The 3 R's for Inclusion of Women in Regenerative Medicine

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Understanding the Problem

CVD is the leading cause of morbidity & mortality in both men & women

Clear sex differences exist in the prevalence, progression & mechanisms underlying CVD

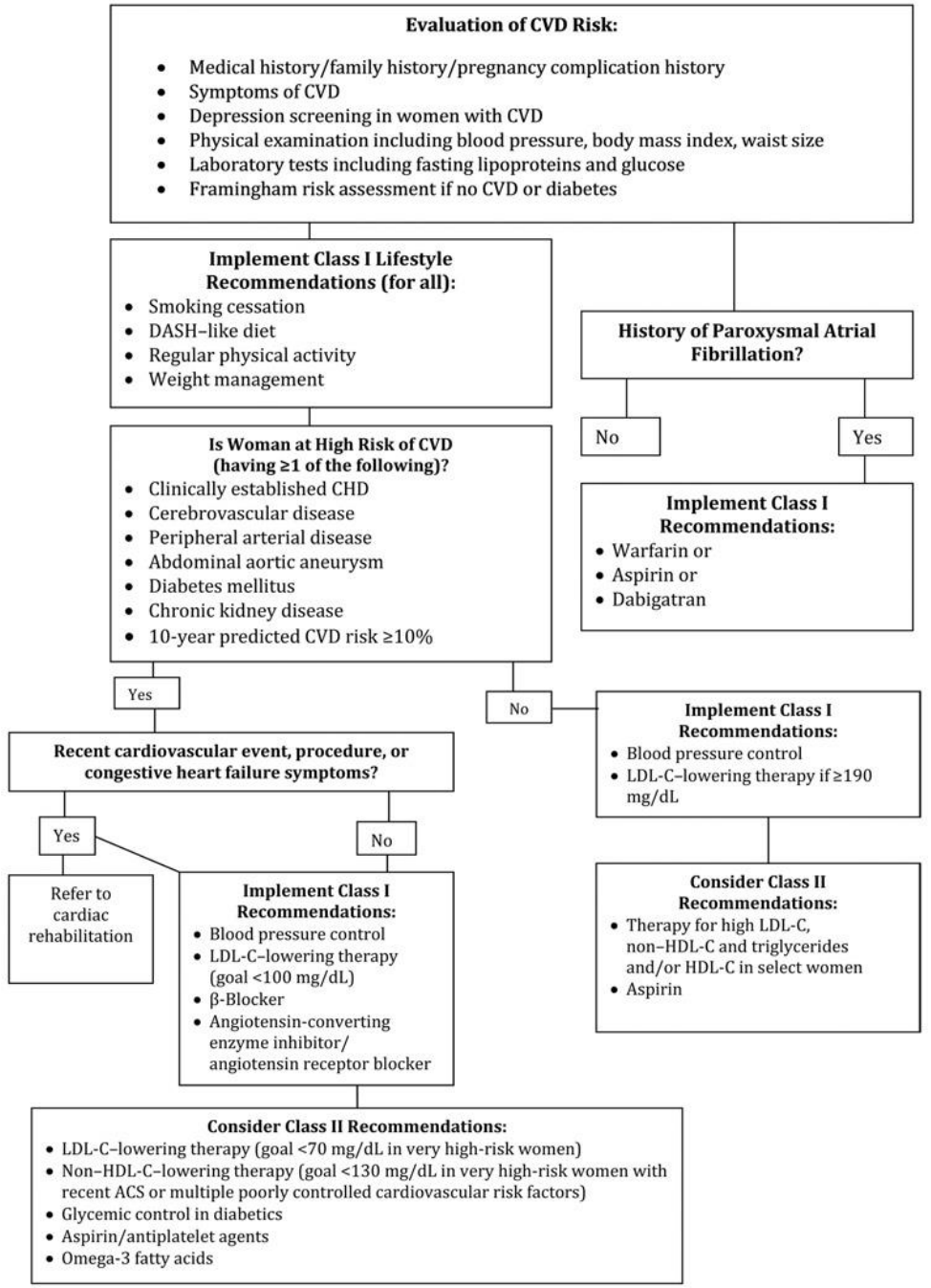
Analyses of biological sex differences are rare in animal research studies

Information is lacking about basic factors that influence CVD & therapeutic capacity

Data analysis on sex-specific differences are lacking in clinical trials

Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women-2011 Update

A guideline from the American Heart Association



J Am Coll Cardiol. 2011 March 22;57(12): 1404-1423.

Acute MI in Women Was only Described Differently in 2016

- January 2016: 1st scientific statement from AHA on acute MI in women
- Comprehensive review of sex -specific differences in presentation, pathophysiological mechanisms & outcomes in patients with acute MI

AHA Scientific Statement

Acute Myocardial Infarction in Women
A Scientific Statement From the American Heart Association

Laxmi S. Mehta, MD, FAHA, Chair; Theresa M. Beckie, PhD, FAHA, Co-Chair; Holli A. DeVon, PhD, RN, FAHA; Cindy L. Grines, MD; Harlan M. Krumholz, MD, SM, FAHA; Michelle N. Johnson, MD, MPH; Kathryn J. Lindley, MD; Viola Vaccarino, MD, PhD, FAHA; Tracy Y. Wang, MD, MHS, MSc, FAHA; Karol E. Watson, MD, PhD; Nanette K. Wenger, MD, FAHA; on behalf of the American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research

***Abstract*—Cardiovascular disease is the leading cause of mortality in American women. Since 1984, the annual cardiovascular disease mortality rate has remained greater for women than men; however, over the last decade, there have been marked reductions in cardiovascular disease mortality in women. The dramatic decline in mortality rates for women is attributed partly to an increase in awareness, a greater focus on women and cardiovascular disease risk, and the increased application of evidence-based treatments for established coronary heart disease. This is the first scientific statement from the American Heart Association on acute myocardial infarction in women. Sex-specific differences exist in the presentation, pathophysiological mechanisms, and outcomes in patients with acute myocardial infarction. This statement provides a comprehensive review of the current evidence of the clinical presentation, pathophysiology, treatment, and outcomes of women with acute myocardial infarction. (*Circulation*. 2016;133:00-00. DOI: 10.1161/CIR.0000000000000351.)**

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ coronary disease ■ myocardial infarction ■ women

Cardiovascular disease (CVD) is the leading cause of mortality for women in the United States[1] and globally.[2] Coronary heart disease (CHD) has traditionally been considered a disease of men, but what has been the odyssey for women in the century since its initial description by Herrick in 1912?[3] Despite stunning improvements in cardiovascular mortality for women in the past 2 decades (Figure),[1] CHD remains understudied, underdiagnosed, and undertreated in women. Since 1984, the annual CVD mortality rate has remained greater for women than for men, and the absolute numbers of individuals living with and dying of CVD in the United States are larger for women than for men.[1] Improved survival for women has been attributed equally to improved therapy for established CVD and to primary and secondary preventive interventions. Transformation of the research landscape and the results of landmark randomized, clinical trials have contributed to improved cardiovascular care for women.

Emerging data highlight important sex differences in the pathophysiology, clinical presentation, and clinical outcomes that were spurred by 2 milestone reports from the Institute of Medicine: *Exploring the Biological Contributions to Human Health: Does Sex Matter?*[4] and *Women's Health Research: Progress, Pitfalls, and Promise.*[5] These reports highlight the fact that although major progress has been made in reducing CVD mortality in women, medical research has historically neglected the health needs of

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on October 8, 2015, and the American Heart Association Executive Committee on October 27, 2015. A copy of the document is available at http://my.americanheart.org/statements by selecting either the "By Topic" link or the "By Publication Date" link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK; on behalf of the American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*. 2016;133:XXX–XXX. doi: 10.1161/CIR.0000000000000351.

Expert peer review of AHA Scientific Statements is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit http://my.americanheart.org/statements and select the "Policies and Development" link.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIR.0000000000000351

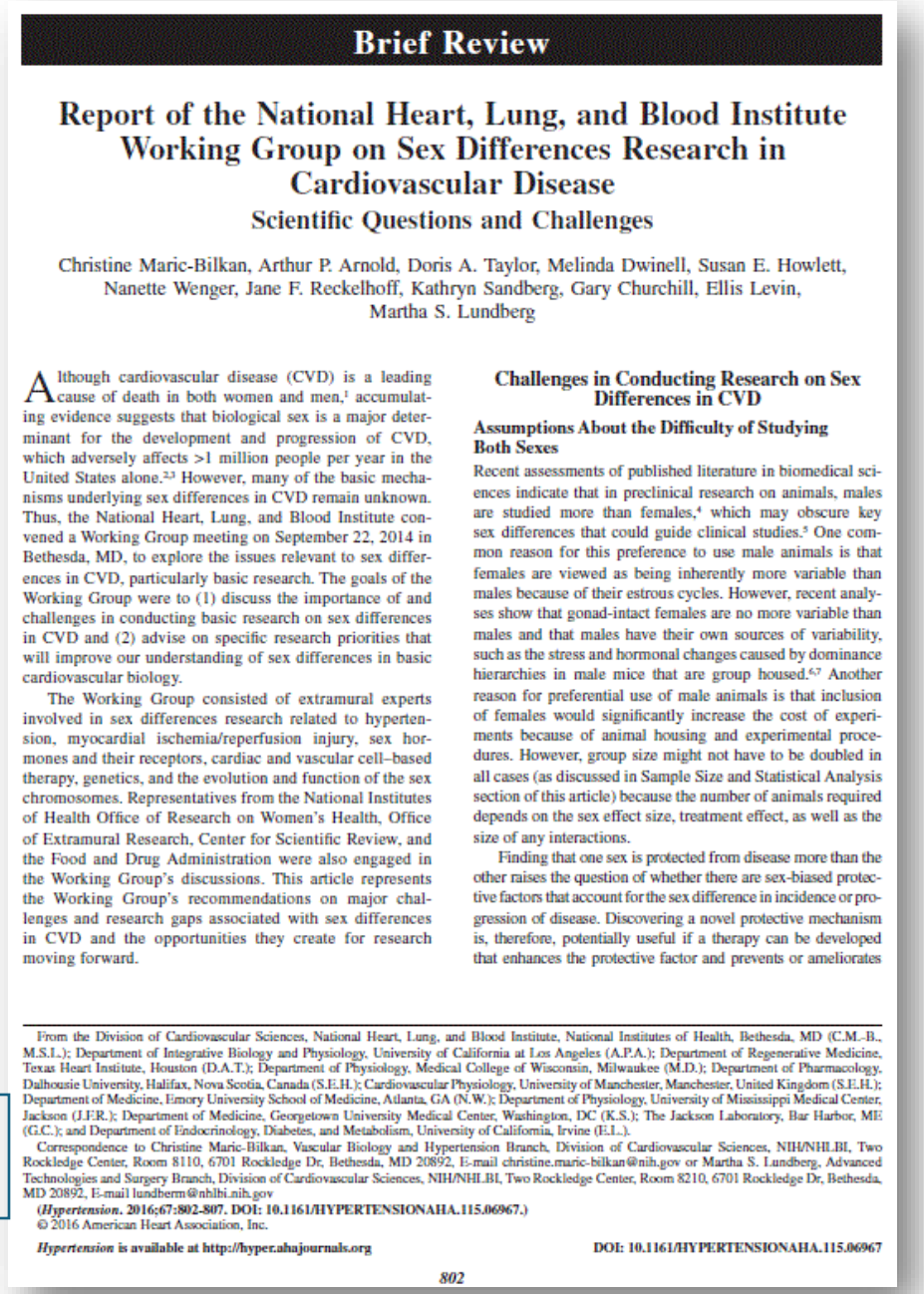
Circulation. 2016;133:00-00.

Report of the NHLBI Working group on Sex Differences Research in CVD

Recommendations regarding research on sex differences in:

1. Immune modulation of blood pressure
2. Obesity-related hypertension
3. Ischemia/ reperfusion injury
4. Cardiac arrhythmias
5. Preservation of ejection fraction with heart failure
6. Signaling mechanisms in CVD
7. Genetic profiles & epigenetic events contributing to CVD
8. Role of sex chromosomes
9. Fetal development
10. Stem & progenitor cells in CVD treatment

Hypertension. 2016;67:802-807



Brief Review

Report of the National Heart, Lung, and Blood Institute Working Group on Sex Differences Research in Cardiovascular Disease

Scientific Questions and Challenges

Christine Maric-Bilkan, Arthur P. Arnold, Doris A. Taylor, Melinda Dwinell, Susan E. Howlett, Nanette Wenger, Jane F. Reckelhoff, Kathryn Sandberg, Gary Churchill, Ellis Levin, Martha S. Lundberg

Although cardiovascular disease (CVD) is a leading cause of death in both women and men,[1] accumulating evidence suggests that biological sex is a major determinant for the development and progression of CVD, which adversely affects >1 million people per year in the United States alone.[2,3] However, many of the basic mechanisms underlying sex differences in CVD remain unknown. Thus, the National Heart, Lung, and Blood Institute convened a Working Group meeting on September 22, 2014 in Bethesda, MD, to explore the issues relevant to sex differences in CVD, particularly basic research. The goals of the Working Group were to (1) discuss the importance of and challenges in conducting basic research on sex differences in CVD and (2) advise on specific research priorities that will improve our understanding of sex differences in basic cardiovascular biology.

The Working Group consisted of extramural experts involved in sex differences research related to hypertension, myocardial ischemia/reperfusion injury, sex hormones and their receptors, cardiac and vascular cell–based therapy, genetics, and the evolution and function of the sex chromosomes. Representatives from the National Institutes of Health Office of Research on Women's Health, Office of Extramural Research, Center for Scientific Review, and the Food and Drug Administration were also engaged in the Working Group's discussions. This article represents the Working Group's recommendations on major challenges and research gaps associated with sex differences in CVD and the opportunities they create for research moving forward.

Challenges in Conducting Research on Sex Differences in CVD

Assumptions About the Difficulty of Studying Both Sexes

Recent assessments of published literature in biomedical sciences indicate that in preclinical research on animals, males are studied more than females,[4] which may obscure key sex differences that could guide clinical studies.[5] One common reason for this preference to use male animals is that females are viewed as being inherently more variable than males because of their estrous cycles. However, recent analyses show that gonad-intact females are no more variable than males and that males have their own sources of variability, such as the stress and hormonal changes caused by dominance hierarchies in male mice that are group housed.[6,7] Another reason for preferential use of male animals is that inclusion of females would significantly increase the cost of experiments because of animal housing and experimental procedures. However, group size might not have to be doubled in all cases (as discussed in Sample Size and Statistical Analysis section of this article) because the number of animals required depends on the sex effect size, treatment effect, as well as the size of any interactions.

Finding that one sex is protected from disease more than the other raises the question of whether there are sex-biased protective factors that account for the sex difference in incidence or progression of disease. Discovering a novel protective mechanism is, therefore, potentially useful if a therapy can be developed that enhances the protective factor and prevents or ameliorates

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(*Hypertension*. 2016;67:802-807. DOI: 10.1161/HYPERTENSIONAHA.115.06967.)

Hypertension is available at http://hyper.ahajournals.org DOI: 10.1161/HYPERTENSIONAHA.115.06967

The 3 R's of Improving Inclusion of Women in Regenerative Medicine

- Recruit/Retain Women
- Report Data
- Research Women and their Hearts
- Sex and Gender are not the same (in CVD)

RECRUIT

Percentage in US population – **50.8%**

Percentage in cardiovascular clinical trials – 38.2%

- < 50% female enrollment - **85.3**% of trials
- <25% female enrollment - 29% of trials

Average percentage enrollment in Regen Med CVD trials – 18.6%

- Rates vary by
  - Disease (HTN PAH vs arrhythmia, CAD, ACS and HF)
  - Trial type (medication vs procedural trials)
  - Age 61-65 yo lowest rate
  - Funding (non-NIH vs NIH-funded)
  - Trial Leadership (men vs women)

Barriers

- **Lack of understanding of the effects of the disease in women** which can lead to under-diagnosing or not referring women to a study.
- **The misperception among study sponsors and investigators that it takes more time and money to recruit women.**

- **Women perceived a greater risk of harm from trial participation**. Women had also been shown to take fewer risks than men under stress, and large health-based decisions could certainly be a source of stress.
- Time constraints
- Apprehension towards being in a clinical trial with an experimental design or therapy,
- Women more often than men reported transportation problems as a reason to decline trial participation.

Call to increase participation of women in cardiovascular clinical trials
European Society of Cardiology 2021

Motivators

- possibility of accessing better and more continuous care
- altruistic values such as the desire to promote science
- high socioeconomic position was associated with an increased willingness to participate among women
- this may marginalise women with a lower socioeconomic position, who stand to benefit the most from better representation.

Call to increase participation of women in cardiovascular clinical trials
European Society of Cardiology 2021

Implications

- Trials aren’t powered to assess effects in women
- Subgroup analyses only allow exploratory findings
- Women enrolled don’t represent majority of women with disease

Solution: Recruit women Leaders

Rates vary by Trial Leadership

- Percentage of women training in cardiology – 25.5%
- 13.8% Black or Hispanic
- Percentage of trials led by women (2010 – 2019) – 18%

RETAIN

- Fewer Women are Enrolled
- Women Drop Out more Often Than Men

- **Average percentage enrollment in Regen Med CVD trials – 18. 6%**
- **Average percentage enrollment in HF trials 20-30% for over 4 decades**

Why Do Women Drop Out?
- Time constraints
- Transportation problems
- Family considerations

Female Academic Attrition Rates
Assistant profs - 6%
Full profs with tenure – 19%

Toxic workplace #1 reason
- Nature 2023

REPORT

Average percentage enrollment in Regen Med CVD trials – 18%

Percentage of Regen Med CT studies reporting data by sex

- **In 2016 – 0%**
- **In 2024 – <2%**

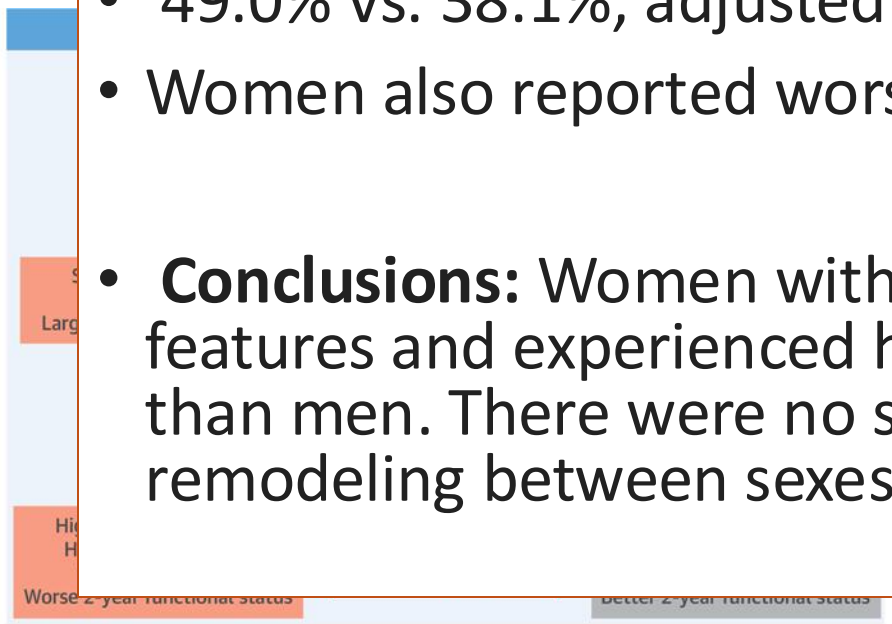
- Report data by sex to enable subgroup and meta-analyses

- **WHY IT MATTERS… OUTCOMES GET IGNORED**

JACC Heart Fail. 2019 Jun;7(6):481-490. doi: 10.1016/j.jchf.2019.03.001.

Sex-Based Differences in Outcomes After Mitral Valve Surgery for Severe Ischemic Mitral Regurgitation: From the Cardiothoracic Surgical Trials Network

Gennaro
Joseph D
Emilia Bag
Patrick O'



- At 2 years, women had higher rates of all-cause mortality
- 27.1% vs. 17.4%, adjusted hazard ratio 1.85;
- and of MACCE
- 49.0% vs. 38.1%, adjusted hazard ratio 1.58
- Women also reported worse QOL and functional status at 2 years.

- **Conclusions:** Women with SIMR displayed different echocardiographic features and experienced higher mortality and worse QOL after MV surgery than men. There were no significant differences in the degree of reverse LV remodeling between sexes.

Giustino, G. et al. J Am Coll Cardiol HF. 2019;7(6):481-90.

Cardiovascular Cell Therapy in 2024

Not yet recruiting (15)
Recruiting (37)
Active, not recruiting (11) **(63)**

Completed (149)
Terminated (36) **(185)**
Suspended (4)
Withdrawn (14)

Approved 0

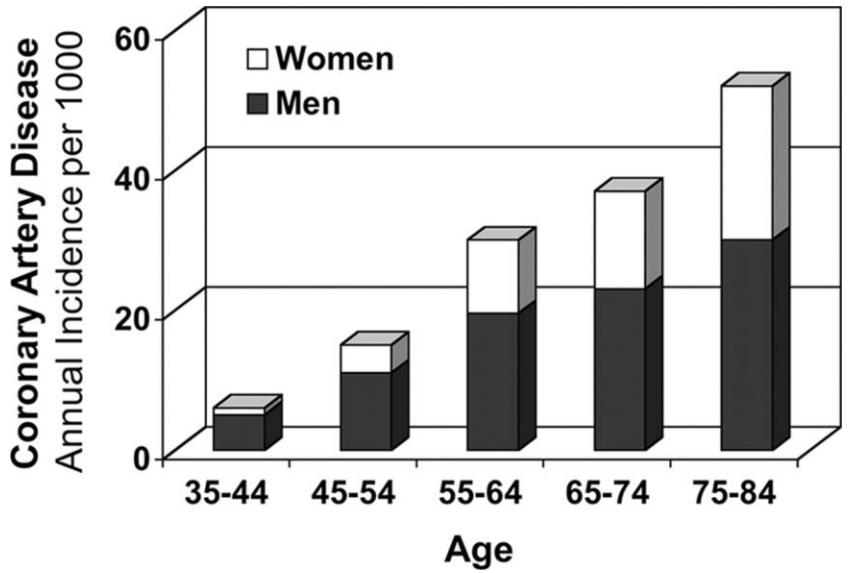
NCT Number	Study Title	Conditions
NCT06147986	Evaluate the Efficacy and Safety of Allogeneic Umbilical Cord Mesenchymal Stem Cells as an Add-On Treatment for Acute ST-elevation Myocardial Infarction (STEMI) Patients	ST Elevation Myocardial Infarction
NCT05068674	Human E	Chronic Ischemic Left Ventricular Dysfunction
NCT03455725	CardiAMI	Refractory Angina|Chronic MI
NCT02781922	Cardiac S	Hypoplastic Left Heart Syndrome
NCT05147766	Safety of	Congestive Heart Failure|Angina
NCT03572660	Use of Bo	Dilated Cardiomyopathy
NCT06340048	Epicardia	Heart Failure
NCT05647213	Autologo	Univentricular Heart
NCT04776239	Allogenei Sympton	Ischemic Heart Disease
NCT03763136	Treating	Heart Failure
NCT05643235	Implante	Ventricular Arrhythmias Cardiac Arrest
NCT05711849	Assessin	Refractory Angina
NCT05566600	Allogenei	Ischemic Heart Failure
NCT05223894	Treating	Heart Failure
NCT04476901	Administ	Non-ischemic Dilated Cardiomyopathy
NCT06154044	Cell Ther	Mechanical Circulatory Support
NCT05669144	Co-trans Candidat	MI |Myocardial Stunning
NCT04924491	Cell Ther Children	Heart Transplantation
NCT05774509	Treatmer Cells	HFrEF
NCT04982081	Treating	Dilated Cardiomyopathy
NCT05043610	MSCs for	Myocardial Infarction
NCT05632432	Atrial Ap	Ischemic Heart Disease
NCT05554484	AMI-DC i	Myocardial Infarction
NCT04684602	Mesench	|Cardiovascular Disorders|
NCT02962661	Donor Bone Marrow Derived Mesenchymal Stem Cells in Controlling Heart Failure in Patients With Cardiomyopathy Caused by Anthracyclines	Cardiomyopathy|Heart Failure

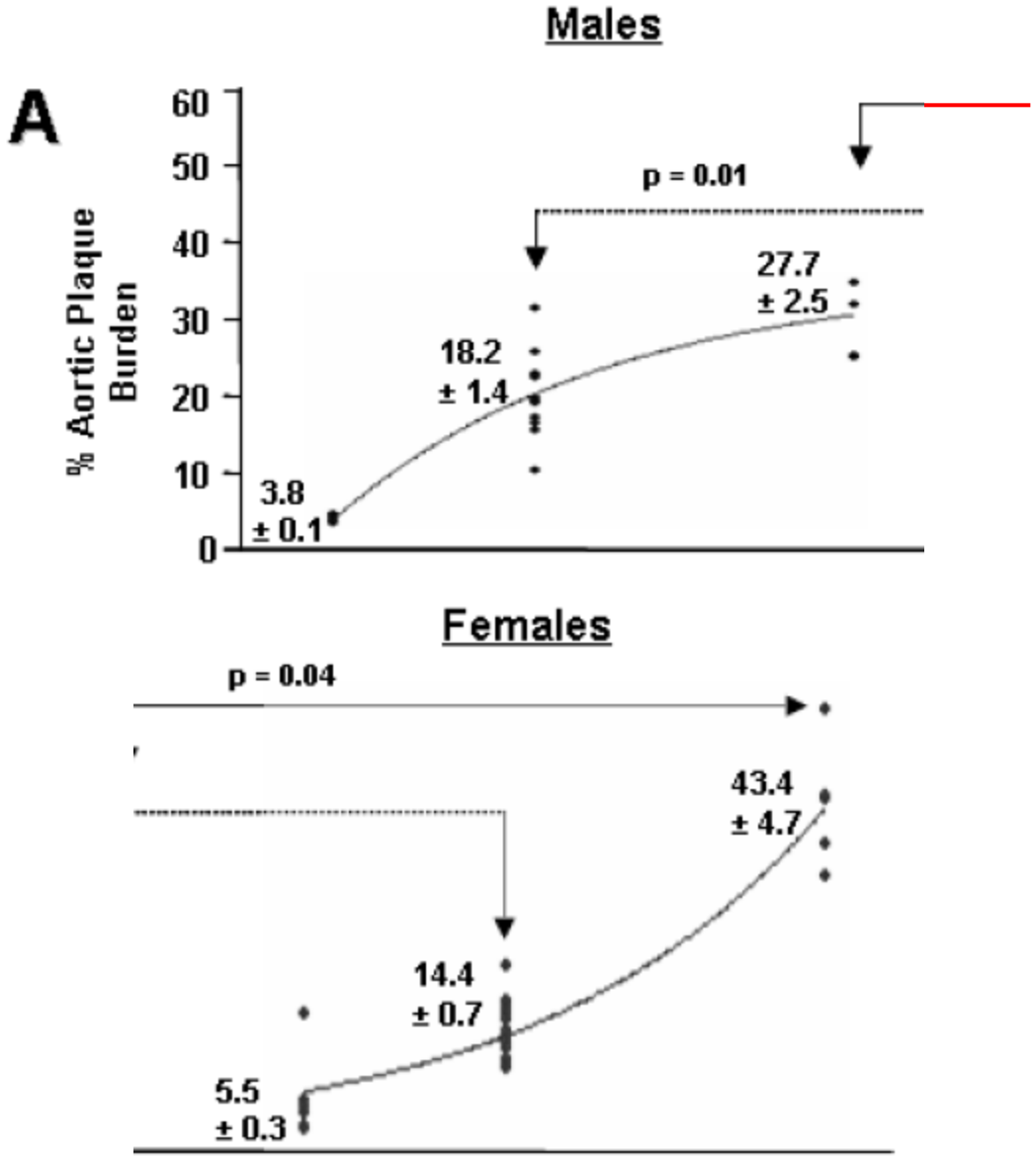
Why isn't Cell Therapy Approved for CVD?

BIOLOGY DIFFERS FROM DRUGS AND IT MATTERS

- **A patient is not a patient**
- **A cell is not a cell; its environment differs endogenously**
- **An exosome is not an exosome**
- **Cells, Genes, Secretome have an effect you know and one you don't**
- **Trial Design, Size and Outcome likely depend on understanding this**
- **Mixing data is bad science**
- **Data have to be reported by sex, gender, race and ethnicity even if underpowered to enable meta-analyses**

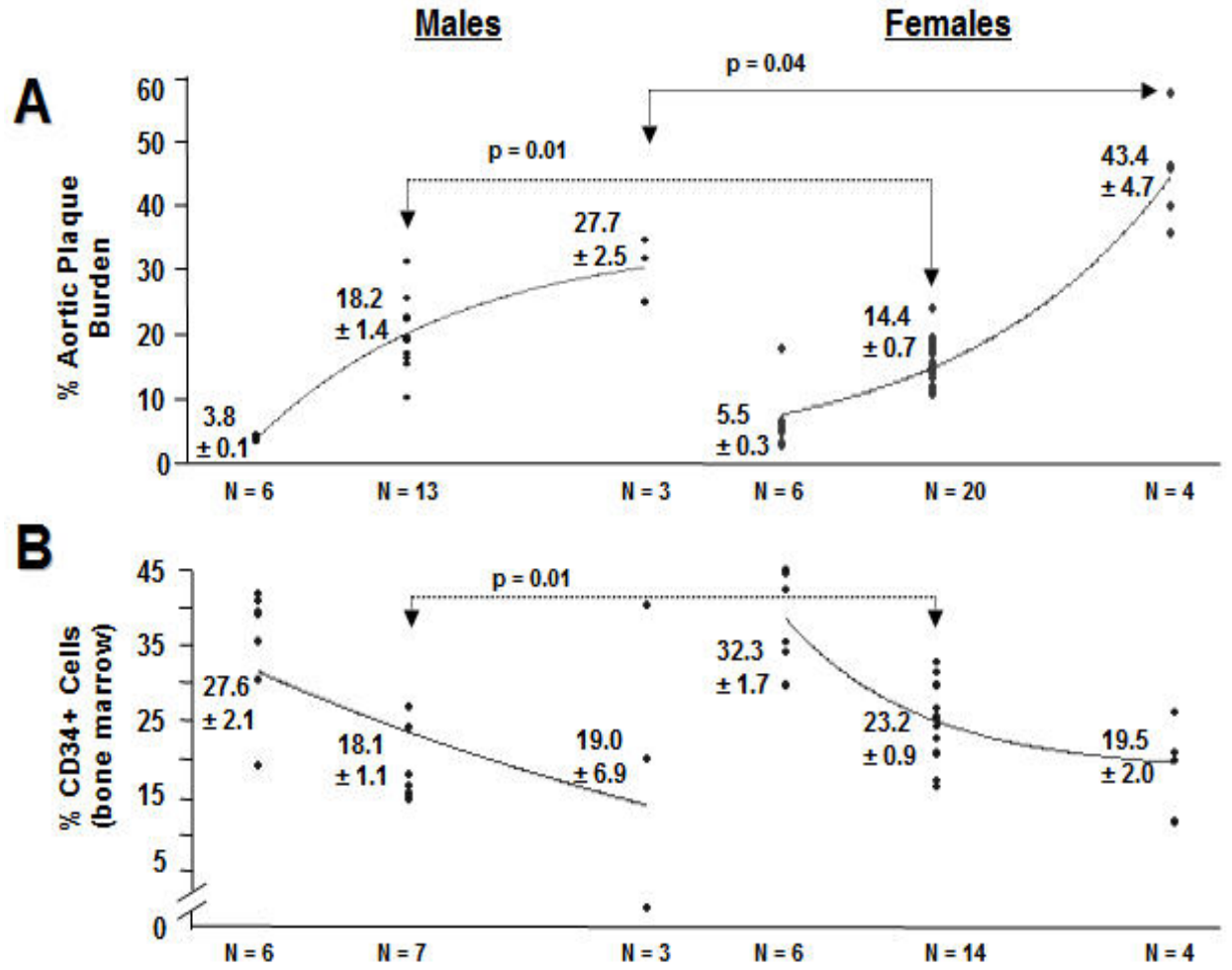
Sex difference in CAD course is similar in humans and mice



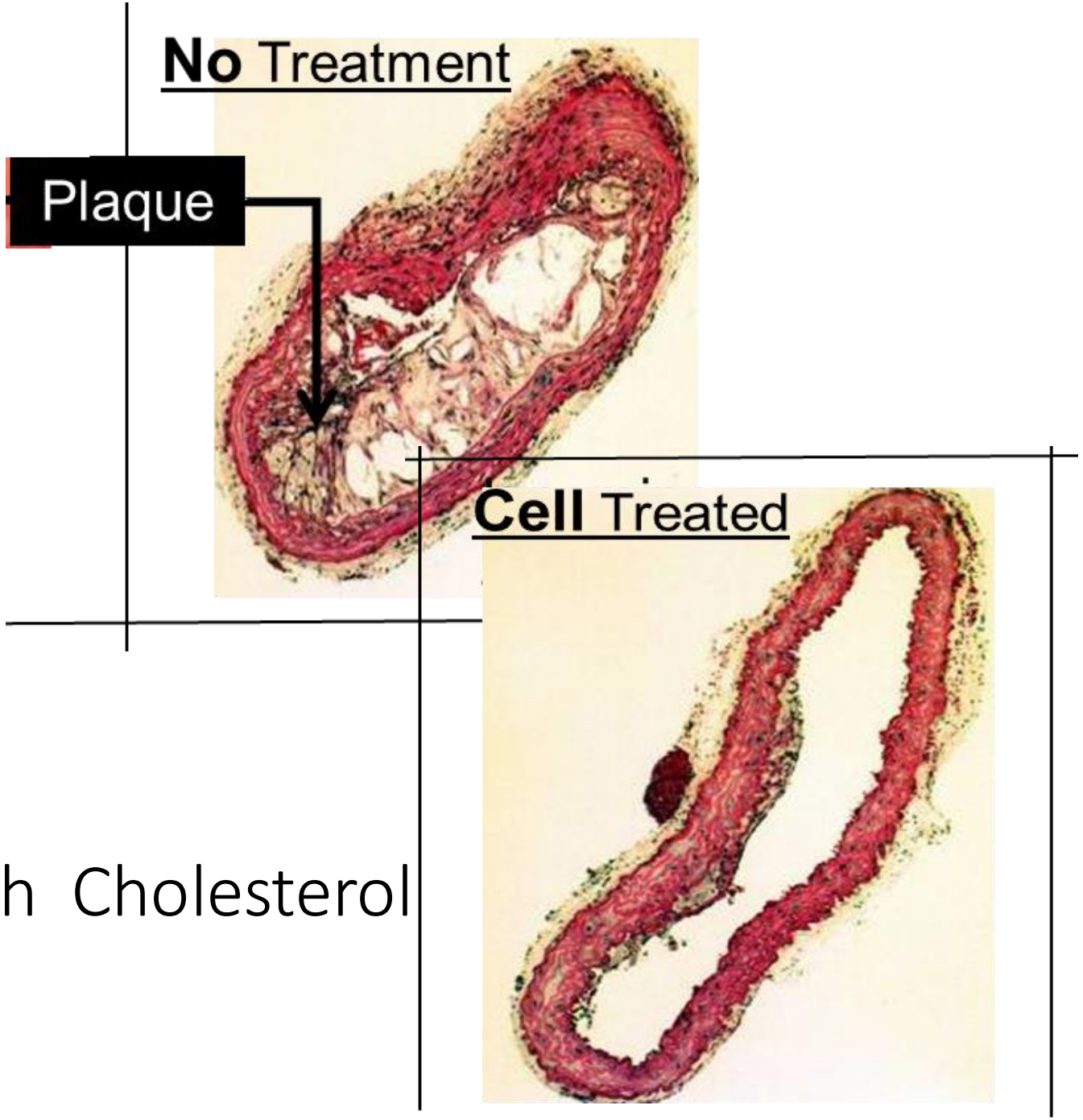


As Atherosclerosis Increases with Age in (ApoE-/- mice) PC populations fall

CD34+EPCs



In animals, YOUNG bone marrow stem cell delivery prevents atherosclerosis

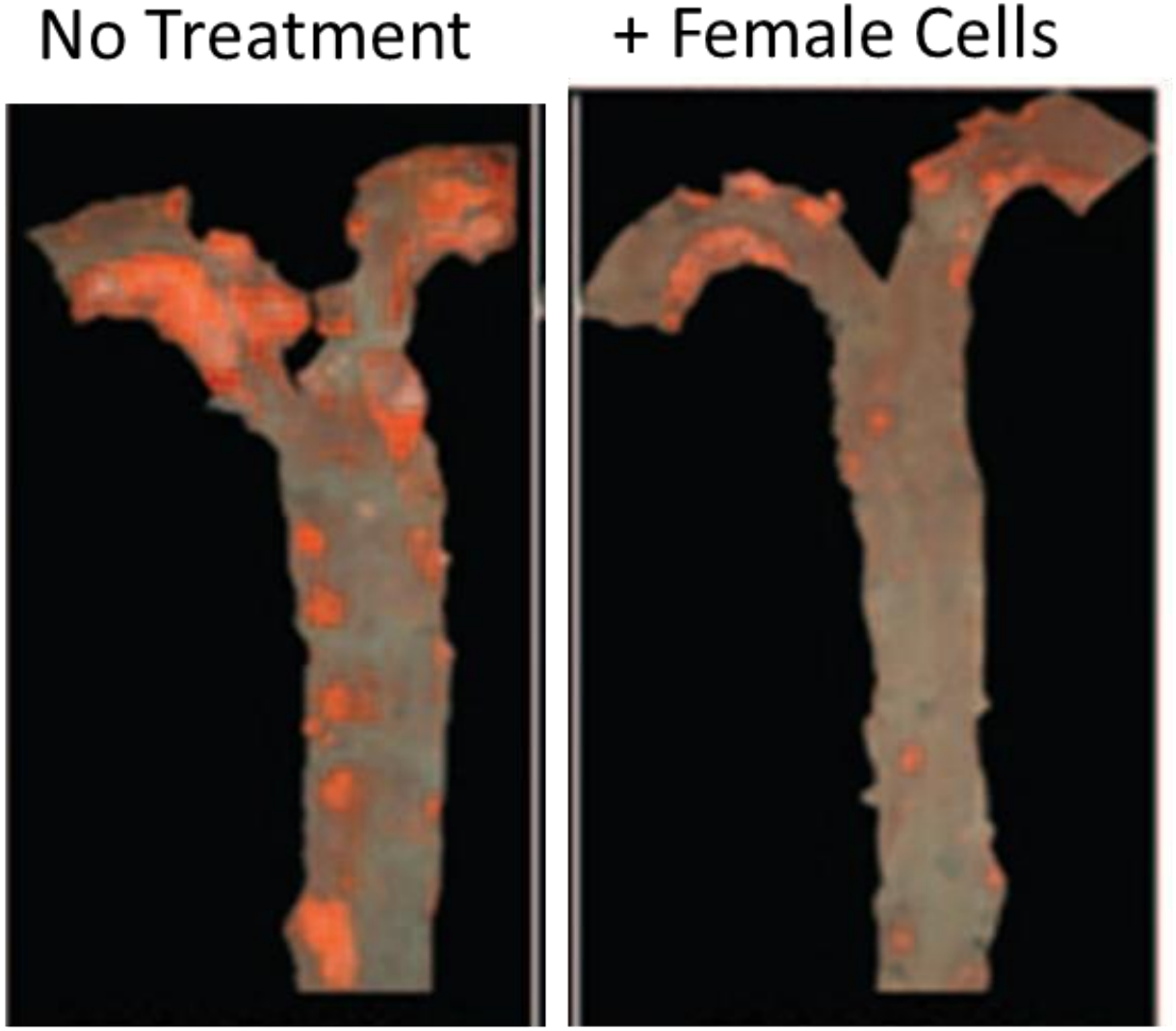


Even with Cholesterol at 1200

But disease regression isn't as simple

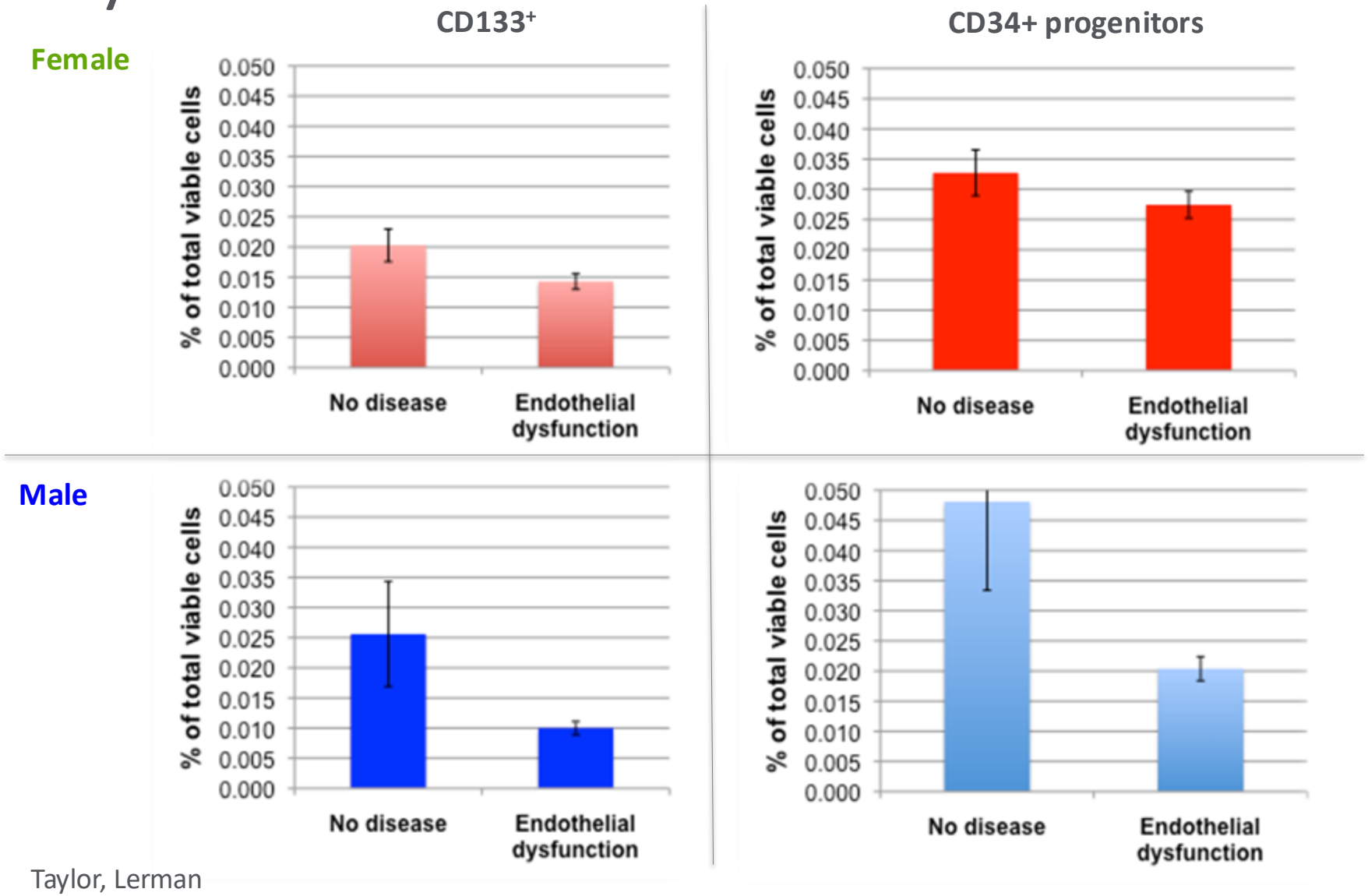
Female cells could regress plaque – in males

Male cells had no effect; trend toward worsening



Transplantation Proceedings, 40, 641-643 (2008)

Circulating progenitor cells decrease very early in disease & differ by sex



Taylor, Lerman

Improvement in HF Outcomes Associates with 6 cell populations

Variable	Group 1 ($n = 17$)	Group 2A ($n = 11$)	p Value
Cell phenotype			
$CD45^+CD31^{bright}$	0.2 (0.1)	0.4 (0.3)	0.046
$CD45^+CD11b^+$	6.2 (2.0)	4.1 (2.0)	0.012
$CD19^+CD11b^+$	1.2 (0.6)	0.6 (0.2)	0.007
$CD45^+$ $CD19^+$	15.8 (6.8)	10.6 (5.4)	0.043
$CD19^+CXCR4^+$	14.4 (6.4)	9.0 (4.9)	0.024
Cell function			
ECFC per dose *	85.0 (87.2)	248.9 (227.8)	0.016

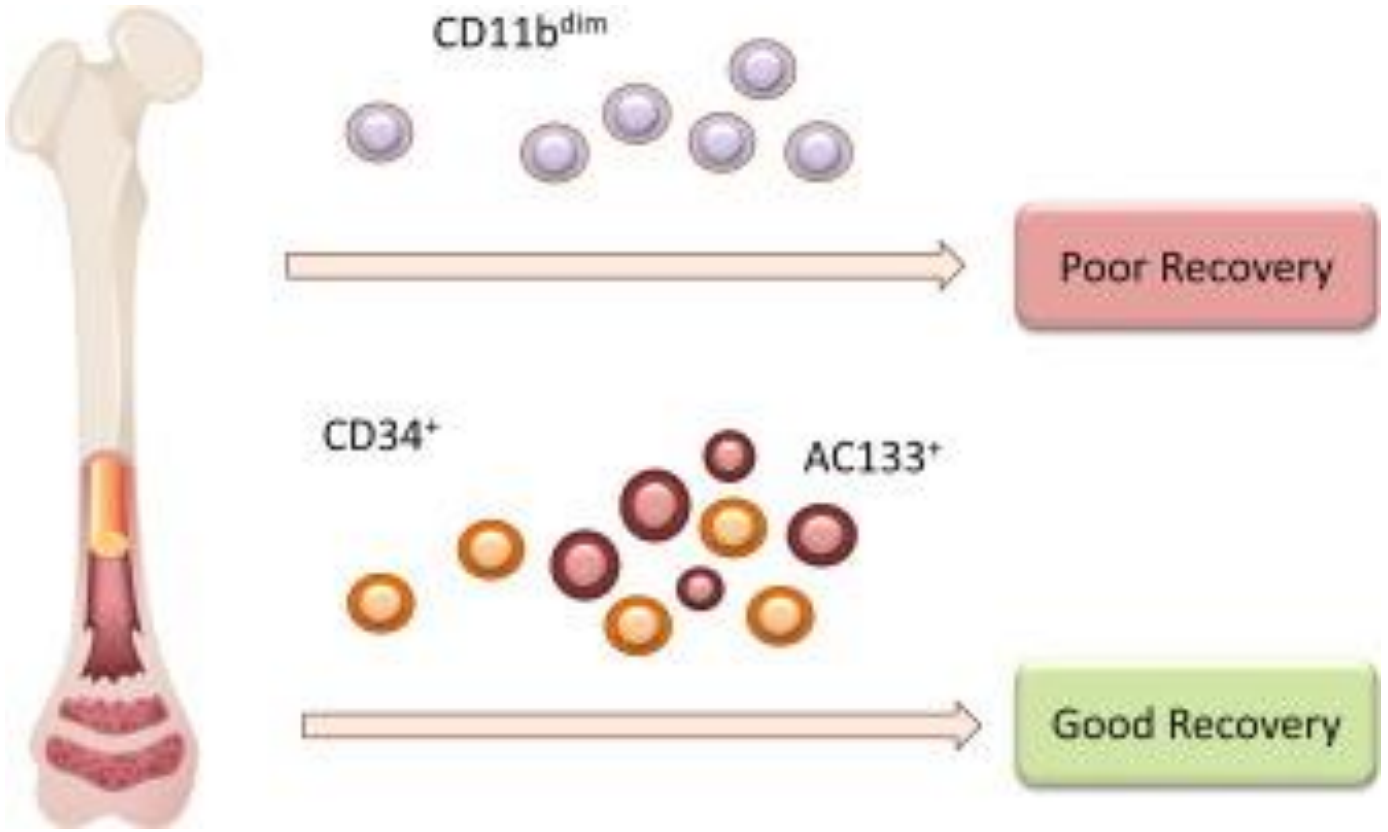
Taylor DA et al, Cell Transplant. 2016;25:1675-1687.

Does it matter?

Bone marrow cell characteristics associated with patient profile and cardiac performance outcomes in the LateTIME-Cardiovascular Cell Therapy Research Network (CCTRN) trial

Bhatnagar, A …Taylor DA
https://doi.org/10.1016/j.ahj.2016.06.018

CCTRN LateTIME



BM Cell products (and potency) differ **by sex** and with **degree of disease**

Phenotype	Sex (female)	
	Effect size (95% CI)	*P* value
[a]CD34+	0.13 (−1.06 to 1.32)	0.833
[b]CD11b+	−6.40 (−11.70 to 1.10)	0.018
[a]CD34+CD31+	0.12 (−1.05 to 1.29)	0.842
CD45+CD31+	1.49 (−2.24 to 5.22)	0.431
CD45+CD3+	3.98 (−0.45 to 8.42)	0.078
[b]CD45+CD14+	−6.61 (−12.49 to 0.72)	0.028
CD45+CD19+	−0.92 (−2.82 to 0.99)	0.343
CD19+CXCR4+	−0.45 (−2.13 to 1.22)	0.594

Contreras A et al, Basic Res Cardiol. 2017 Jan;112(1) :3

Variable	Healthy (n=20)	>2CVRF (n=20)	P value
CD34+	3.200 6± 1.419	5.8416± 3.114	0.0028
CD34+ CD133+	1.657 ± 2.015	2.955 ± 0.8458	0.0269
CD34+ CD31+	3.179 ± 1.440	7.312 ± 7.878 P= 0.0099	0.0182

Patients also differ by sex
A meta-analysis of sex differences in AMI CT trials

Baseline Characteristics by Sex

Variable	Women (N=233)	Men (N=1019)	Total (N=1252)	p value
Group				0.126
CELL-ic	153 (65.7%)	614 (60.3%)	767 (61.3%)	
control-	80 (34.3%)	405 (39.7%)	485 (38.7%)	
Age	60.4 (10.7)	56.5 (10.3)	57.2 (10.5)	< 0.001
Hypertension	131 (57.2%)	497 (48.8%)	628 (50.4%)	0.022
Pre-EDV	117.9 (38.8)	148.9 (49.5)	143.7 (49.3)	< 0.001
Pre-ESV	65.2 (29.9)	84.8 (38.9)	81.5 (38.2)	< 0.001
Pre-EF	45.6 (12.1)	44.2 (11.9)	44.4 (11.9)	0.119
Smoking	100 (48.8%)	539 (58.5%)	639 (56.7%)	0.011

Outcomes Characteristics by Sex

Variable	Women (N=233)	Men (N=1019)	Total (N=1252)	p value
FUP EDV	125.9 (43.1)	165.1 (55.9)	158.6 (55.9)	< 0.001
FUP ESV	66.4 (36.9)	90.2 (47.3)	86.2 (46.6)	< 0.001
FUP EF	50.1 (14.2)	47.2 (13.6)	47.7 (13.7)	0.010
Delta EDV	9.4 (30.5)	15.6 (38.7)	14.6 (37.5)	0.048
Delta ESV	2.8 (27.2)	5.2 (31.1)	4.8 (30.5)	0.348
Delta EF	4.1 (10.6)	3.0 (9.0)	3.2 (9.3)	0.154

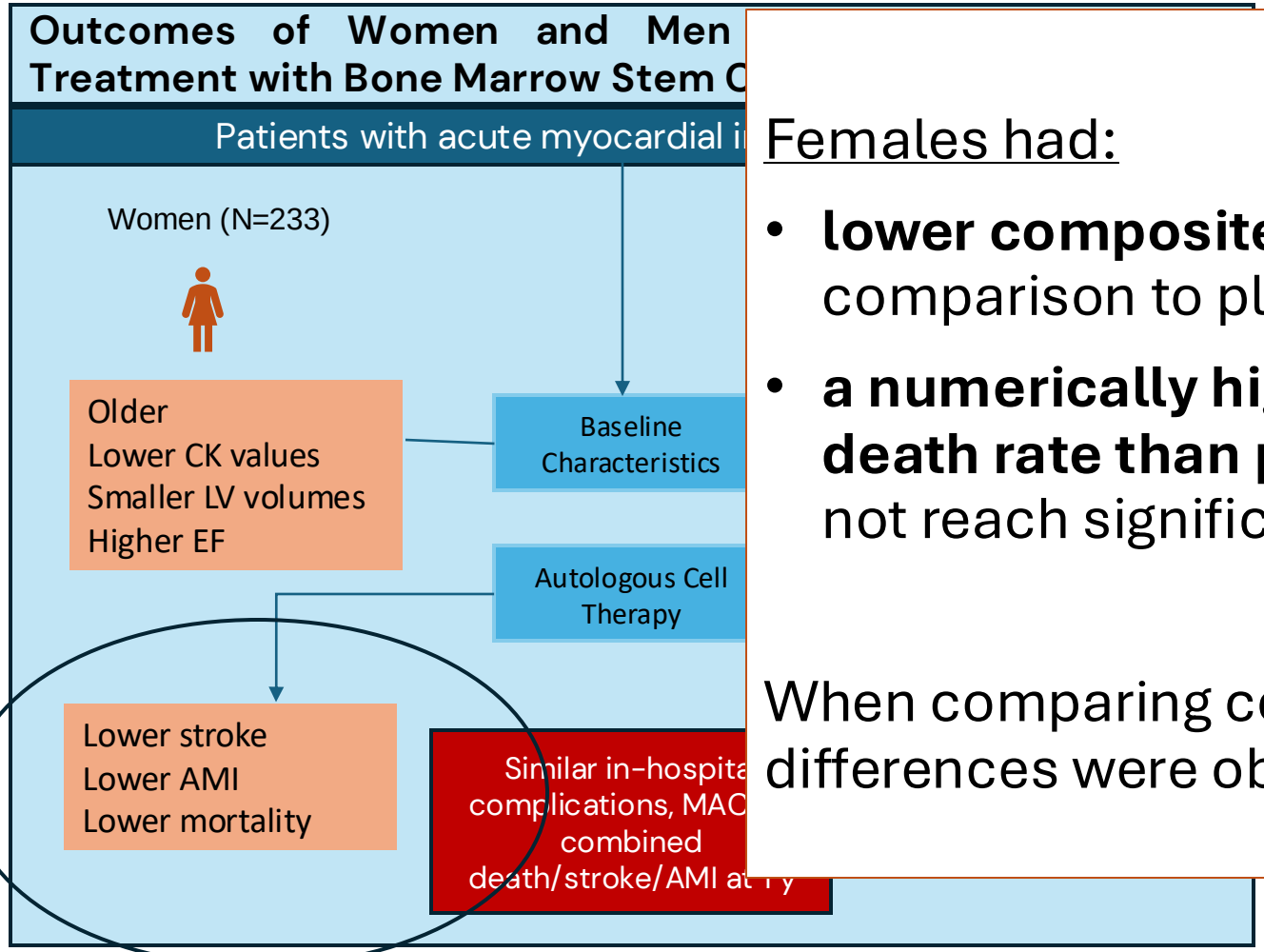
Race/Ethnicity – PROPEL sub-analysis

Abstract 14598: Gender Differences in Intracoronary Cardiac Cell Therapy Trials

Paul M Haller, Mariann Gyöngyösi, Micheline M Resende, Lourdes I Chacon, Doris A Taylor, and ACCRUE Investigators

Front Cardiovasc Med. 2021 May 26:8:664277. doi: 10.3389/fcvm.2021.664277. eCollection 2021.

Sex-Based Differences in Autologous Cell Therapy Trials in Patients With Acute Myocardial Infarction: Subanalysis of the ACCRUE Database



Females had:

- **lower composite end point (stroke, AMI and death**) in comparison to placebo-treated females.
- **a numerically higher delta EF and numerically lower death rate than placebo-treated females** but this did not reach significance. (small numbers)

When comparing cell therapy vs placebo in males no differences were observed.

One of the more promising articles about evaluating mechanism doesn't mention the word women or female…

Special Article

OPEN

Phase 3 DREAM-HF Trial of Mesenchymal Precursor Cells in Chronic Heart Failure

A Review of Biological Plausibility and Implementation of Flexible Clinical Trial Design

Kenneth M. Borow, Alex Yaroshinsky, Barry Greenberg,* Emerson C. Perin*

Abstract: **Advanced heart failure (HF) is a progressive disease characterized by recurrent hospitalizations and high risk of mortality. Indeed, outcomes in late stages of HF approximate those seen in patients with various aggressive malignancies. Clinical trials assessing beneficial outcomes of new treatments in patients with cancer have used innovative approaches to measure impact on total disease burden or surrogates to assess treatment efficacy. Although most cardiovascular outcomes trials continue to use time-to-first event analyses to assess the primary efficacy end point, such analyses do not adequately reflect the impact of new treatments on the totality of the chronic disease burden. Consequently, patient enrichment and other strategies for ongoing clinical trial design, as well as new statistical methodologies, are important considerations, particularly when studying a population with advanced chronic HF. The DREAM-HF trial (Double-Blind Randomized Assessment of Clinical Events With Allogeneic Mesenchymal Precursor Cells in Advanced Heart Failure) is an ongoing, randomized, sham-controlled phase 3 study of the efficacy and safety of mesenchymal precursor cells as immunotherapy in patients with advanced chronic HF with reduced ejection fraction. Mesenchymal precursor cells have a unique multimodal mechanism of action that is believed to result in polarization of proinflammatory type 1 macrophages in the heart to an anti-inflammatory type 2 macrophage state, inhibition of maladaptive adverse left ventricular remodeling, reversal of cardiac and peripheral endothelial dysfunction, and recovery of deranged vasculature. The objective of DREAM-HF is to confirm earlier phase 2 results and evaluate whether mesenchymal precursor cells will reduce the rate of nonfatal recurrent HF-related major adverse cardiac events while delaying or preventing progression of HF to terminal cardiac events.**

DREAM-HF is an example of an ongoing contemporary events-driven cardiovascular cell–based immunotherapy study that has utilized the concepts of baseline disease enrichment, prognostic enrichment, and predictive enrichment to improve its efficiency by using accumulating data from within as well as external to the trial. Adaptive enrichment designs and strategies are important components of a rational approach to achieve clinical research objectives in shorter clinical trial timelines and with increased cost-effectiveness without compromising ethical standards or the overall statistical integrity of the study. The DREAM-HF trial also presents an alternative approach to traditional composite time-to-first event primary efficacy end points. Statistical methodologies such as the joint frailty model provide opportunities to expand the scope of events-driven HF with reduced ejection fraction clinical trials to utilize time to recurrent nonfatal HF-related major adverse cardiac events as the primary efficacy end point without compromising the integrity of the statistical analyses for terminal cardiac events. In advanced chronic HF with reduced ejection fraction studies, the joint frailty model is utilized to reflect characteristics of the high-risk patient population with important unmet therapeutic needs. In some cases, use of the joint frailty model may substantially reduce sample size requirements. In addition, using an end point that is acceptable to the Food and Drug Administration and the European Medicines Agency, such as recurrent nonfatal HF-related major adverse cardiac events, enables generation of clinically relevant pharmacoeconomic data while providing comprehensive views of the patient's overall cardiovascular disease burden. The major goal of this review is to provide lessons learned from the ongoing DREAM-HF trial that relate to biologic plausibility and flexible clinical trial design and are potentially applicable to other development programs of innovative therapies for patients with advanced cardiovascular disease.

Clinical Trial Registration: **URL: https://www.clinicaltrials.gov. Unique identifier: NCT02032004. (*Circ Res.* 2019;125:265-281. DOI: 10.1161/CIRCRESAHA.119.314951.)**

Key Words: clinical trial ■ goals ■ heart failure ■ humans ■ immunotherapy ■ inflammation

Building personalized cell therapy is not unusual …in cancer but it is new in CVD

BioCardia CardiAMP

250 patients double blind RCT

Screening

Small sample bone marrow harvested in an outpatient procedure.
Centralized diagnostic lab tests the sample.

Treatment:

ONLY PATIENTS WHOSE BONE MARROW HAS THE CELLS ARE ENROLLED

- Only then a clinician harvests and prepares the patient's bone marrow mononuclear cells, by using the CardiAMP point of care cell processing platform.
- A cardiologist then delivers the cells into the heart using the Helix biotherapeutic delivery system.

Estimated Primary Completion Dec 2023

Estimated Study Completion Dec 2024

Optimizing Cardiovascular Disease Research in Women

Nanette Wenger, MD; Doris A. Taylor, PhD; Jay R. Kaplan PhD; Jane Reckelhoff, PhD; Janet Rich-Edwards, ScD; Meir Steiner, MD, MSc, PhD, FRCPC, C. Noel Bairey Merz, MD; Virginia M. Miller, PhD; Leslee J. Shaw PhD; Sarah Berga, MD; Clinton Webb PhD; Pamela Ouyang, MBBS

Reporting of Reproductive and Pyschosocial History in CV Studies

Using online study information, we reviewed major studies evaluating CVD risk in women for data collection on variables shown. (Detailed , limited ,or no data collected.

Name of the Study	Type of Study	Pregnancy	Pregnancy Disorders	Contraceptives Menopause Hysterectomy HT	Psycho-social	Depression
Multi Ethnic Study of Atherosclerosis (MESA)	Observational					
Nurses' Health Study (NHS 2 & 3)	Observational					
Nurses' Health Study (NHS 1)	Observational					
Jackson Heart Study (JHS)	Observational					
Coronary Artery Risk Development in Young Adults (CARDIA)	Observational					
Danish National Birth Cohort (DNBC)	Obser					
Action to Control Cardiovascul in Diabetes (ACCORD)						
Kronos Early Study						
	Observational	Not known	Not known	Not known	Not known	Not known

In addition to increased enrollment of women in CVD research studies and analysis of clinical and genetic studies by sex, expansion of study design to include these understudied uniquely or predominantly female characteristics will enhance the quality and quantity of evidence-based medicine to guide CVD care in women and men.

Conclusions

In addition to increased enrollment of women in CVD research studies and analysis of clinical and genetic studies by sex, expansion of study design to include these understudied uniquely or predominantly female characteristics will enhance the quality and quantity of evidence-based medicine to guide CVD care in women and men.

RESEARCH

Being a woman increases your CV Risk

Enrollment lags

Funds have to match intent

Review panels have to be educated

- Data repositories by sex and gender will enable subgroup and meta-analyses
- Funding of sex-based mechanistic studies are key
- Sex ≠ gender

Sex vs. Gender

SEX is biology

XX
XY

Sex vs gender

DEI

Hormone status

Opting out

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A Personalized Cure for the
Number One Killer Worldwide

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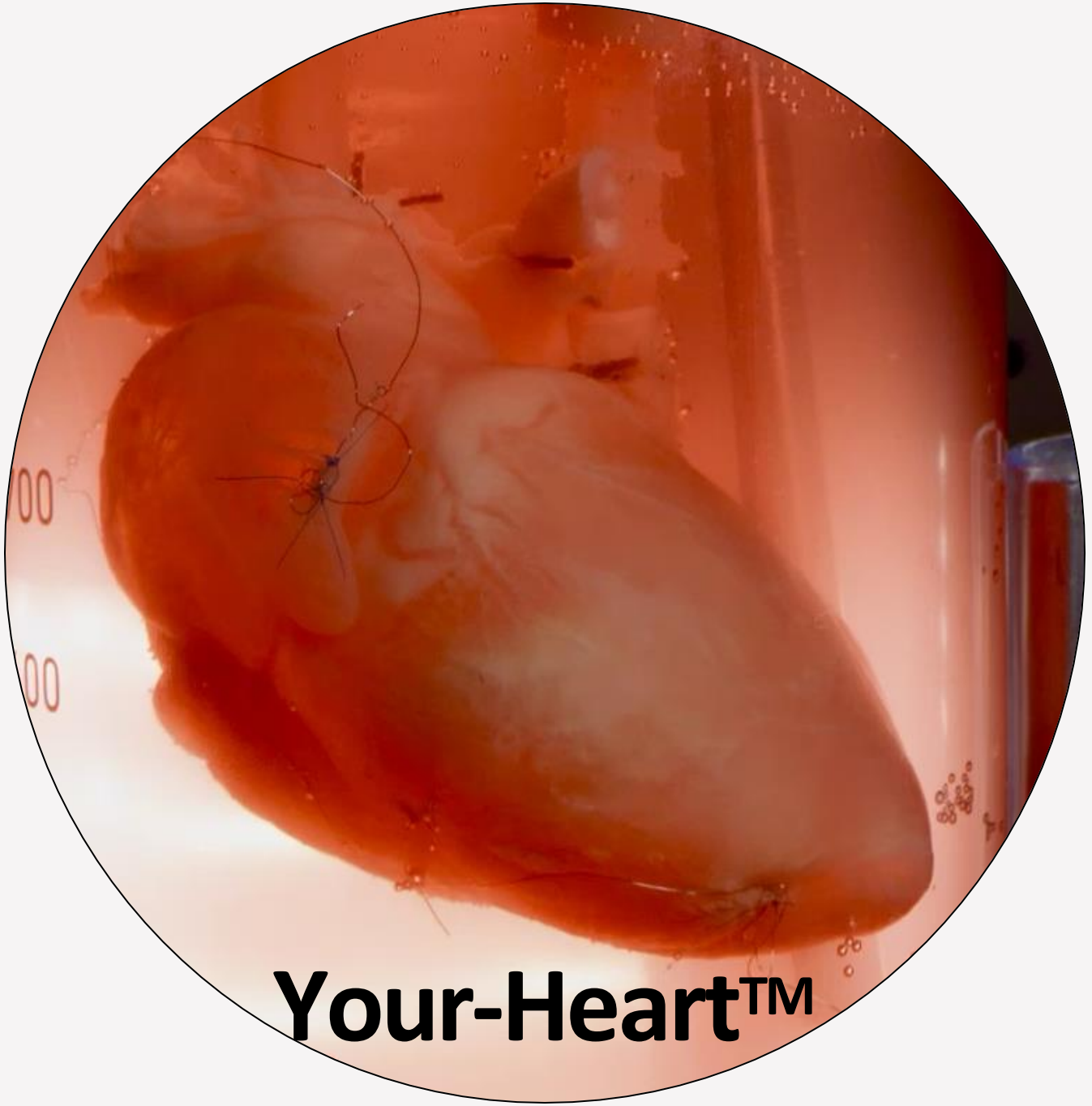

HEART FAILURE INEQUITIES

6 M patients in US living with HF

Increasing after COVID

Circulation

ORIGINAL RESEARCH ARTICLE

Sex Disparities in Longitudinal Use and Intensification of Guideline-Directed Medical Therapy Among Patients With Newly Diagnosed Heart Failure With Reduced Ejection Fraction

- Although male and female patients have similar lifetime risks of clinical HF, there are substantial sex differences in the type of HF, risk factor burden, and HF clinical presentation.[4–6]

- Female (compared with male) patients are less likely to have HFrEF than HF with preserved ejection fraction and are more likely to be older at the time of diagnosis.[7–9]

- Female (compared with male) patients are less likely to receive evidence-based device therapy or to undergo coronary revascularization and are more likely to receive treatments that could worsen HF.[10]

- Furthermore, female (compared with male) patients with HF have a higher burden of symptoms, worse health-related quality of life, higher long-term risk of readmission, and greater loss of survival time after HF hospitalization.[7,9,11,12]

- Occurs in only a few Very ill Patients
- Is an Emergency Surgery If a Heart is Available
- Results in a Requirement for Daily Toxic Expensive Meds

Donor Heart Transplant is Today's Imperfect Solution

ORGANAMET BIO

HEART TRANSPLANT INEQUITIES

Black patients and women have disproportionately lower rates of receipt of a heart transplant than White patients and men.

Approximately 40% of heart transplant recipients are from minoritized racial and ethnic groups, and approximately 25% of heart transplant recipients are women. Aha Mar 25, 2024

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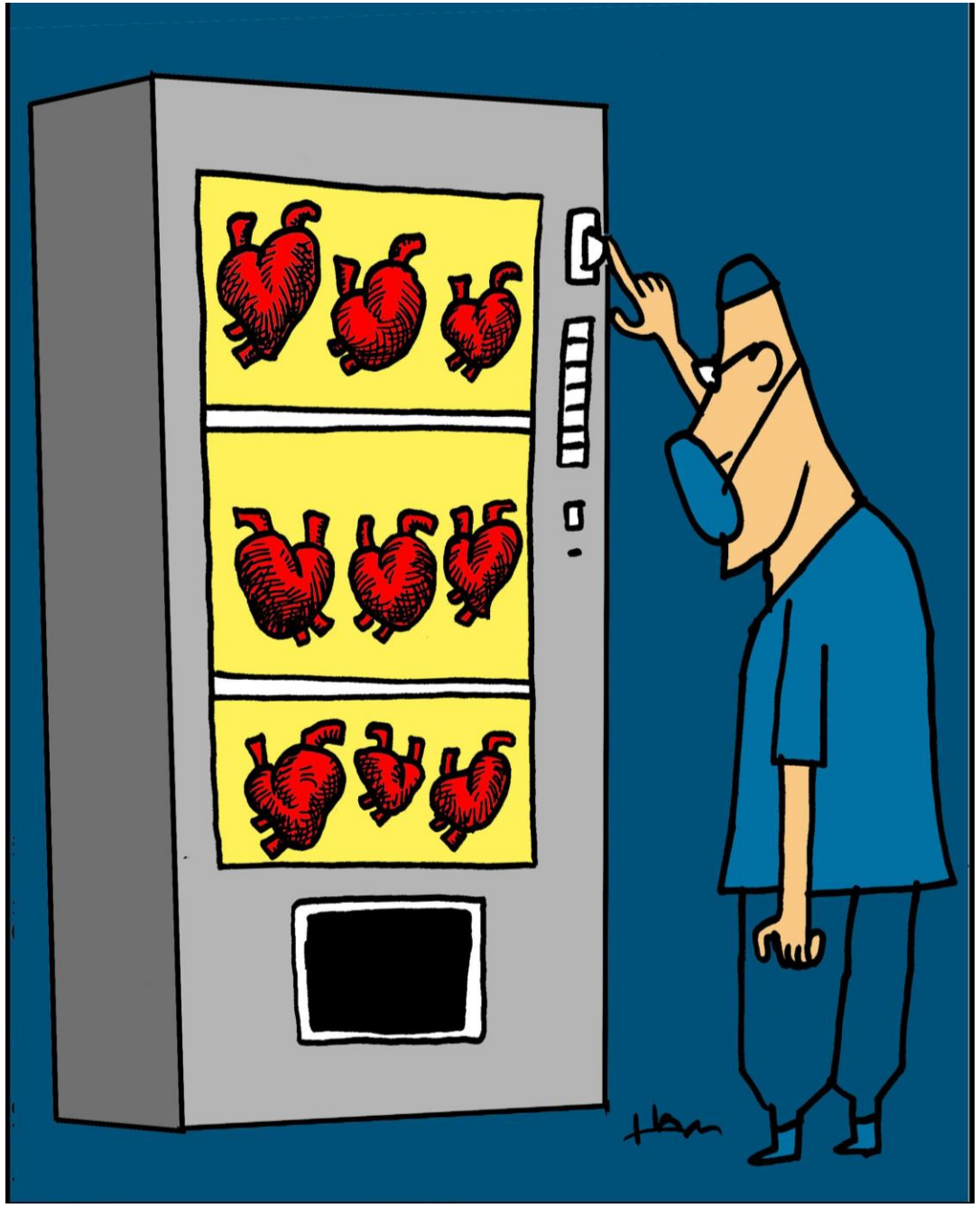
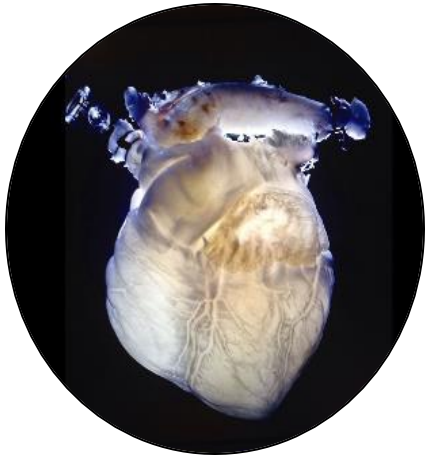


Imagine a Future where:

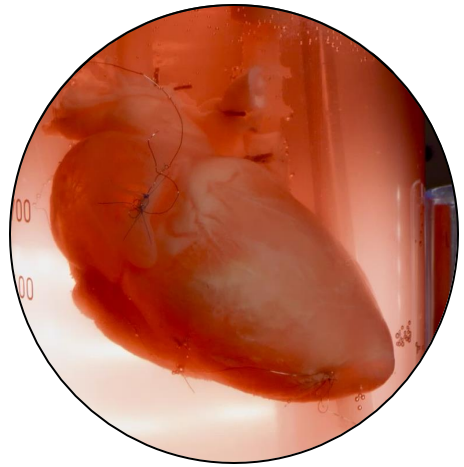
A personalized heart is available for transplant

- Patients provide a sample of their blood or bone marrow at the lab

Patient-derived Stem Cells



Universal Scaffold (Ghost Heart)



On Demand Personalized Replacement Heart

The Organamet Solution: Your-Heart™

Eliminate the Need for a Donor Heart

Organamet Bio's Your-Heart™ solution will will eliminate the need for a donor heart, which is a critical limitation of current heart heart transplant procedures.

Reduce/Eliminate Immunosuppression

Organamet Bio will reduce or eliminate eliminate the need for lifelong immunosuppressive medications required required with traditional heart transplants.

Make Heart Transplant a Planned Procedure

Organamet Bio will transform heart transplant from an emergency surgery to a planned, scheduled procedure.

Increase Availability and Access to Hearts

The Your-Heart™ solution will increase the the availability of and access to hearts for for those in need, addressing the severe severe shortage of donor hearts.

Reduce Total Transplant Costs

The Your-Heart™ solution will reduce the reduce the total costs associated with with heart transplant procedures.

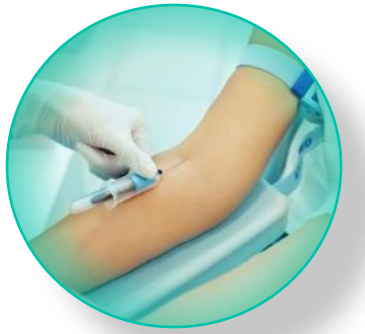
Increase Equitable Distribution of Hearts

The Your-Heart™ solution will help increase the equitable distribution of available hearts to those in need.

ORGANAMET BIO

It's Not a Cartoon Any More

Your-Heart™ Technology is real



Patient-derived banked stem Cells

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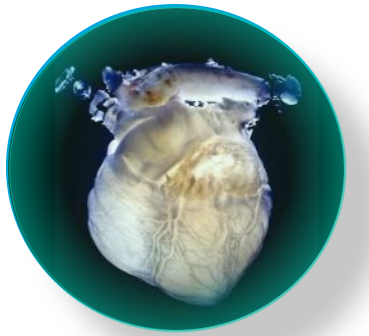

Universal off-the-shelf acellular porcine scaffold

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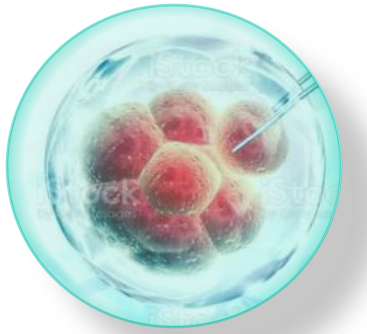

Proprietary process for depositing necessary heart cell types into scaffold

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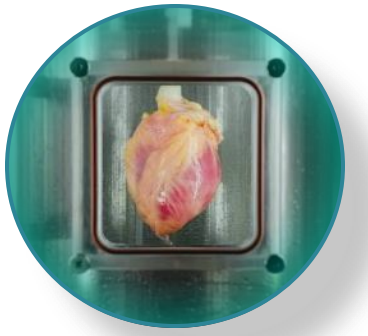

Unique proprietary maturation process

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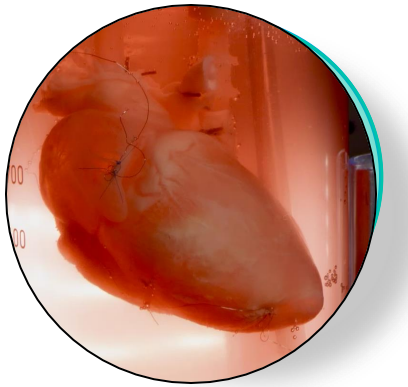

Your-Heart™ personalized for implantation

5 Years to F-I-H

Recruit Retain and Support Women

Thank you

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713-882-9945