#HerHeartMatters: Bridging the Sex and Gender Gaps in Cardiovascular Research

Canadian Cardiovascular Congress 2021

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Disclosure Statement

We do not have an affiliation (financial or otherwise) with a commercial organization that may have a direct or indirect connection to the content of this presentation.

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Dr. Christine Pacheco - Consulting fees/honoraria - KYE, Novartis, Pfizer
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Dr. Harriette Van Spall - Canadian Institutes of Health Research; Heart and Stroke Foundation

Learning Objectives

At the conclusion of this session, participants will be able to:

1. Name structural barriers to gender-equal research participation, representation, and leadership in cardiology;
2. List multi-level strategies that can bridge the gender gaps in cardiovascular research leadership;
3. Recognize implicit biases as they relate to sex and gender and identify ways to tackle them.

Canadian Women’s Heart Health Alliance (CWHHA)

LAUNCHED IN 2018

Mission: Disseminate education and best practices re: Women’s cardiovascular (CV) health among **healthcare providers and women with lived experience**

Goal: Eliminate knowledge gaps in specific CV issues and develop new practice considerations in care for women, thereby improving the health of Canadian women

CWHHA WORKING GROUPS

Advocacy

Training and Education

Knowledge Translation and Mobilization

Health Systems and Policy

CANADIAN WOMEN'S HEART HEALTH CENTRE | NATIONAL ALLIANCE

Perspectives from a Kounis Patient

Karen E. Jacques, BA, JD
Patient Advocate Co-Chair, Knowledge Translation and Mobilization Working Group
Past Co-Chair, Patient Advisory Committee
Woman with Lived Experience
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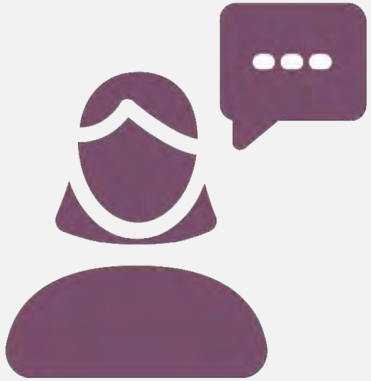
Karen’s Story

- Kounis driven MINOCA in April 2018 at age 42.
- Encountered misconceptions that continue to abound thanks to the historic research gender-gap.

  e.g. Dr. “You’re Too Young” and Dr. “Only Cocaine Users”.

- Participation in Challenge Cath physiology study was a key step. Clear understanding of the mechanism in my heart. Study report led directly to increasing safety for me in going to the ER.



Those study results, combined with identification of mast cell activation, led to more appropriate-for-me treatment!

Gender Gap

- Informal survey of fellow patients has found there isn't a current gender-gap in current research they have taken part in. That's progress!
- However, the impacts of historical gaps are still being felt.
- Some overcorrection may be in order to level up the field and create more equal footing to go forward from.
- However, don't create the opposite problem of a potential gender-gap by not adequately considering non-obstructive issues in males.

Recommendations

- Make research funding contingent upon gender equality in all aspects of research:
  (1) subjects;
  (2) researchers; and,
  (3) grant application reviewers.

- Seek advance input from patients. Peer support group insight might help inform the path research takes.

- Take a cue from nuclear industry. Root cause investigations, a full hindsight analysis, could be critical to developing a better understanding of non-obstructive conditions such as Kounis syndrome.

Women’s Participation & Clinical Practice Guidelines

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Professor and Clinician Scientist, Faculties of Nursing, Medicine & Dentistry, and School of Public Health, University of Alberta
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Women's Participation & Clinical Practice Guidelines

"Clinical practice guidelines are systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific clinical circumstances." (Institute of Medicine, 1990)

There is no conventional approach for systematically including sex or gender-specific information in guidelines.

Sex

- Biological construct assigned at birth (female/male)
- Encompasses hormones, genes, anatomy, physiology, etc.

Gender

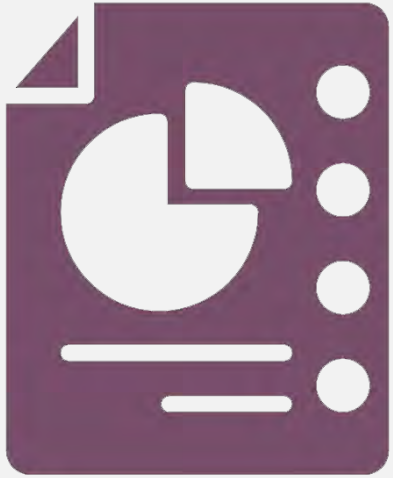
- A social construct (man/woman)
- Is culturally specific and temporal

We sought to determine the feasibility and outcomes of a structured process for considering sex and gender in the STEMI Guideline update.

CCS Pilot Project
Incorporating Sex and Gender into STEMI Guidelines

RESULTS

- 180 studies, of which 175 studies were included
- The mean percentage of women:
  - 24.5% (min 0%, max 51%)
- The mean participation to prevalence ratio (PPR):
  - 0.62 (min 0.00, max 1.19)
    - A PPR of 1 indicates that the sex composition of the study is that of the population
    - By convention, a PPR of less than 0.8, or greater than 1.2 indicates that one sex was underrepresented or overrepresented



Wong, G. C., Welsford, M., Ainsworth, C., Abuzeid, W., Fordyce, C. B., Greene, J., . . . Norris CM. (2019). Canadian Journal of Cardiology, 35(2), 107-132.

STEMI Guidelines

RESULTS (Cont.)

- 16/175 studies reported main outcomes stratified by sex
- No studies included gender as a variable

Based on PPR and the analyses presented:

*Only **one study provided sufficient evidence** to confirm the applicability of recommendations for the management of STEMI for female as well as male patients.*

STEMI Guidelines Conclusions

"While we make the agnostic assumption that the recommendations in this guideline hold equally for both men and for women, we acknowledge that the published literature are inadequate to confirm this clearly and objectively".

Barriers include:

- Inadequate enrollment of women in randomized trials (PPR < 0.8)
- Lack of publication of main outcomes stratified by sex
- Lack of inclusion of gender as a study variable

Atrial Fibrillation Guidelines - 2020
A Sex and Gender ‘replication’ study

- Total of 885 studies included in the Canadian guidelines were considered.
- 467 met the inclusion and exclusion criteria.
- Overall, females represented 39.1% (25.2 – 53%) of the overall population in all studies.
- RCTs had the lowest proportions of females - PPR: 0.80 (.47 - .93) (a PPR of less than 0.8 indicates that females were underrepresented)
- Total of 140 (29.9%) studies had sex-specific analyses.
- Of those, randomized controlled trials, specifically single centered RCTs had the lowest rate of sex specific analyses (11.5%).

*Alipour, Pilote, Raparelli, McMurtry, Norris – **Representation of sex differences in evidence utilized for guideline recommendations on Atrial Fibrillation management** in submission*

The **Under-representation** of females in national guidelines introduces numerous challenges for practitioners

- The clinical and physiological variation that exists between the sexes are often neglected.
- Until we have **enough women enrolled in clinical trials with sufficient sample size, sex disaggregated data might provide indications & guidelines for treatment regimens**.
- It is imperative to acknowledge the existence of such disparities in treatment and management plans.

Closing the Gender Gap in CV Clinical Trial Leadership

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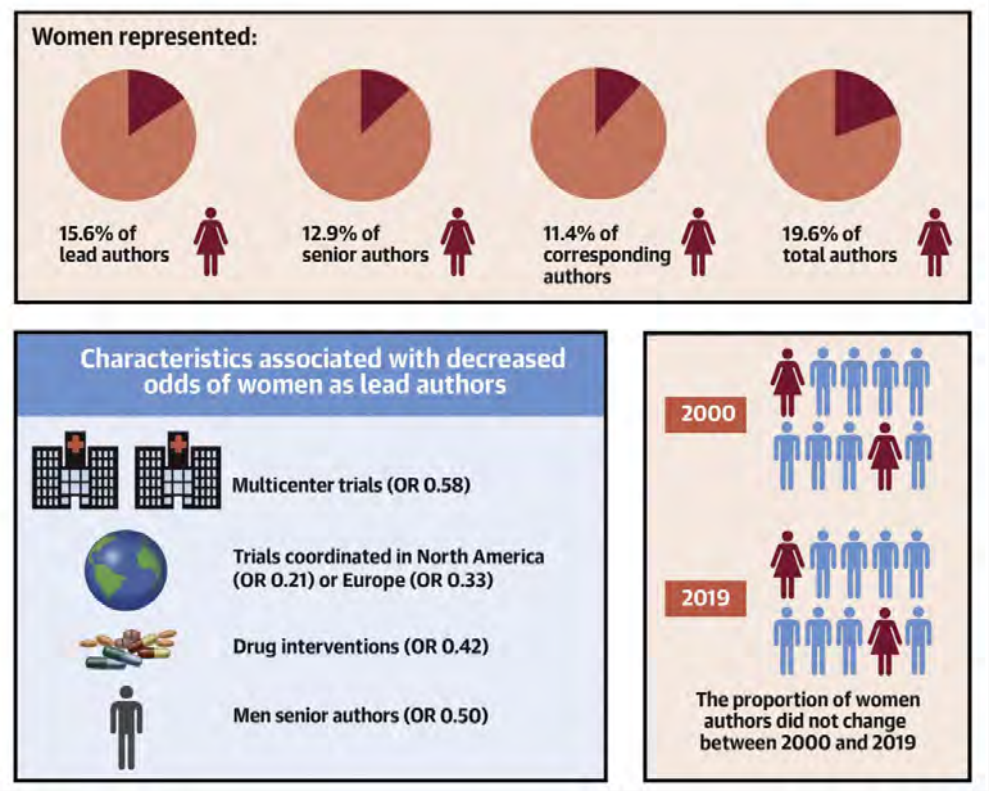
Objectives

- To present data on gender representation among CV clinical trial leaders
- To discuss the benefits associated with women clinical trial leaders
- To provide possible solutions to the gender gap in clinical trial leadership

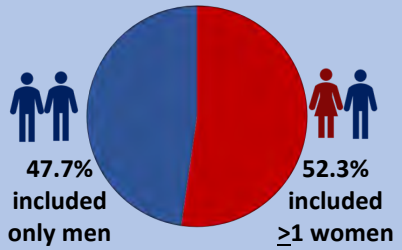
Under-representation of Women as Authors in Randomized Controlled Trials of Heart Failure 2000-2019



*Whitelaw S, Thabane L, Mamas M, Reza N, Brethett, K, Douglas PS, **Van Spall HGC**. JACC 2020.*

Under-representation of Women in HF Trial Steering Committees (TSCs) 2000-2019

107 TSCs reported TSC member names



Women had greater odds of TSC inclusion in RCTs led by women

aOR **2.48** 95% CI, 1.05-8.72

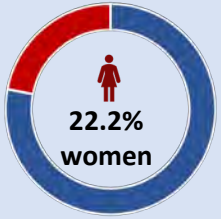
This association was not significant when TSCs restricting women to RCT leaders were excluded

aOR **1.46** 95% CI, 0.43-4.91

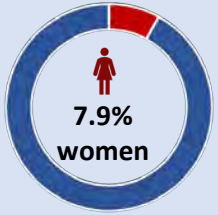
Women comprised 11.1% of 1213 TSC members

No change in % over time

Gender composition of TSCs

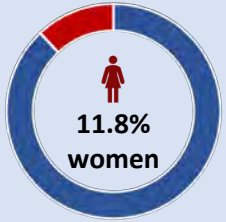


Women-led RCTs

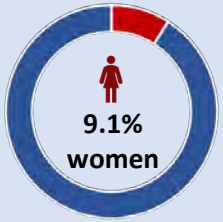


Men-led RCTs

Gender composition of TSCs excluding RCT leaders



Women-led RCTs

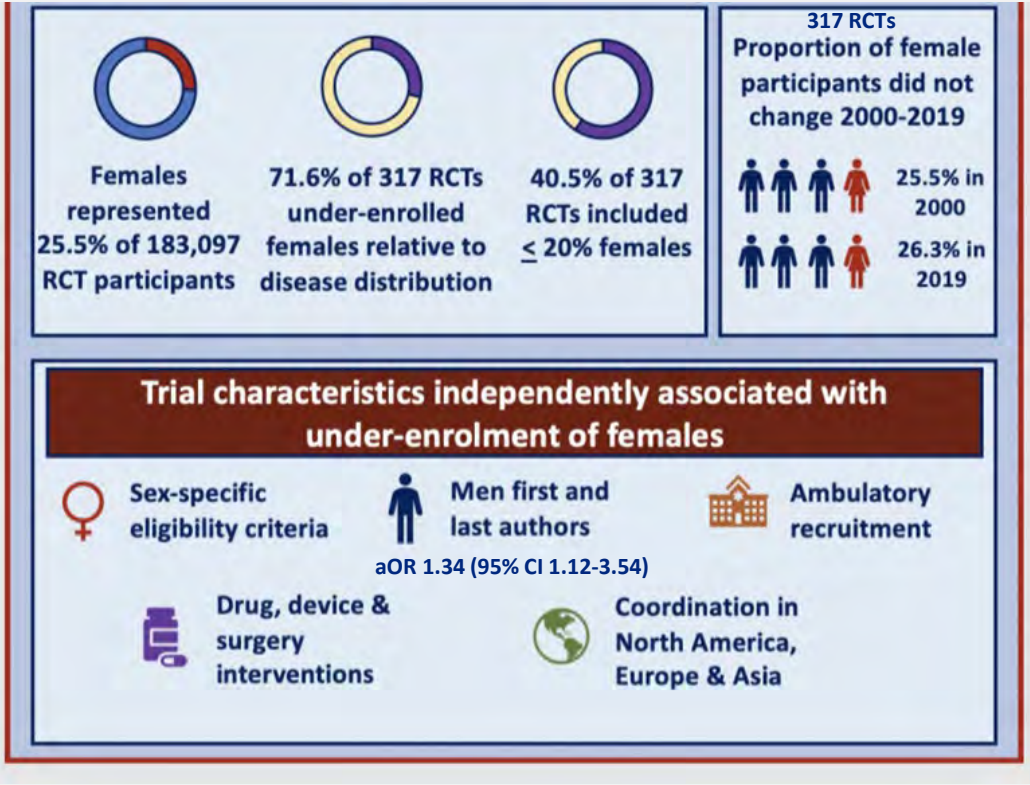


Men-led RCTs

*Eiya Y, Whitelaw S, Thabane L, Voors AA, Douglas PS, **Van Spall HGC**. 2021.Circulation HF 2021*

Under-enrollment of Females in Randomized Controlled Trials of Heart Failure with Reduced Ejection Fraction 2000-2019

Under-enrollment
= 20% below F : M distribution of HFrEF

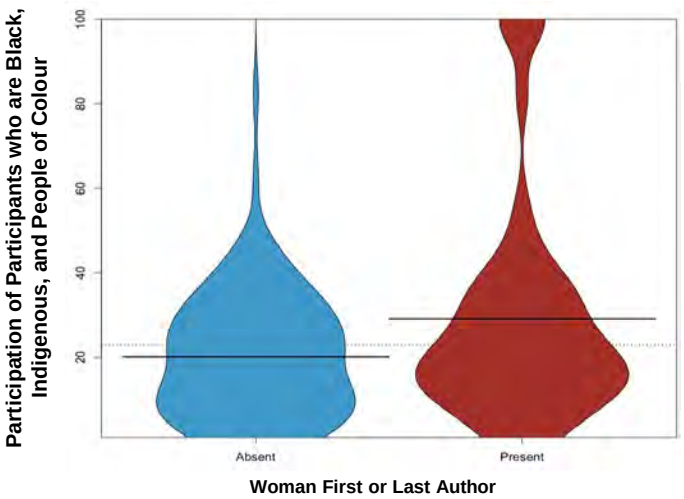


*Whitelaw S, Sullivan K, Eliya Y, Alruwayeh M, Mehran R, Yancy C, Mamas MA, **Van Spall HGC.** Eur J Heart Fail 2020.*

Association Between Women Trial leaders and % of BIPOC Participants in HF RCTs (157 RCTs, 158,200 participants)

Univariate Analysis	Adjusted Analysis
8.9% (95% CI: 2.5-15.5%) p=0.007	8.4% (95% CI: 1.9-15.0%) p=0.0125

*no significant association between funding source, trial size or number of countries of participant enrolment and enrolment of participants who are Black, Indigenous and People of Colour



Wei S, Le NN, Zhu JW, Greene S, Breathett K, Mamas M, Zannad F, ***Van Spall HGC****. 2021. Circulation HF*

SCIENTISTS / TRIALISTS

- Implicit Bias Awareness
- Leadership and Institutional Accountability
- Mentorship to Women and Under-represented Groups
- Diversity in Research Teams
- Equal Opportunity for Team Members
- Harassment-Free Culture - Stand up, Speak Up

ENDING GENDER INEQUALITY IN CV CLINICAL TRIAL LEADERSHIP

PROFESSIONAL SOCIETIES

- Advocacy
- Funding contingent on Equity, Diversity, Inclusion (EDI)
- Research education
- Profile women and international trialists as discussants, speakers at society mtgs

CATALYZERS

- Advocacy
- Talent directories
- Research networks
- Training, mentorship, sponsorship

INDUSTRY

- EDI Policies
- Open calls, objective criteria for RCT leadership and TSC members with attention to gender, geographic diversity
- Equal pay for equal work
- Transparent reporting

ACADEMIC INSTITUTIONS

- Open calls, objective criteria for recruitment, promotion, awards, leadership
- Gender-disaggregated reporting of advancement & salary

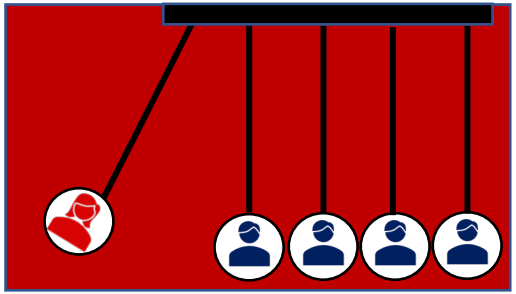
GRANT AGENCIES

- Charters with academic institutions
- Diverse reviewers, blinded reviews
- Gender-disaggregated reporting of panel, chairs, applicant : award ratios

JOURNALS

- EDI policies
- Diverse editorial board
- Blinded reviews
- Publication contingent on diverse research teams

BENEFITS



- ❑ Leadership by women associated with
  - ❑ Enrollment of Diverse Populations in Clinical Trials
  - ❑ Greater generalizability of study results
  - ❑ Inclusion of women as first authors and TSC members
  - ❑ Greater research capacity among women

Van Spall HGC, Lala A, Deering T et al. JACC 2021

Strategies for Academic Institutions to End the Gender Inequality in Research Leadership

1. Purposeful recruitment, retention, and promotion policies that reduce barriers to entry and advancement of women
2. Implicit bias training for all selection committee members for recruitment, leadership and research awards
3. Mentorship and leadership training programs for and by women and under-represented groups
4. Flexible promotion policies to account for life circumstances (e.g., “stop the clock” policies so faculty members do not fall behind in achieving promotion metrics during parental leave)
5. Fair distribution of internal research funding awards to ensure equal opportunity in external funding competitions
6. Open calls for leadership positions, funding opportunities, and research chairs
7. Leadership training and development for those from under-represented groups
8. Equal pay for equal work
9. Transparent reporting of gender-disaggregated metrics on recruitment and advancement
10. Zero tolerance policies for discrimination, sexual and gender harassment, implementation of gender, race/ethnicity transformative policies to achieve excellence in diversity and equality

***Van Spall HGC**, Lala A, Deering T et al. JACC 2021*

Summary

- There is a gross under-representation of women in clinical trial leadership
  - Under-representation is associated with industry-led trials
- Trial leadership by women is independently associated with
  - greater enrolment of women trial participants
  - greater enrolment of BiPOC trial participants
  - more women in trial steering committees
  - twice the odds of a women first author when the senior author is a woman
- To address root causes, approaches at multiple levels required to close the diversity gap in clinical trial leadership

References

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Implicit Biases of Sex and Gender in Cardiovascular Research

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Implicit Bias

- **Bias** = an **unfair prejudice** in favor of or against one person or group

- **Implicit Bias** = positive or negative **unconscious associations** that can influence behaviours and judgements
  - Activated by: stressors, time constraints, multi-tasking, need for closure
  - Drives clinical decision-making independent of evidence-based care that can contribute to healthcare disparities & micro-aggressions
  - Malleable with steps taken to minimize consequences

- Impact on **sex and gender** in cardiovascular research?

Implicit Bias in Cardiovascular Research

Women as research investigators

- Nearly half are doctorate awardees (45%) but few are active researchers (38%) or full professors (19%) [1]
- Less CIHR funding not due to proposal quality of female PI [2]
- Few are scientific advisory board members (n=6/129 in 12 companies) [3]

- Less hired or promoted despite skillset (perceived as less competent)
- Less career mentoring for hard & soft skills
- Unequal pay, research funding & workplace disparities
- Less institutional, scientific, industry or editorial board membership

1) Muhlenbruch B & Jochimsen MA. Nature 2013; 495: 40-42; 2) Hui K CMAJ 2020; 192: E1269-1270; 3) McCook A. Nature 2013; 495: 25-27

Implicit Bias in Cardiovascular Research

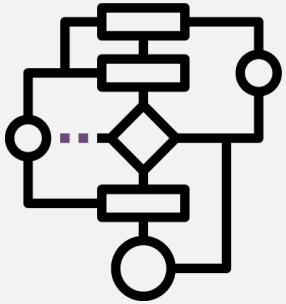
Women in research studies

- In 207 CV trials from 2001-2018, women & minorities are under-represented [1]
- Propagation of biased health datasets for artificial intelligence & other clinical research [2]
- Sex-specific differences exist within cells, animals & humans (further impacted by age-related estrogen changes) [3]
- In 2010, <20% of basic scientists in Canada undertook sex & gender research – this has doubled over time but remains low overall [3]

1) Tahhan AS et al JAMA Cardiol 2020; 5: 714-722; 2) Tat E et al The Lancet Digital Health 2020; 2 (12): E635-E636; 3) Ventura-Clapier R et al Cardiovasc Res 2017; 113 (7): 711-724

The Bottom Line

Leaky pipelines & glass ceilings persist for women researchers



Leads to **biased algorithms or guidelines** for clinical care of women despite changing demographics

Addressing Implicit Biases on Sex and Gender

Individual	• Self-awareness (Implicit Association Test) • Contact between socially dissimilar groups • Facilitated training on bias literacy
Institution	• Objective hiring, retention, evaluation & promotion criteria • Recruitment quotas for diversity • Flexible workplace policies
CV Research Community	• Women participation at all levels of research • Mandated inclusion of sex & gender data by funding agencies & journals **(Sex and Gender Equity in Reporting guidelines)**

Do You Really Know Me?

In a global sea of diversity…

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- Ventura-Clapier R, Dworatzek E, Seeland U, et al. Sex in basic research: concepts in the cardiovascular field. Cardiovasc Res 2017; 113 (7): 711-724.

"It is not only what we do, but also what we do not do, for which we are accountable." ~ Moliere

In Conclusion...

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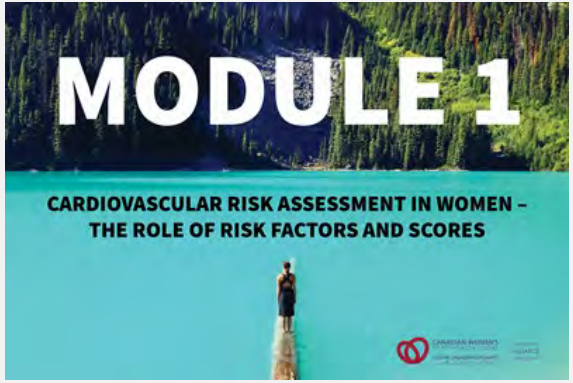
List of Resources - visit CWHHA.CA

- Norris C.M., Yip C.Y.Y., Nerenberg K.A., et al. State of the science in women's cardiovascular disease: a Canadian perspective on the influence of sex and gender. J Am Heart Assoc. 2020; 9: e015634
- The Canadian Women's Heart Health Alliance ATLAS on the Epidemiology, Diagnosis, and Management of Cardiovascular Disease in Women
  - Chapter 1: Introduction to the ATLAS
  - Chapter 2: Scope of the Problem
  - Chapter 3: Patient Perspectives
- Canadian Women's Heart Health Education Course + Teaching Toolkit
- The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030



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JOIN US!

Wear Red Canada

Sunday February 13, 2022

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Thank you!

Contact Us

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The University of Ottawa Heart Institute is the convening body of the Canadian Women's Heart Health Alliance, which is a network of experts and advocates from across Canada aiming to improve women's cardiovascular health across the lifespan.

POWERED BY

CANADIAN WOMEN'S HEART HEALTH CENTRE

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Visit CWHHA.ca for more information.

Questions?