Women, Research, and Cardiovascular Disease

“There is nothing as powerful as an idea whose time has come.”
Victor Hugo, 1877

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<tr>
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“There is nothing as powerful as an idea whose time has come.”

Victor Hugo
Histoire d’un Crime
1877
WE HAVE STUDIES OF FRUIT FLIES, MICE, HAMSTERS, FROGS, MONKEYS AND MEN WITH THIS CONDITION–BUT MEDICAL RESEARCH USING WOMEN AS SUBJECTS JUST NEVER OCCURRED TO ANYBODY.
Women, Research, and Cardiovascular Disease

Cardiovascular Disease Mortality Trends US Men and Women

United States: 1979-98

Deaths in Thousands

Years

1979 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98

Source: CDC/NCHS and the American Heart Association.

Women, Research, and Cardiovascular Disease

SAFEGUARDS
TO REDUCE
RISK OF
HEART ATTACKS

DECREASE SATURATED FATS
REDUCE IF OVERWEIGHT

EXERCISE REGULARLY
STOP SMOKING CIGARETTES

SHUN NEEDLESS TENSIONS
CONTROL HIGH BLOOD PRESSURE

CORONARY
HEART
DISEASE

QUESTIONS AND ANSWERS

From
Hearts and Husbands
FIRST WOMEN'S CONFERENCE ON
CORONARY HEART DISEASE
Memorial Coliseum, Portland, Oregon
November 6, 1964
By
OREGON HEART ASSOCIATION

OREGON HEART ASSOCIATION
1133 S. W. Morrison, Portland, Ore., Phone 226-2375
THE WAY TO A MAN’S HEART

A fat-controlled, low cholesterol meal plan to reduce the risk of heart attack

American Heart Association
Woman's Vulnerability

Dr. Nanette Wenger, left, and Dr. Harriet Dustan discuss women's vulnerability to heart attacks and the effects of birth control pills, diet, obesity, alcohol, smoking and health education on the likelihood of heart attacks in women in a two part series on women's heart disease, on "Woman" at 11 p.m. Thursday on TV-10.
Steps on the Journey (1)

- 1992 NHLBI Conference: Cardiovascular Health and Disease in Women
  - Based on 1986 NHLBI Workshop Coronary Heart Disease in Women
  - Highlighted new information appropriate for clinical application
  - Identified knowledge gaps that impede optimal CV care for women

Wenger, NEJM 329:247, 1993
Steps on the Journey (2)

- 2001 IOM Report
  - Exploring the Biological Contributions to Human Health. Does Sex Matter?
  - Need for evaluation of sex-based differences in human disease and in medical research
  - Translation of these differences into clinical practice

Wizemann, National Academy Press, 2001
Steps on the Journey (3)

- Randomized controlled trials of menopausal hormone therapy
  - Heart and Estrogen/progestin Replacement Study (HERS)
  - Women’s Health Initiative (WHI)
  - Menopausal hormone therapy did not prevent incident or recurrent CVD
  - Menopausal hormone therapy not indicated for primary or secondary prevention of CVD
  - Refocused attention on established CV preventive therapies for women

Hulley, JAMA 280:605, 1998
Steps on the Journey (4)

  - Systematic review of relevant research
  - Most contemporary recommendations for prevention, diagnostic testing, medical and surgical treatments of CHD in women extrapolated from studies conducted predominantly in middle-aged men
  - Fundamental knowledge gaps regarding biology, clinical manifestations, optimal management strategies for women

AHRQ, No. 03-#045, DHHS, Washington, 2003
AHRQ, No. 03-E036, DHHS, Washington, 2003
Women, Research, and Cardiovascular Disease

2004 – NHLBI Heart Truth Campaign

Heart Disease doesn’t Care What You Wear

It’s the #1 Killer of Women

Being a woman doesn’t protect you from heart disease. Try these risk factors on for size: Do you have high blood pressure? High blood cholesterol? Diabetes? Are you inactive? Are you a smoker? Overweight? If so, this could damage your heart and lead to disability, heart attack, or both.

Talk to your doctor to get answers that may save your life. The truth is, it’s best to know your risks and to take action now.

www.nhlbi.nih.gov/health/hearttruth

U.S. Department of Health and Human Services
National Heart, Lung, and Blood Institute; National Institutes of Health • Office on Women’s Health
American Heart Association • WomenHeart: the National Coalition for Women with Heart Disease
2004 – AHA Go Red for Women
Steps on the Journey (5)

- Women’s Health Study (WHS)
  - Aspirin prevents stroke, but not incident MI in women < age 65
  - Converse results in men (Physicians’ Health Study), where aspirin provided MI but not stroke protection

Ridker, NEJM 352:1293, 2005
Steering Committee PHS, NEJM 321:129, 1989
Steps on the Journey (6)

- CRUSADE Quality Improvement Registry: Women with NSTE-ACS
  - ACS prognosis worse in women: ↑ hospital death, MI, HF, stroke, transfusion
  - Women less likely to receive coronary interventions, guideline-based medical therapies despite their high-risk status
  - ? Worse prognosis related to raised baseline risk, suboptimal admission and discharge therapies
  - ? Biology, bias, or both

Blomkalns, JACC 45:832, 2005
Steps on the Journey (7)

- NHLBI Women’s Ischemia Syndrome Evaluation (WISE) Study
  - Myocardial ischemia associated with adverse clinical outcomes in absence of obstructive coronary disease
  - Importance of microvascular disease in women

Bairey-Merz CN, JACC 47:521, 2006
Women’s Antioxidant Cardiovascular Study (WACS), Women’s Antioxidant and Folic Acid Cardiovascular Study (WAFACS)

- Vitamins E, C, and beta carotene do not prevent incident or recurrent CVD in women
- Folic acid and vitamin B supplements do not prevent incident or recurrent CVD in women
- Ineffective therapies removed from recommended preventive regimens

Cook, Arch Intern Med 167:1610, 2007
Albert, JAMA 229:2027, 2008
Steps on the Journey (9)

- Get with the Guidelines CAD Database
  - Women ↑ STEMI mortality, 10.2% vs 5.5%
  - Predominantly initial 24 hr
    - ↓ early aspirin, ↓ beta blockers
    - ↓ reperfusion therapy
    - ↓ timely reperfusion
  - Opportunities to ↓ gender disparities in care, ↑ clinical outcomes

Steps on the Journey (10)

- 2010 IOM Report on Women’s Health Research: Progress, Pitfalls, and Promise (1)
  - Medical research historically neglected health needs of women
    - “Bikini medicine”
  - Women’s health
    - Sex differences – biological factors
    - Gender differences – affected by broader social, environmental, community factors
  - Major progress in reducing CV mortality
    - Need greater research attention to quality of life issues – functionality, mobility, wellness

Institute of Medicine, The National Academies Press, Washington, DC, September 2010, www.nap.edu
Steps on the Journey (11)

- 2010 IOM Report on Women’s Health Research: Progress, Pitfalls, and Promise (2)

  - Disparities in disease burden among subgroups of women
    - Socially disadvantaged because of race, ethnicity, income level, educational attainment
    - Targeted research on women with highest risks, burdens of disease

  - Lack of analysis, lack of reporting of sex-stratified analyses limit ability to identify potentially important sex/gender differences
    - Including differences in care
    - Journal editors should require clinical trial outcome presentations separately for women and men

  - Translation of women’s health research findings into clinical practice and public health policies

  - Effective communication of research-based health messages to women, the public, providers, policy makers
Steps on the Journey (12)

- AHA Women’s CVD Prevention Guidelines – 2011 Update
  - Pregnancy complications: preeclampsia, gestational diabetes, pregnancy-induced hypertension: early indicators of ↑ CV risk
  - Detailed history pregnancy complications – routine component of RF assessment for women
  - ↑ risk CVD with systemic autoimmune collagen vascular disease → screening for RF

Mosca, Circulation 123:1243, 2011
Women, Research, and Cardiovascular Disease

*Steps on the Journey (13)*

- The 10Q Report: A Research Roadmap to Improve Women’s CV Health (1)
  - What factors influence or explain disparities in cardiovascular epidemiology and disease outcomes between men and women?
  - What are the best strategies to assess, modify, and prevent a woman’s risk of heart disease?
  - What are the most accurate and effective approaches to assess and recognize chest pain and other symptoms suggesting coronary heart disease in women?
  - What role does a woman’s reproductive history and menopausal hormone therapy play in the development of heart disease?
  - What are the risk factors for cardiovascular disorders associated with pregnancy and how are they best treated?


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**Steps on the Journey (14)**

- The 10Q Report: A Research Roadmap to Improve Women’s CV Health (2)
  - What is the best method for studying sex differences in vascular injury so that cardiovascular repair therapies may be improved?
  - What are the most effective treatments for diastolic heart failure (heart failure with preserved pumping function of the heart) in women?
  - Why are young women more likely than men to die after a heart attack or after surgical revascularization procedure?
  - How do psychosocial factors affect cardiovascular disease in women?
  - What biological variables are most influential in the development and clinical outcomes of heart disease and what can be done to reduce mortality rates in women?

Wenger, Clin Cardiol 35:134, 2012
Steps on the Journey (15)

- Noninvasive Testing in Women: Suspected SIHD
  - Most low-risk symptomatic women not candidates for diagnostic testing
  - Exercise ECG initial strategy for low-intermediate IHD risk women
  - Symptomatic women with functional disability, abnormal rest ECG or indeterminate ETT → echocardiography, MPI or CMR reasonable
    - Prefer echocardiography or CMR for premenopausal women re radiation exposure
  - CCTA reasonable for women at intermediate IHD risk
    - Unique provision of information on obstructive, nonobstructive CAD burden
  - Risk stratification based on extent, severity inducible abnormalities

Mieres, Circulation 130:350, 2014
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Contemporary Help for Sisyphus
Women in Clinical Trials

- Women underrepresented in mixed-gender NIH trials (27%) 1997-2006
  - Disadvantaged by absence of gender-specific analyses

- ↑ Women in CHD clinical trials over time
  - Only 20% ACS study population 1966-1990

- Cochrane Reviews of 258 cardiovascular clinical trials
  - Only 1/3 examined outcomes by sex
  - Among trials with sex-based analyses, 20% reported significant differences in outcomes between women and men

- Exclusion elderly patients from clinical trials doubly disadvantages women – predominance of coronary events in women at older age

Harris, NEJM 343:475, 2000
Lee, JAMA 286:708, 2001
Heiat, Arch Intern Med 162:1682, 2002
Decreasing Barriers to Participation of Women in Clinical Trials

- Recommendations for maximal inclusion of women (extend to other subgroups)
  - Require trials to enroll subgroups proportional to prevalence/affected populations as a condition of drug, device approval
  - Implement strategy to increase public knowledge about available clinical trials, increase awareness of clinical research
  - Communicate trial opportunities, information via patient-friendly adaptation of clinical trials.gov
  - Publicize favorable experiences of participants in clinical trials
  - Communicate to public, healthcare professionals, consumers/patients, researchers through FDA website, advocacy groups, professional associations
U.S. Food and Drug Administration Safety and Innovation Act (FDASIA)

- 29 Steps to ↑ participation of women, minorities, elderly in all phases of clinical research trials
  - Consistent with disease prevalence in population
- IF implemented
  - ↑ representation of underserved populations in clinical trials
  - ↑ analyses on how medical drugs and devices affect women and men differently
- PL 112-144 (2012)


NHLBI Initiatives

• 2015 Announcement by NIH Director Dr. Francis Collins: development of policies that require research grant applicants
  • To report plan for balance of male and female cells and animals in pre-clinical studies
  • Development and delivery of training modules to include evaluation of sex differences
  • Funding to add subjects, animals, tissues and cells of sex opposite to that in original grant or to ↑ power of a study to analyze for sex and gender differences

• 2015 “Scientific Roundtable on Optimizing Cardiovascular Health of Women”
  • Nearly 2 dozen experts in basic, translational and clinical CV research
  • Assess current state of research on CV health of women: basic → clinical → implementation
  • Provide input toward shared vision of research to advance CV health of women
  • Provide input on shaping scientific priorities for research on CV health of women for NHLBI Strategic Visioning Process

• Established multidisciplinary working group focused on Women’s CV Health
2015 AHA Strategically Focused Research Network: WOMEN

- Women’s Cardiovascular Health Center application
  - One proposal: basic science discovery
  - One proposal: clinical science discovery
  - One proposal: population science discovery

- $12-15 M Network funding

- Network is 3-4 institutions or centers, working on 3 projects each
H.R. 2101: Research for All Act of 2015

• Introduced April 2015

• Mandate updating reports on women and minority inclusion in medical research at NIH and FDA by Government Accountability Office

• National Institutes of Health
  • Insure that both male and female cells, tissues, or animals be included in basic research; results disaggregated according to sex and sex differences examined.
  • Update guidelines on inclusion of women and minorities in research

• Direct FDA to guarantee that clinical drug trials for expedited drug products sufficient to determine safety and effectiveness for both women and men
Expanding the Landscape of Women’s Cardiovascular Health Research

- Contributions to vision of women’s cardiovascular health research in the next decade
  - Beliefs and behaviors
  - Community (local, national, global)
  - Economic
  - Environmental
  - Ethical
  - Legislative/political
  - Public policy
  - Societal/sociocultural
Gender Differences in Coronary Heart Disease