chikwe J, Gaudino M, Wijeyesundera HC. The cost-effectiveness of transcatheter aortic valve replacement in low surgical risk patients with severe aortic stenosis [published online ahead of print, 2020 Jul 9]. *Eur Heart J Qual Care Clin Outcomes*. 2020;qcaa058. doi:10.1093/ehjqcco/qcaa058
- Tam DY, Dharma C, Rocha RV, Ouzounian M, Wijeyesundera HC, Austin PC, Chikwe J, Gaudino M, **Fremes SE**. Transcatheter ViV Versus Redo Surgical AVR for the Management of Failed Biological Prosthesis: Early and Late Outcomes in a Propensity-Matched Cohort. *JACC Cardiovasc Interv*. 2020;13(6):765-774. doi:10.1016/j.jcin.2019.10.030

- Tam DY, Wijeyesundera HC, Naimark D, Gaudino M, Webb JG, Cohen DJ, **Fremes SE**. Impact of Transcatheter Aortic Valve Durability on Life Expectancy in Low-Risk Patients With Severe Aortic Stenosis. *Circulation*. 2020;142(4):354-364. doi:10.1161/CIRCULATIONAHA.119.044559

3. Myocardial Protection and Cardiopulmonary bypass Management

I have been a steering committee member and/or Co-Investigator of several large multi-centre RCTs in cardiac surgery addressing important clinical question over the past 25 years including: CORONARY, SIRS, TRICSIII, LEVO-CTS and SUSTAIN CSX. CORONARY compared on- and off-pump coronary surgery in higher risk CABG patients (4752 patients) finding that outcomes were similar after on- and off-pump CABG. SIRS evaluated the role of steroids to reduce mortality in high risk cardiac surgery (7000 patients) and found that high dose steroids did not have any beneficial effect on hard clinical outcomes. TRICSIII compared two different transfusion algorithms (liberal vs. conservative) in high risk cardiac surgery (5243 patients). A restrictive strategy regarding red-cell transfusion was noninferior to a liberal strategy with respect to the primary composite outcome, with less blood transfused. LEVO-CTS study evaluated the role of levosimendan in patients with decreased left ventricular ejection fraction undergoing CABG +/- valve surgery (849 patients). The 2 co-primary outcomes did not differ between groups although secondary endpoints related to low cardiac output syndrome did. SUSTAIN CSX which evaluates the role of high dose selenium in high risk cardiac has completed recruitment.

- Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, Khanykin B, Gregory AJ, de Médicis É, McGuinness S, Royse A, Carrier FM, Young PJ, Villar JC, Grocott HP, Seeberger MD, **Fremes S**, Lellouche F, Syed S, Byrne K, Bagshaw SM, Hwang NC, Mehta C, Painter TW, Royse C, Verma S, Hare GMT, Cohen A, Thorpe KE, Jüni P, Shehata N; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. *N Engl J Med*. 2017 Nov 30;377(22):2133-2144.
- Mehta RH, Leimberger JD, van Diepen S, Meza J, Wang A, Jankowich R, Harrison RW, Hay D, **Fremes S**, Duncan A, Soltesz EG, Luber J, Park S, Argenziano M, Murphy E, Marcel R, Kalavrouziotis D, Nagpal D, Bozinovski J, Toller W, Heringlake M, Goodman SG, Levy JH, Harrington RA, Anstrom KJ, Alexander JH; LEVO-CTS Investigators. Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery. *N Engl J Med*. 2017 May 25;376(21):2032-2042.
- Stoppe C, McDonald B, Rex S, Manzanares W, Whitlock R, **Fremes S**, Fowler R, Lamarche Y, Meybohm P, Haberthür C, Rossaint R, Goetzenich A, Elke G, Day A, Heyland DK. Sodium Selenite Administration in Cardiac Surgery (SUSTAIN CSX-trial): study design of an international multicenter randomized double-blinded controlled trial of high dose sodium-selenite administration in high-risk cardiac surgical patients. *Trials*. 2014 Aug 28;15:339.

Complete List of Published Work in My Bibliography:

<http://www.ncbi.nlm.nih.gov/pubmed/?term=fremes+s>

D. Research Support and/or Scholastic Performance

Canadian Institutes of Health Research (CIHR) PI: Fremes 04/2022-03/2029
The Canadian CABG or PCI in Patients with Ischemic Cardiomyopathy (STICH 3.0) Trial USD 2,048,291
Role: Principal Investigator

NIH NHLBI PIs: Gaudino/ M Creber/Swartz 07/2021-06/2026
Randomized Comparison of the Clinical Outcomes of Single versus Multiple Arterial Grafts: Cognition (ROMA:Cog). USD\$ 2,498,700
Role: Co-Investigator

EMHSeed program, University of Toronto PIs: Jimenez Juan/Craig 09/2021-08/2023
A patient-specific experimental and computational platform to identify failure mechanisms of coronary artery bypass grafts USD 88,221
Role: Collaborator

Boston Scientific Ltd PI: Sam Radhakrishnan 07/2020-06/2030

Accurate IDE Study. USD 352,884

Role: Co-Investigator

NIH NHLBI

PIs: Gaudino/ M Creber

04/2020-03/2025

Randomized Comparison of the Clinical Outcomes of Single versus Multiple Arterial Grafts: Quality of Life (ROMA: QOL). USD\$ 4,164,370

Role: Co-Investigator

Canadian Institutes of Health Research (CIHR)

PI: Mazer

10/2020-09/2023

TRICS IV: Transfusion Requirements in Younger Patients Undergoing Cardiac Surgery USD 1,223,784

Role: Co-applicant

Canadian Institutes of Health Research (CIHR)

PI: Andre Lamy

04/2020 – 03/2023

Decreasing Postoperative Blood Loss by Topical vs. Intravenous Tranexamic Acid in Open Cardiac Surgery (DEPOSITION Trial). USD 1,165,252

Role: Co-applicant

FED DEV Ontario Grant

PI: Wijeyesundera

01/2020-1/2023

REdireCT TAVI Remote Ecg Monitoring to Reduce Complications following Transcatheter Aortic Valve Implantations USD 73,517

Role: Co-Investigator

Canadian Institutes of Health Research (CIHR)

PIs: Whitlock/ Belley-Côté

04/2020-03/2022

VISION Cardiac Surgery - ECG Evaluation Sub-Study. USD 393,200

Role: Co-Investigator

Canadian Institutes of Health Research (CIHR)

PIs: Fremes/Gaudino

04/2019-03/2026

Randomized Comparison of the Clinical Outcome of Single versus Multiple Arterial grafts: the ROMA trial – The Definitive Phase. USD 3,925,495

Role: Principal Investigator

Amgen Inc

PIs: Mazer/Verma

10/2018-03/2023

A randomized trial of evolocumab on saphenous vein graft patency following coronary artery bypass surgery (NEWTON-CABG) USD 403,740

Role: Co-Investigator

Medtronic Inc.

PI: Sam Radhakrishnan

04/2017-03/2027

TAVR 'Low Risk Study'. USD 193,556

Role: Co-Investigator

Lotte & John Hecht Memorial Foundation.

PI: Darren Keith Heyland

01/2016-08/2020

Sodium Selenite Administration IN Cardiac Surgery (SUSTAIN CSX®-trial). USD 2,193,355

Role: Steering Committee- Co-Investigator- Collaborator

Medtronic Inc. (Physio-Control International Corporation)

PIs: Fremes/Radhakrishnan

07/2013-06/2026

Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI). USD 379,904

Role: Co-Principal Investigator