

# CONSIDERATIONS OF SEX DIFFERENCES IN FDA DEVICES

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# **Speaker Disclosure**



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** 

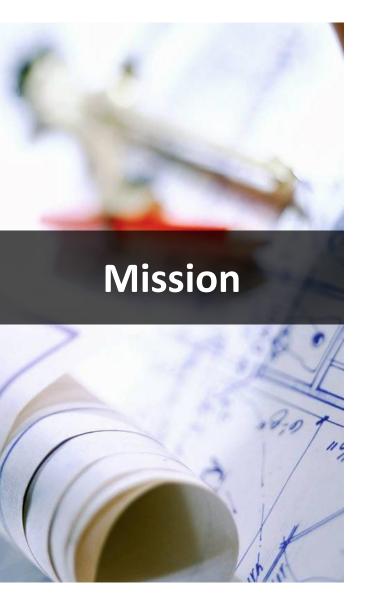


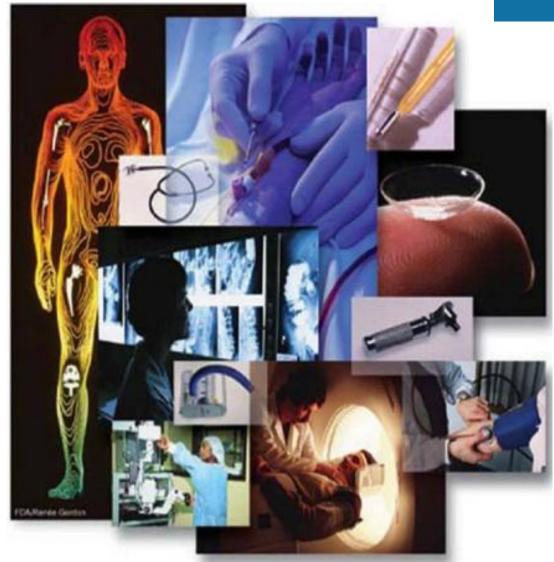
**Observed Sex Differences in Devices** 



**CDRH Research Spotlights** 









# **Medical Device Technology**

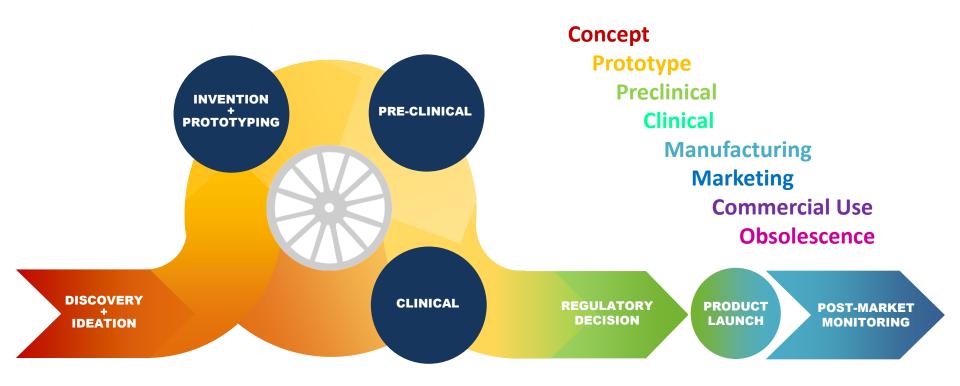
1,700 types of medical devices within 16 medical device specialties





# **Medical Device Development**

#### The Total Product Life Cycle



# CDRH Health of Women Program

Origin





# The CDRH Health of Women Program is charged to:

Because of the steadily growing importance

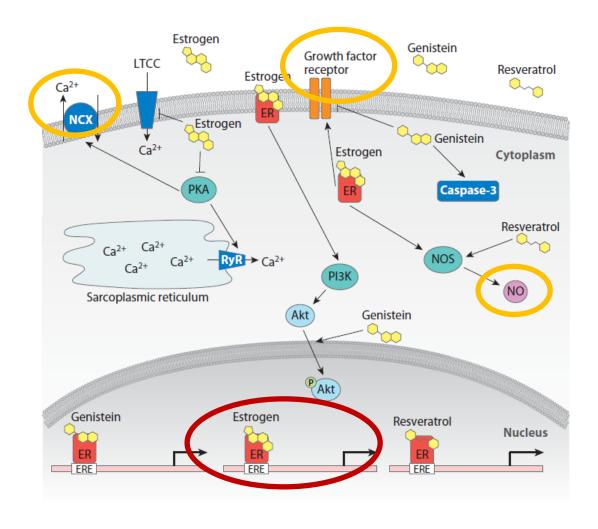
- of sexo and regarders specific issues anising in performation it debrology, women design and development,
- improve the this application of sex/pendentales specific data for the safe and effective use of medical devices
- CDRH formalized the creation of the develop and implement major health of Women Program 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?



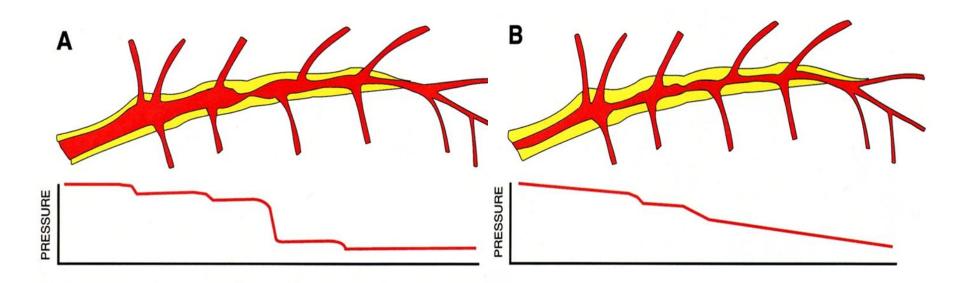
# **Estrogen Signaling in the Heart**





# **Cardiovascular Disease**

#### in women



Single segmental stenoses Suitable for angioplasty

Diffuse disease or multiple stenoses Not appropriate for angioplasty

Gould KL, 1999



# Cardiovascular Disease

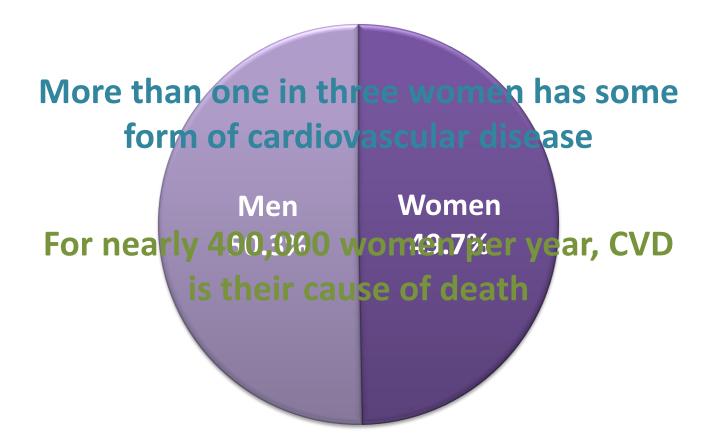
#### in women

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**

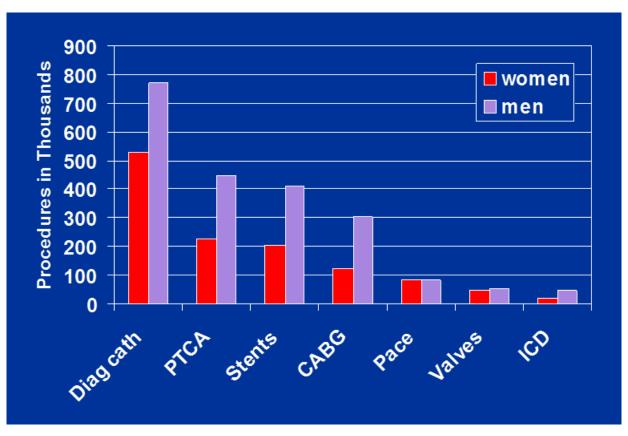
#### in women versus men





# Cardiovascular Disease

#### in women



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



# Guidance

#### Evaluation of Sex-Specific Data in Medical Device Clinical Studies

#### Guidance for Industry and Food and Drug Administration Staff

Document issued on August 22, 2014.

The draft of this document was issued on December 19, 2011

For questions regarding this document, contact CDRH at 301-796-5900 or Kathryn O'Callaghan (kathryn ocallaghan@tda hhs gov); for Office of Device Evaluation specific questions, Jismi Johnson (jismi johnson@tda hhs gov); for Statistics specific questions, Lilly Yue (lilly vue@fda hhs gov); for Office of In Vitro Diagnostics and Radiological Health specific questions, Robert Becker (robert becker@fda hhs gov); or for Epidemiology specific questions, Nilsa Loyo-Bernios (misa loyo-bernios@fda hhs gov).

For questions about this document regarding CBER regulated devices, contact the Office of Communication, Outreach and Development (OCOD) by calling 1-800-835-4709 or240-402-7800.





U.S. Department of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health Center for Biologics Evaluation and Research 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, postapproval studies provide additional data



### **FDA**

#### **Center for Devices and Radiologic Health**

Ventricular Assist Devices (VADs)

Cardiac
Resynchronization
Therapy Defibrillators
(CRT-D)

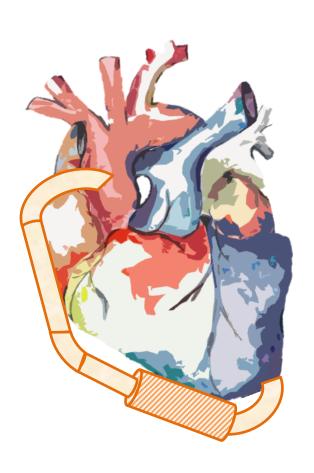
Drug-Eluting Coronary
Stents

**Endovascular Grafts** 



# **Left Ventricular Assist Devices**

#### in Women

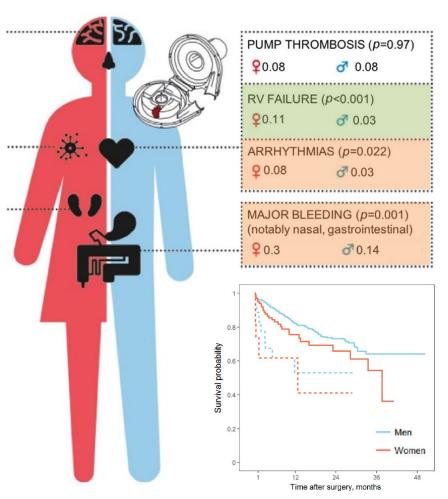


# Ventricular Assist Devices (VADS)

- More frequently in lagnosis, cardiogenic shock
- Require longer ventilator and inotropic support
- Higher risk for RV failure
- Higher stroke incidence
  - \_ TIA/CVA = 4.67 HR
  - A CVA = 1.4 3.1 HR

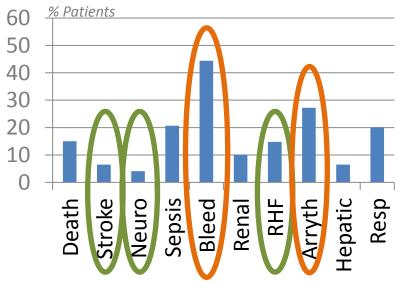
# FDA

# **Left Ventricular Assist Devices**



Whole bleeding and thrombosis cascade in women versus men

#### **Serious Adverse Events**





### **FDA**

#### **Center for Devices and Radiologic Health**

Ventricular Assist Devices (VADs) Cardiac Resynchronization Therapy Defibrillators (CRT-D)

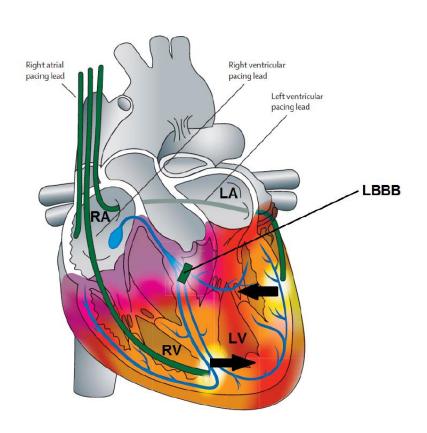
Drug-Eluting Coronary Stents

**Endovascular Grafts** 



# **Cardiac Resynchronization Therapy**

#### In Women



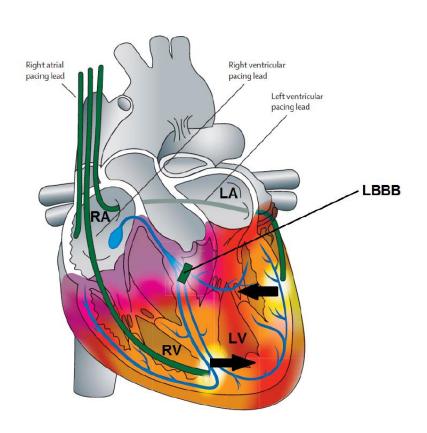
#### **Heart Failure**

- 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**

#### In Women



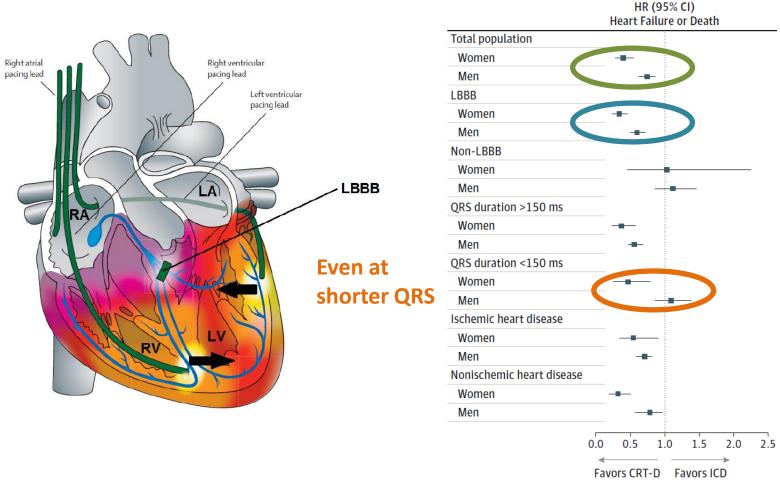
#### Cardiac Resynchronization Therapy (CRT)

- Significant improvement in:
  - cardiac left ventricular function
  - survival
  - exercise capacity
  - quality of life
- Underenrollment in studies

• ≤ 35%



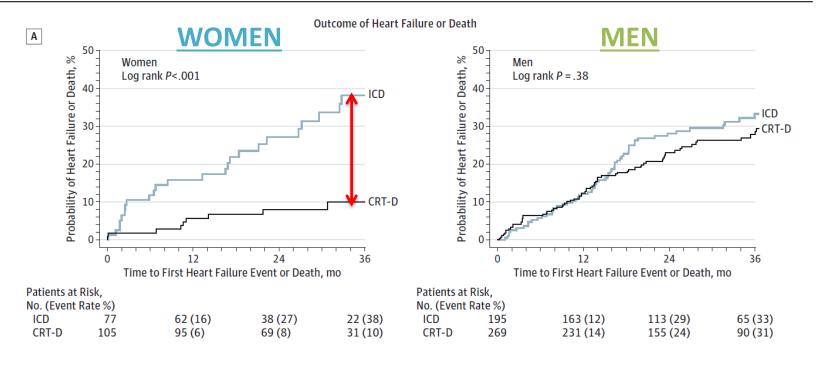
# **Cardiac Resynchronization Therapy**



#### FDA V

# **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 <u>less likely</u> to receive CRT than men but clearly derive more benefit



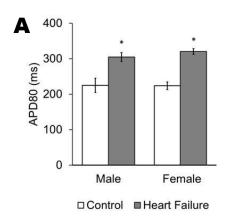
# **Transmural Repolarization**

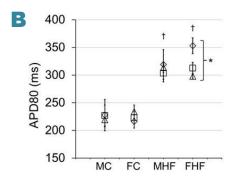
Pre-pubertal females exhibit reversed transmural repolarization gradients and increased dispersion of repolarization in porcine heart failure model

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

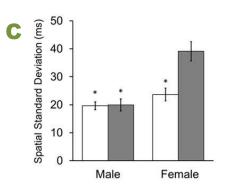
- However, the APD80 in the different layers of the transmural surface (Fig B),
- standard deviation of APD80
   of the entire transmural
   surface (Fig C)
- difference in APD80 between EPI and ENDO layers (Fig D),

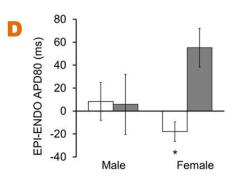
were all **significantly increased in FHF** compared to
other groups (MHF, FC, MC)





♦ Subepicardial ☐ Midmyocardial △ Subendocardial





□ Control ■ Heart Failure

[Stohlman J, Gray RA, Moreira T, Klein M, Shou M, Haigney M, submitted]



# **FDA**

#### **Center for Devices and Radiologic Health**

Ventricular Assist Devices (VADs) Cardiac Resynchronization Therapy Defibrillators (CRT-D)

Drug-Eluting Coronary
Stents

Endovascular Grafts



# **Drug-Eluting Coronary Stents**



Rai SV. JACC 2014;7:857-867 J.L. Anderson. J Am Coll Cardiol, 50 (2007), pp. 652-726 A.J. Lansky. Circulation, 111 (2005), pp. 940-953

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

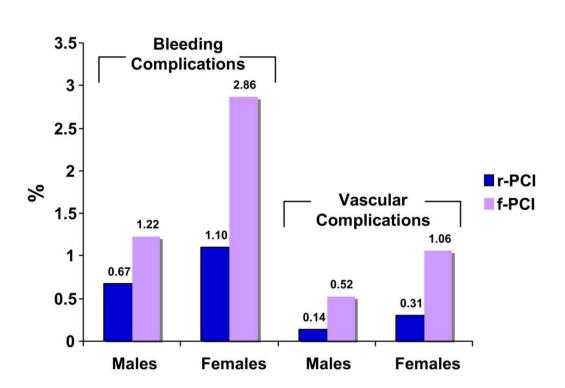
- Bleeding is the most common complication
- Associated with morbidity and mortality
- Female sex predicts bleeding and death after PCI

K.P. Alexander. Circulation, 114 (2006), pp. 1380-1387
F.W. Verheugt. J Am Coll Cardiol Intv, 4 (2011), pp. 191-197
Duvernoy CS. American Heart Journal. 2010;159:677-683 e671
R. Mehran. J Am Coll Cardiol, 55 (2010), pp. 2556-2566



# **Drug-Eluting Coronary Stents**

#### In Women



#### **Favors Radial Approach**

- Higher risk for bleeding
- Higher risk for vascular complications

#### **Favors Femoral Approach**

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

Rao SV, et al. JACC Cardiovasc Interv 2008;1:379-86.

Hess CN, et al. *A report from the Cardiac Safety Research Consortium*. Am Heart J 2013;165:344-53.



# **FDA**

#### **Center for Devices and Radiologic Health**

Ventricular Assist Devices (VADs) Cardiac Resynchronization Therapy Defibrillators (CRT-D)

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#### **Abdominal Aortic Aneurysms in Women**

#### **Anatomy**

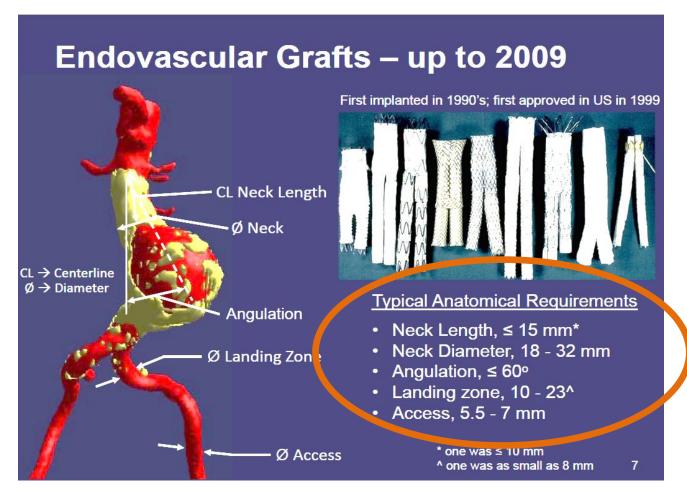
- Four-fold higher risk of rupture
- Rupture risk factor:
  - Men: aneurysm diameter
  - Women: aneurysm diameter/BSA

#### 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%)

Lo RC, et al. J Vasc Surg 2014;59:1209-16

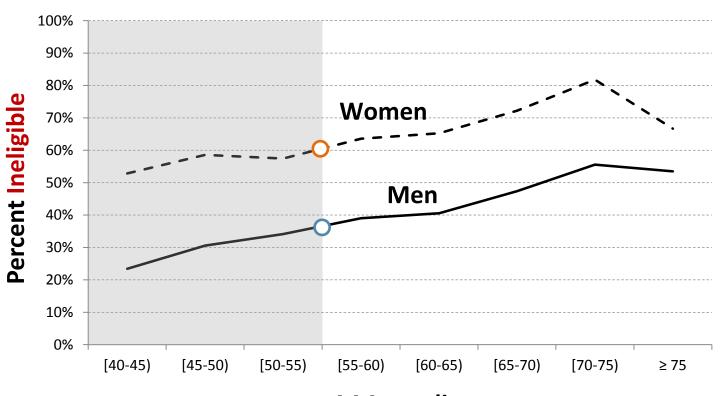




Morrison et al, FDA ODE Division of Cardiovascular Devices



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



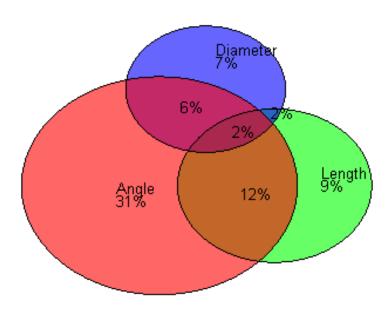
snAAA sac diameter



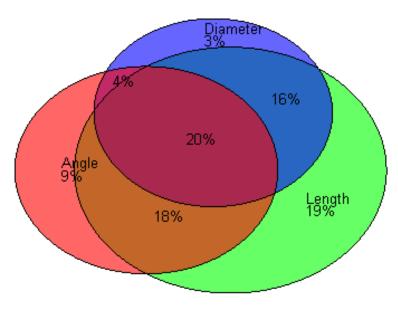
#### Reasons for Ineligibility in Women

# infrarenal and suprarenal neck angulation

# infrarenal neck angulation and length



**Cook Fenestrated** 



**Trivascular Ovation** 

#### **FDA**



#### **Center for Devices and Radiologic Health**

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



# **Every Cell is Sexed Every Person is Gendered**



# **Challenges Ahead**

WOMEN ARE ONE THIRD

