CONSIDERATIONS OF SEX DIFFERENCES IN FDA DEVICES

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Views presented are those of the speaker and do not reflect official FDA, DHHS or other government opinion or policy.

I have no real or apparent conflicts to disclose.

Any mention or representation of a particular device is for educational purposes only and does not convey endorsement of that device.

I am however, a federal employee...
Overview

- CDRH 101
- CDRH Health of Women Program
- Observed Sex Differences in Devices
- CDRH Research Spotlights
As a science-based regulatory entity, it is the principle mission of CDRH to assure that patients in the U.S. have timely access to:

- safe, effective, and high quality medical devices
- accurate medical diagnostics
- safe radiation emitting products

Mission
Medical Device Technology

1,700 types of medical devices within 16 medical device specialties
Medical Device Development
The Total Product Life Cycle

- Concept
- Prototype
- Preclinical
- Clinical
- Manufacturing
- Marketing
- Commercial Use
- Obsolescence

- Invention + Prototyping
- Pre-Clinical
- Clinical
- Regulatory Decision
- Product Launch
- Post-Market Monitoring

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The CDRH Health of Women Program is charged to:

Because of the steadily growing importance of sex- and gender-specific issues arising in regards to medical technology, design and development,

- improve analysis and communication of sex/gender-specific data for the safe and effective use of medical devices

CDRH formalized the creation of the Health of Women Program

- develop and implement major health science and medical programs, strategies and initiatives across CDRH
Every Cell is Sexed | Every Person is Gendered

What implication does this have for the performance of every medical device and diagnostic in the health care for both women and for men?
Cardiovascular Disease in women

Single segmental stenoses
Suitable for angioplasty

Diffuse disease or multiple stenoses
Not appropriate for angioplasty

Gould KL, 1999
Cardiovascular Disease in women

Women with coronary disease do not get the 90% lesions but get 30-40%.

Plaques erode

In lieu of cracking

Dysynchrony is different
Cardiovascular Deaths

in women versus men

More than one in three women has some form of cardiovascular disease

For nearly 400,000 women per year, CVD is their cause of death
Cardiovascular Disease

in women

2004 data, American Heart Association. Heart Disease and Stroke Statistics – 2007 Update
Guidance

Sex-specific patient enrollment, data analysis, and reporting of study information

- Consideration of sex during the study design
- Sex-specific statistical analyses of study data
- Reporting sex-specific information
Consider Sex and Gender

*Balanced by Least Burdensome Approach*

Always include a **sex/gender analysis** of the important safety and effectiveness endpoints:

- Target lesion failure composite
- Cardiac death
- Myocardial infarction
- Need for repeat target lesion intervention
- Stent thrombosis
- Bleeding

Acknowledge that sub-group analyses are **underpowered** for statistical significance.

Use analyses stratified by gender to look for **signals**, and if there are concerns, post-approval studies provide additional data.

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- Ventricular Assist Devices (VADs)
- Cardiac Resynchronization Therapy Defibrillators (CRT-D)
- Drug-Eluting Coronary Stents
- Endovascular Grafts
Left Ventricular Assist Devices in Women

Ventricular Assist Devices (VADs)

- More frequently in cardiogenic shock
- Require longer ventilator and inotropic support
- Higher risk for RV failure
- Higher stroke incidence
  - TIA/CVA = 4.67 HR
  - CVA = 1.4 – 3.1 HR
Left Ventricular Assist Devices

Whole bleeding and thrombosis cascade in women versus men

Serious Adverse Events

PUMP THROMBOSIS ($p=0.97$)
- Women: 0.08
- Men: 0.08

RV FAILURE ($p<0.001$)
- Women: 0.11
- Men: 0.03

ARRHYTHMIAS ($p=0.022$)
- Women: 0.08
- Men: 0.03

MAJOR BLEEDING ($p=0.001$)
- Notably nasal, gastrointestinal
  - Women: 0.3
  - Men: 0.14

Survival probability

Time after surgery, months

% Patients

Death
Stroke
Neuro
Sepsis
Bleed
Renal
RHF
Arryth
Hepatic
Resp

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Cardiac Resynchronization Therapy
In Women

Heart Failure
- Older
- HTN and DM
- Less atrial fibrillation/flutter
- Less ischemic HF etiology
- More non-ischemic cardiomyopathy
- Smaller and less dense scar
- More diastolic dysfunction/HF
- Preserved ejection fraction
- Shorter QRS, smaller ventricles
- More LBBB
Cardiac Resynchronization Therapy (CRT)

- **Significant improvement** in:
  - cardiac left ventricular function
  - survival
  - exercise capacity
  - quality of life
- **Underenrollment** in studies
  - ≤ 35%
Cardiac Resynchronization Therapy

Even at shorter QRS

Cardiac Resynchronization Therapy

Figure 2. Kaplan-Meier Estimates of Outcomes in LBBB and QRS of 130 to 149 Milliseconds Stratified by Sex

- Women benefited with LBBB and QRS 130-149 ms
- Men only benefited with LBBB and QRS ≥ 150 ms
- Important to communicate since women are less likely to receive CRT than men but clearly derive more benefit

Transmural Repolarization

Pre-pubertal females exhibit reversed transmural repolarization gradients and increased dispersion of repolarization in porcine heart failure model

HF condition increased APD80 in males and females to a similar extent (Fig A).

- **However, the APD80 in the different layers of the transmural surface (Fig B),**
- **standard deviation of APD80 of the entire transmural surface (Fig C)**
- **difference in APD80 between EPI and ENDO layers (Fig D),**

were all **significantly increased in FHF compared to other groups (MHF, FC, MC)**

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Drug-Eluting Coronary Stents

Antithrombotic therapy and revascularization improve outcomes in patients with unstable angina and MI

Women undergoing PCI are at increased risk for drug-related bleeding and vascular complications

- **Bleeding is the most common complication**
- **Associated with morbidity and mortality**
- **Female sex predicts bleeding and death after PCI**

Duvernoy CS. American Heart Journal. 2010;159:677–683 e671
Drug-Eluting Coronary Stents in Women

- Higher risk for bleeding
- Higher risk for vascular complications

Favors Radial Approach
- Smaller radial arteries
- More prone to spasm
  - Procedure failure
  - Conversion to femoral access
- Higher rates of radial artery occlusion
- Higher rates of hematoma

Favors Femoral Approach


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Ventricular Assist Devices (VADs)

Cardiac Resynchronization Therapy Defibrillators (CRT-D)

Drug-Eluting Coronary Stents

Endovascular Grafts
Endovascular Grafts
Abdominal Aortic Aneurysms in Women

Anatomy

- Four-fold higher risk of rupture
- Rupture risk factor:
  - Men: aneurysm diameter
  - Women: aneurysm diameter/BSA

Repair

- Endovascular aneurysm repair (EVAR) reduces peri-procedural mortality
- Women had higher perioperative
  - morbidity (17.8% vs 10.6%)
  - mortality (3.4% vs 2.1%)

Endovascular Grafts

Typical Anatomical Requirements

- Neck Length, \( \leq 15 \text{ mm} \)\(^*\)
- Neck Diameter, 18 - 32 mm
- Angulation, \( \leq 60^\circ \)
- Landing zone, 10 - 23\(^\wedge\)
- Access, 5.5 - 7 mm

\(^*\) one was \( \leq 10 \text{ mm} \)
\(^\wedge\) one was as small as 8 mm

Morrison et al, FDA ODE Division of Cardiovascular Devices
Endovascular Grafts

Based solely on anatomy, nearly 35% of Men and 60% of Women are ineligible for EVAR in the treatment range.

Morrison et al, FDA ODE Division of Cardiovascular Devices
Endovascular Grafts
Reasons for Ineligibility in Women

infrarenal and suprarenal neck angulation

Cook Fenestrated

infrarenal neck angulation and length

Trivascular Ovation

Morrison et al, FDA ODE Division of Cardiovascular Devices

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Proposed sex-specific criteria for LBBB
Remodeling of myocardial scar tissue
Size of coronary sinus
Capture thresholds
Normal electrophysiology
Vascular inflammation
Endothelial cell biology
  • Vasodilator and vasoconstrictor expression
  • Oxygen toxicity effects
  • Impairment in angiogenesis

Tissue repair capacity

Not just a matter of anatomy, but a matter of cell physiology

Somatic / sensory motor development
Inflammatory response
Immunology
Diagnostics
  • Sensitivity and specificity
  • Cut-off values and normal ranges

If we do not ask the question, we will not know the answer

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Every Cell is Sexed
Every Person is Gendered
Challenges Ahead

*WOMEN ARE ONE THIRD*

1. **Consider Multiple Clinical Factors**
2. **Collect, Analyze, Report**
3. **Design Studies for Women**
4. **Know Baseline Characteristics**
5. **Improve Patient-Specific Selection**
THANK YOU

HEALTH OF WOMEN

CENTER FOR DEVICES & RADIOLOGICAL HEALTH

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