



Transgender Medicine

Faculty



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Purpose

Efforts must be made to improve care for transgender and gender diverse people who often lack access to trained providers to include:

- Focus on comfort with diagnosis of diverse gender identity and/or gender dysphoria.
- Knowledge of available evidence-based treatment guidelines.
- Emphasis on personalization of treatment options based on the gender identity of the individual.

Purpose

Lack of gender affirming hormone therapy or inappropriate dosing of hormone therapy may raise several issues for transgender people:

- Patients can experience increased or worsening gender dysphoria which is associated with depression and self-harm
- Inadequate sex hormone doses may result in osteoporosis and inadequate treatment of gender dysphoria
- Supraphysiologic dosing of sex hormones can result in thromboembolism, cardiovascular risks, or erythrocytosis

Outcome Objectives



Upon successful completion of the activity, participants should be able to:

- Use appropriate terms and definitions that best describe transgender and gender diverse people.
- Apply the basics of transgender medicine and hormone therapy to provide adequate care for transgender patients.
- Incorporate long-term medical and surgical monitoring and management in the treatment of transgender patients.

Introduction

- Transgender people express a gender identity that differs from the gender that was recorded at birth.
- Everyone has a gender identity which can be male, female, neither, or someone between male or female.
- Cisgender people express a gender identity that matches the gender recorded at birth.

Introduction

Transgender and gender diverse people represent a large diverse population of individuals. These people may seek a variety of ways to affirm their gender identity. These may include:

- Social transition (e.g. changing names and pronouns)
- Hormone therapy
- Surgery: genital and non-genital
- Voice therapy

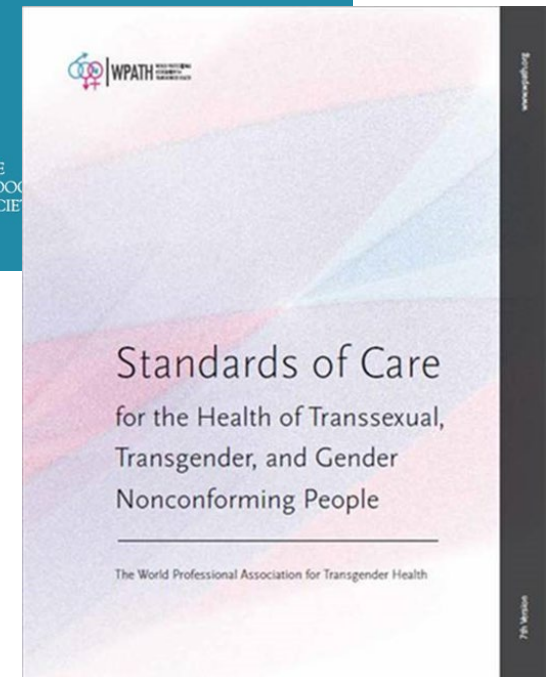
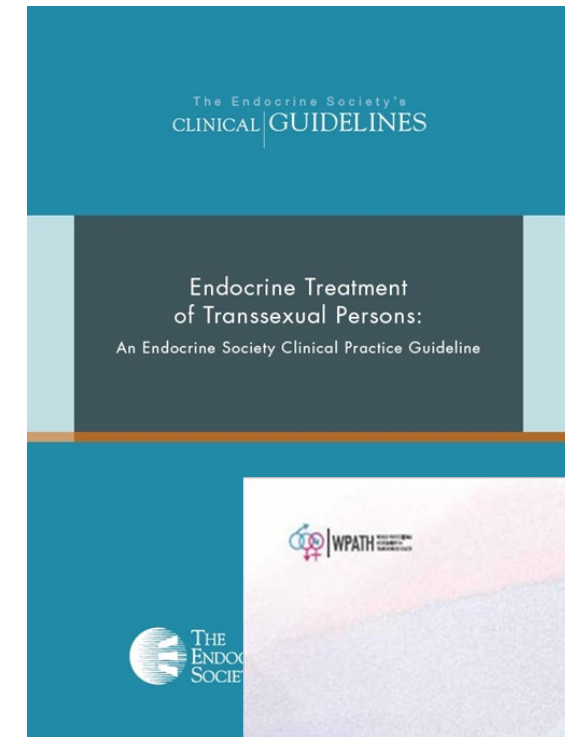


Introduction

Several guidelines exist to help aid the clinician in determining the best treatment for transgender/gender diverse individuals:

Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline co-sponsored by AACE

World Professional Association for Transgender Health, Standards of Care, Version 7 (version 8 forthcoming)



Introduction

Current recommendations state that adults and post-pubertal children older than age 16 can be started on gender affirming hormone therapy provided that the individual can provide informed consent* and there are no medical contraindications.

* The age of consent for medical therapies may vary by locale



Introduction



For transgender youth under the age of 16, a multidisciplinary team with experience in working with gender diverse youth should determine the timing of social and medical interventions.

For transgender youth entering early puberty, medical interventions could include puberty blocking hormone therapy with GnRH agonists and the addition of sex steroid hormones at the appropriate time as deemed by the multidisciplinary team.

It is not recommended that any medical interventions are initiated in youth who have not reached puberty.

Basic Terminology



Sex: Attributes that characterize biological “maleness” or “femaleness” usually based on internal and external genitalia and secondary sex characteristics.

Sex Recorded at Birth: The sex provided to an individual at birth usually based on anatomy – male/female

Gender Identity: One's *internal*, deeply held sense of one's gender.

Transgender: People who express that their gender identity does not match the sex they were assigned at birth (termed *gender dysphoria*). Most people have a gender identity of man or woman (or boy or girl-binary). Cisgender are people who have the gender identity that matches the one recorded at birth.

Gender Non-conforming or Non-Binary: Behaviors that are viewed as incompatible with the binary “male” or “female” gender.

Transgender Identity Diagnosis

Currently the diagnosis is made using the DSM V criteria; although, most experts in the field do not classify a transgender diagnosis as having a mental health disease.

Future versions of the DSM have plans to move the transgender/gender dysphoria definitions to another chapter focused on sexual health.

Gender Dysphoria in Adults DSM V

SYNOPSIS

- 1. A marked incongruence between one's expressed gender and assigned gender of at least 6 months duration – and -**
- 2. Strong Desire to:**

Rid of one's sex characteristics

Obtain the sex characteristics of another gender

Desire to be another gender

Desire to be treated as another gender

Transgender Epidemiology

- Previous estimates of transgender identity were based on medical (ICD) diagnosis codes which yield very low prevalences.
- Current estimates of a transgender identity based on self report or more in-depth examination of the electronic medical record yield a prevalence of a transgender identity in at least 1 out of 1000.
- More recent estimates demonstrate that 0.6% of the United States population have a transgender or gender diverse identity.



Transgender Identity and Risk of Suicide

Transgender people have increased risk of suicide which may be due to many factors including discrimination, access to healthcare, physical abuse and sexual trauma.

41% of transgender individuals surveyed reported a past suicide attempt compared to 1.6% of the U.S. population.

Transgender Veterans have twice the rate of suicide compared to other Veterans and eight times the rate of suicide compared to the general U.S. population.

Timing of Gender Affirming Hormone Therapy

According to the WPATH Standards of Care, individuals with a transgender identity can start on sex hormones when there are the following criteria:

1. Persistent, well-documented gender dysphoria
2. Capacity to make a fully informed decision and to consent for treatment
3. Age of consent in a given country (USA is 18 without parents)
4. If significant medical or mental health concerns are present, they must be reasonably well controlled

Transfeminine Hormone Therapy

| Early Pubertal Children | Adults |
|--|--|
| GnRH Agonists + | Spironolactone 100-400 mg (USA) Cyproterone 25- 50 mg (Europe) GnRH Agonists (UK) |
| Oral estradiol 0.5 - 4 mg Estradiol patch 0.00625-0.05 mg/day | Oral estradiol 2- 6 mg Estradiol patch 0.05 – 0.2 mg/day Estradiol valerate 10-20 mg IM q2week |

| Laboratory Monitoring |
|-------------------------------------|
| Estradiol and Testosterone |
| Potassium on spironolactone |
| Prolactin at baseline and 1-2 years |
| Lipids |

Transfeminine Hormone Therapy

| Early Pubertal Children | Adults |
|---|--|
| GnRH Agonists + | Testosterone |
| Testosterone esters 25-200 mg IM q2weeks | Testosterone esters 100-200 mg IM q2weeks |
| Testosterone gels and patches | |

Laboratory Monitoring

Estradiol and Testosterone

CBC

Lipids

Nonpharmacologic Therapy

- Fertility preservation should be offered to all transgender people prior to initiation of gender affirming hormone therapy with a referral to a reproductive specialist.
- Voice therapy should be offered to transgender people not satisfied with the quality of their voice and ability to live in the affirmed gender.
- Ongoing mental health support is helpful for individuals to disclose their gender identity to family, friends, employers.
- Legal help may be necessary to change legal documentation to the affirmed gender.

Nonpharmacologic Therapy

- Regular, weight-bearing, resistance exercise since gender affirming hormone therapy is associated with weight gain (esp. in transgender women).
- Address healthy diet given changes in lipids in response to gender affirming hormone therapy.
- Avoiding tobacco (especially in transgender women).
- Address social and work situation and risk factors for depression/suicide.



Testosterone Levels in Transmen

Table 3 Serum concentrations of total testosterone in trans men by route of administration and dose*

| Regimen characteristics | Level (ng/dL) Median (IQR) | Route-specific P-value** by dose |
|--|-------------------------------|-------------------------------------|
| <u>Injectable (n=274)</u> | 524.5 (333.8 – 756.0) | 0.018 |
| ≤50 mg/week (n=80) | 442.5 (257.5 – 644.3) | |
| 51-75 mg/week (n=50) | 483.0 (317.8 – 645.3) | |
| >75 mg/week (n=144) | 588.0 (380.3 – 840.3) | |
| <u>Transdermal (n=20)</u> | 326.0 (85.5 - 441.0) | 0.660 |
| ≤50 mg/week (n=13) | 303 (61.5 – 442.0) | |
| 51-75 mg/week (n= 0) | - | |
| >75 mg/week (n=7) | 349.0 (188.0 - 447.0) | |
| P-value for all routes, by dose | 0.006 ** | |
| P-value for all doses, by route | <0.001*** | |

* Based on individual visits

**Simple linear regression analysis

***Mann-Whitney U test



Testosterone Levels in Transwomen

Table 4 Serum concentrations of total estradiol in trans women by route of administration and dose*

| Regimen characteristics | Level (ng/dL) Median (IQR) | Route-specific P-value** by dose |
|--|-------------------------------|-------------------------------------|
| Oral (n=366) | 102.0 (61.8 - 155.0) | <0.001 |
| ≤14 mg/week (n=66) | 58.0 (47.6 - 104) | |
| 15-30 mg/week (n=167) | 90.7 (58.7 - 138.8) | |
| >30 mg/week (n=133) | 140.0 (91.6 - 215.5) | |
| Intramuscular (n=242) | 366.0 (159.5 - 629.0) | 0.481 |
| ≤5 mg/week (n=24) | 155.5 (62.28 - 605.0) | |
| 6-9 mg/week (n=29) | 371.0 (227.5 - 550.0) | |
| ≥10 mg/week (n=189) | 365.0 (165.3 - 633.0) | |
| Transdermal (n=39) | 70.8 (38.1 - 119.0) | 0.157 |
| ≤2 mg/week (n=24) | 71.5 (35.1 - 115.0) | |
| 2.1-5 mg/week (n=9) | 105.0 (50.9 - 159.5) | |
| >5 mg/week (n=6) | 50.3 (28.9 - 83.6) | |
| P-value for all doses, by route | <0.001*** | |

* Based on individual visits

** Simple linear regression analysis

***Kruskal-Wallis test

STRONG Study

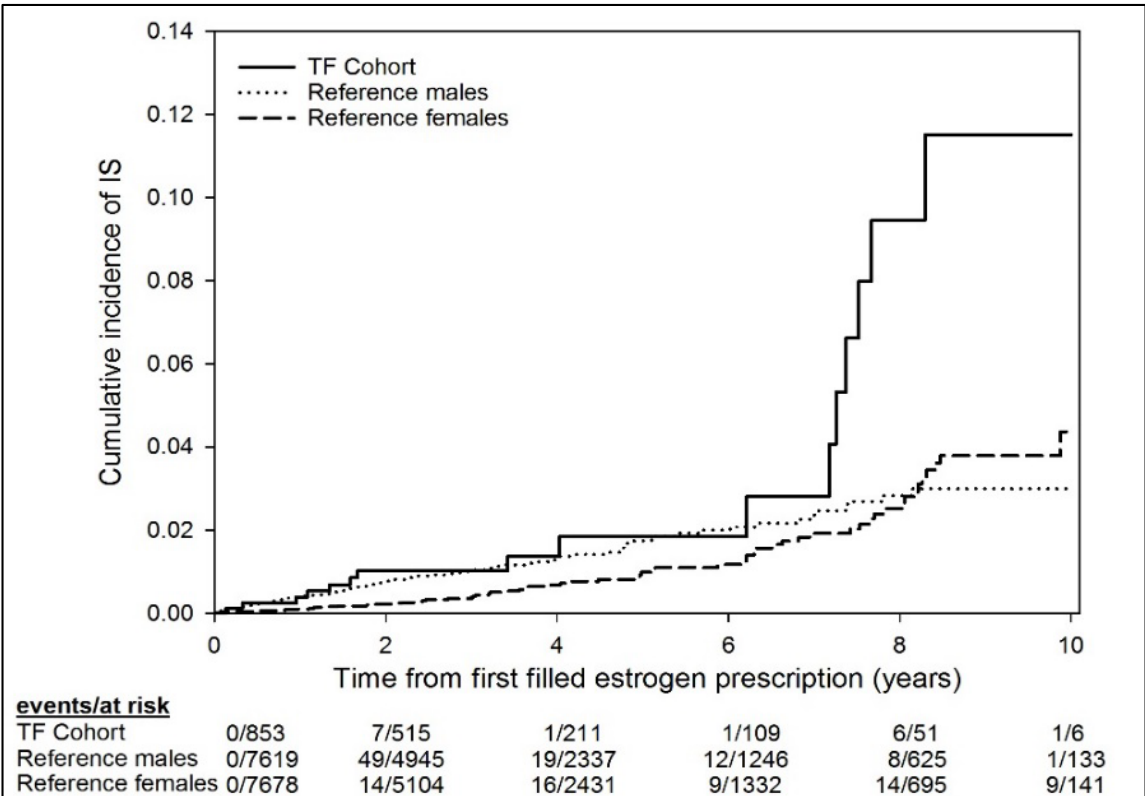
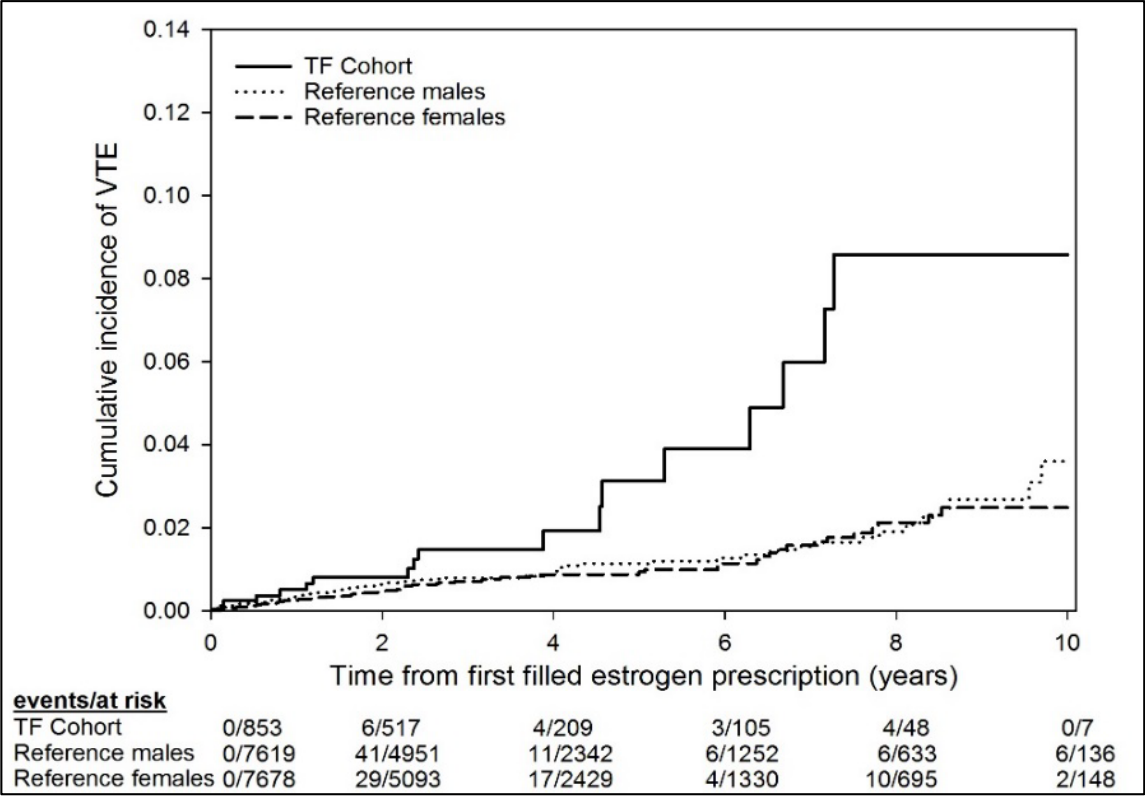


Study: Cohort study of transgender people receiving healthcare at three Kaiser Healthcare sites (Northern CA, Southern CA, Georgia)

- Primary endpoints: Thromboembolism, Ischemic Stroke or MI.
- Transgender individuals matched one transgender person for ten non-transgender male and ten non-transgender female.
- Cohort members followed up to ten years for risk of primary endpoints.

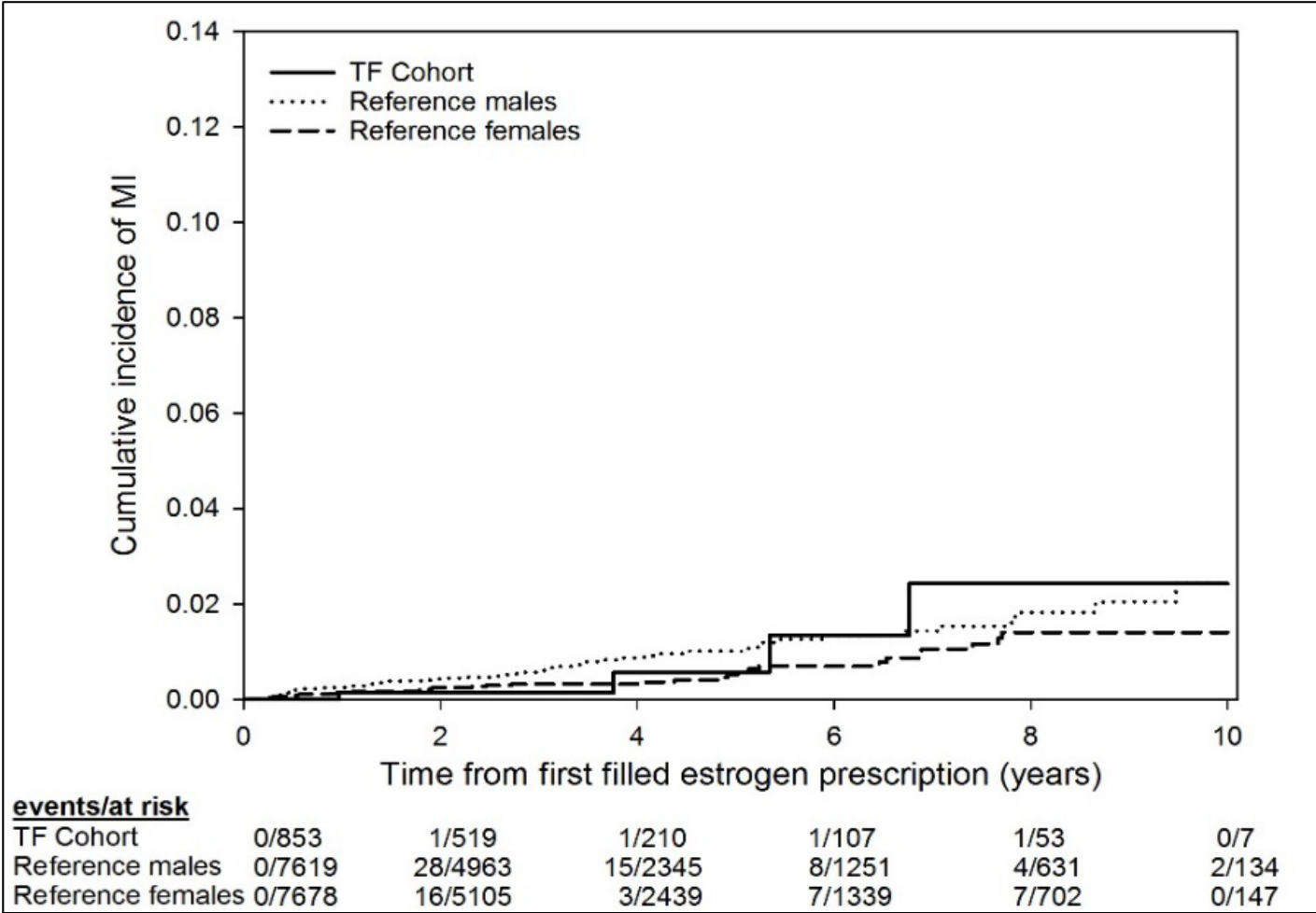


Risk of Venous Thrombembolism or Ischemic Stroke among Transfeminine Patients in the STRONG cohort





Risk of MI among Transfeminine Patients in the STRONG Cohort

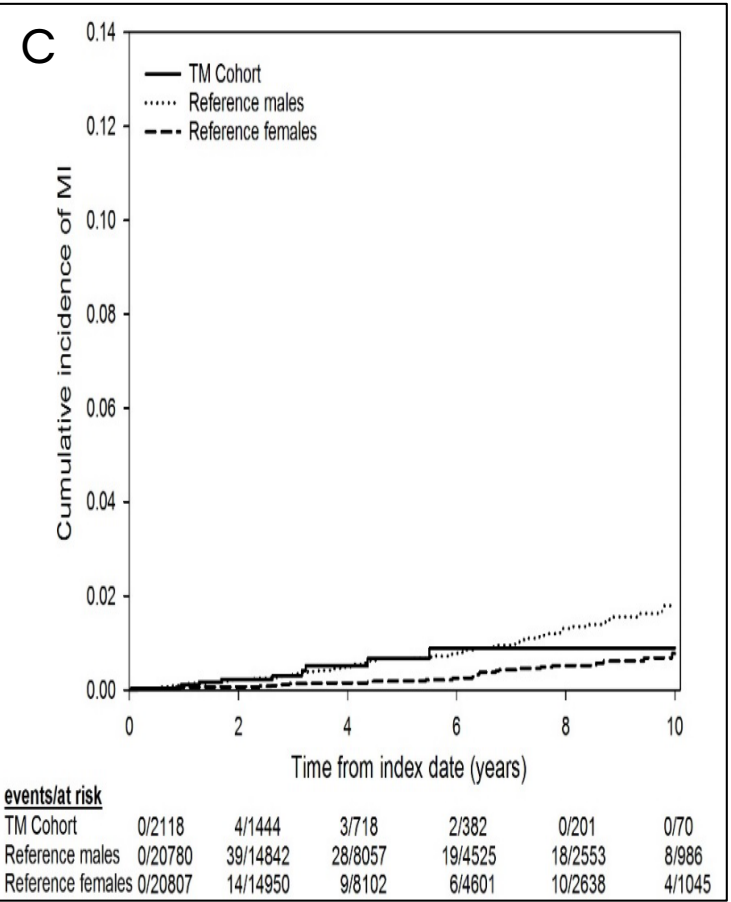
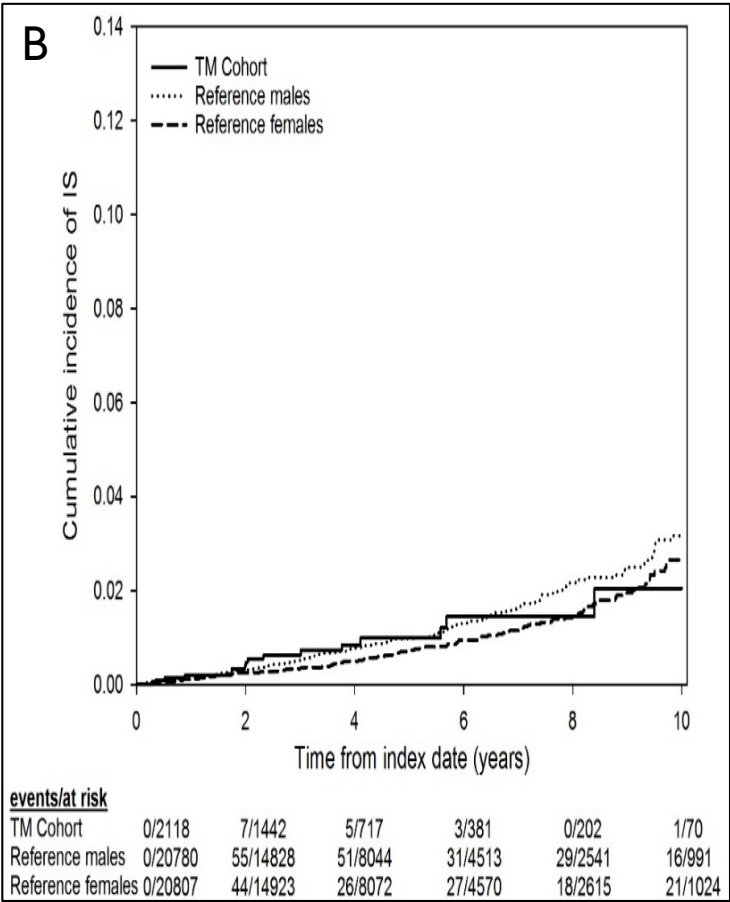
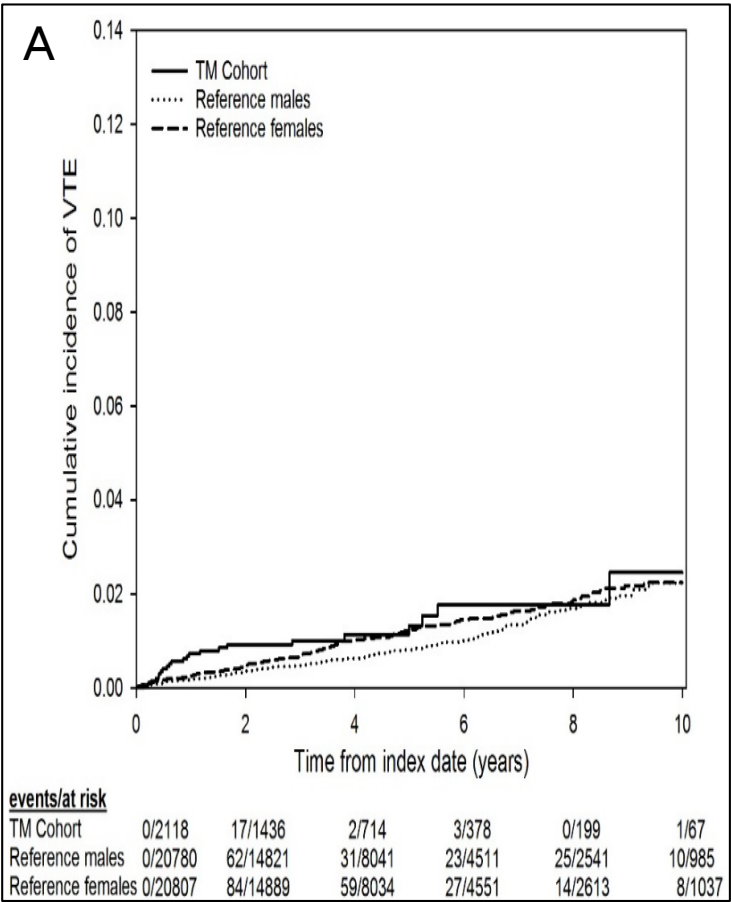


Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons:

A Cohort Study. Ann Intern Med. 2018 Aug 21;169(4):205-213.



Risk of VTE/IS/MI in Transmasculine Patients in the STRONG Cohort





Sex Steroids and Cardiovascular Outcomes

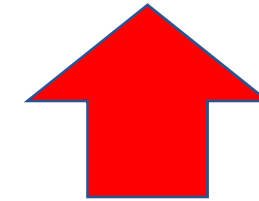
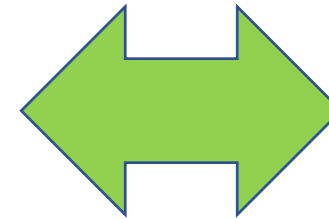
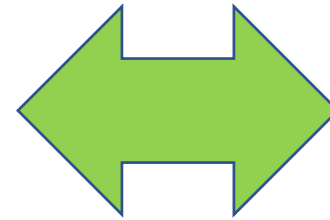
LDL

HDL

TG

Transfeminine

29 studies reviewed



- No change in LDL, HDL for 6, 12, 24 months of follow-up
- Increase in TG by 31.9 mg/dL (95% CI: 3.9 – 59.9) by 24 months



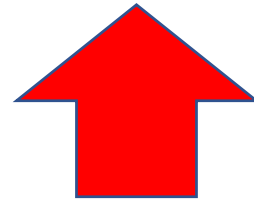
Effect of Sex Steroids on Bone Health



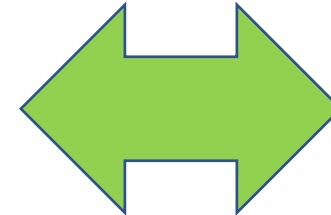
Transfeminine

639 Subjects, 1 – 2-year studies

Spine



Hip



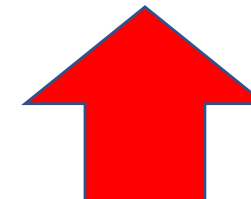
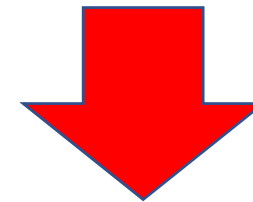
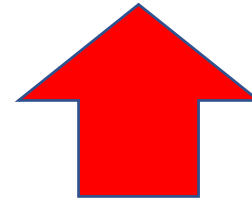


Changes in Lipid Profiles

LDL HDL TG

Transmasculine

29 studies reviewed



Increase in LDL by 12 and 24 months

Decrease in HDL by 6, 12, 24 months

Increase in TG by 6 and 24 months



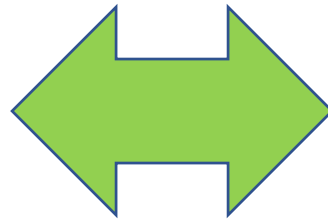
Effect of Sex Steroids on Bone Health



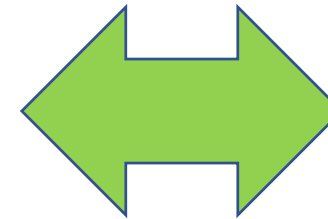
Transmasculine

639 Subjects, 1 - 2-year studies

Spine



Hip





Prevalence of Cancer (STRONG Cohort)

| Cancer Site | Trans-feminine | | Non-Trans Males | | Non-Trans Females | |
|---------------|----------------|--------|-----------------|--------|-------------------|--------|
| | n | (%) | n | (%) | n | (%) |
| Prostate | 24 | (0.69) | 430 | (1.24) | | |
| Skin | 11 | (0.31) | 223 | (0.64) | 177 | (0.51) |
| Lung | 10 | (0.29) | 59 | (0.17) | 57 | (0.16) |
| Colorectum | 9 | (0.26) | 109 | (0.31) | 79 | (0.23) |
| Hematopoietic | 8 | (0.23) | 87 | (0.25) | 35 | (0.10) |

Other endpoints of possible interest (not shown due n<5):

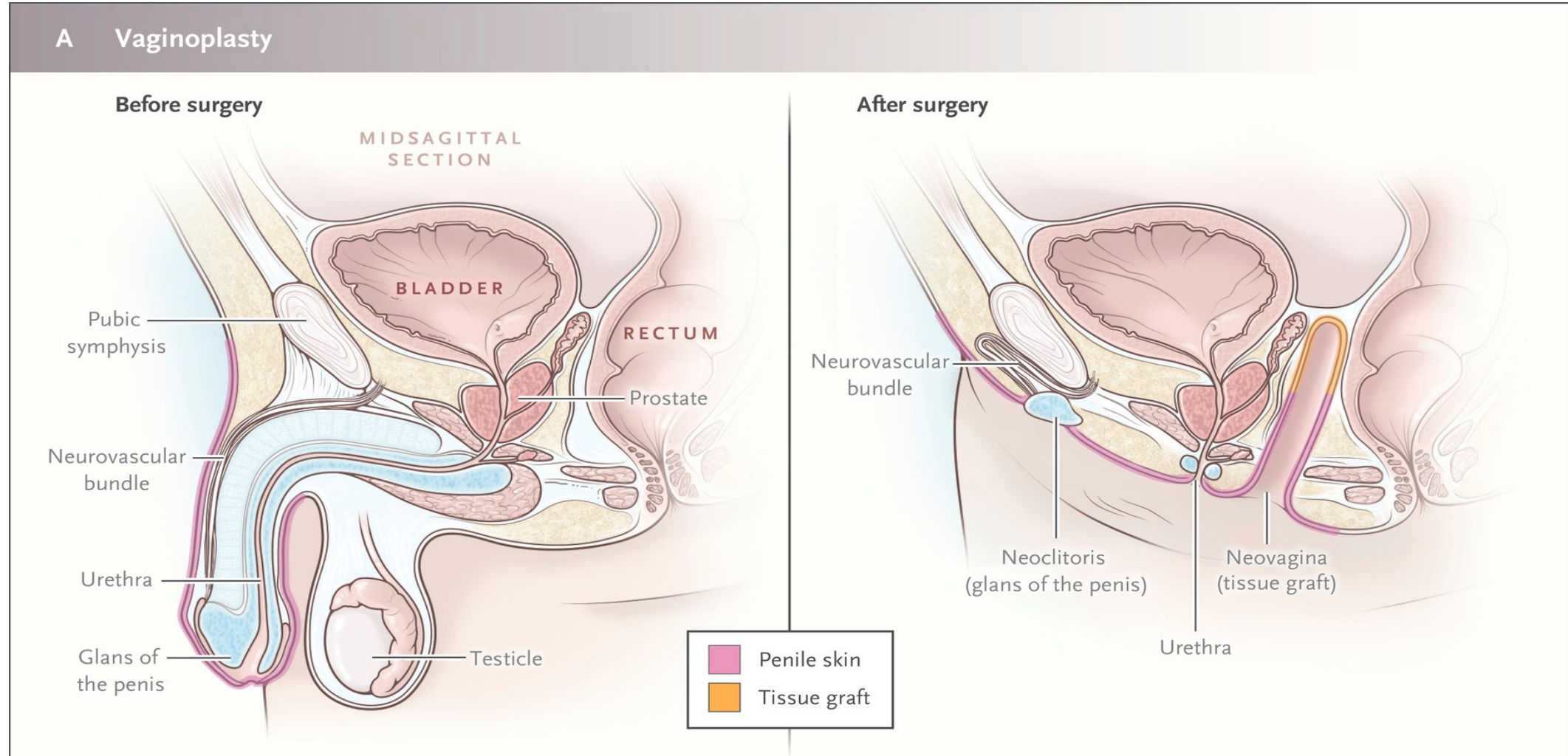
- Meningioma (relative to reference males)
- Brain (relative to both reference groups)



Guidelines for Gender Affirming Surgery

- Persistent, well-documented gender dysphoria
- Legal age of consent in a country
- On hormone therapy for 12 months (unless medical contraindication to hormones)
- Successful full time living in affirmed gender role
- Medical and mental health concerns controlled
- Knowledge of risks and benefits of surgery including all practical aspects (costs, length of stay)

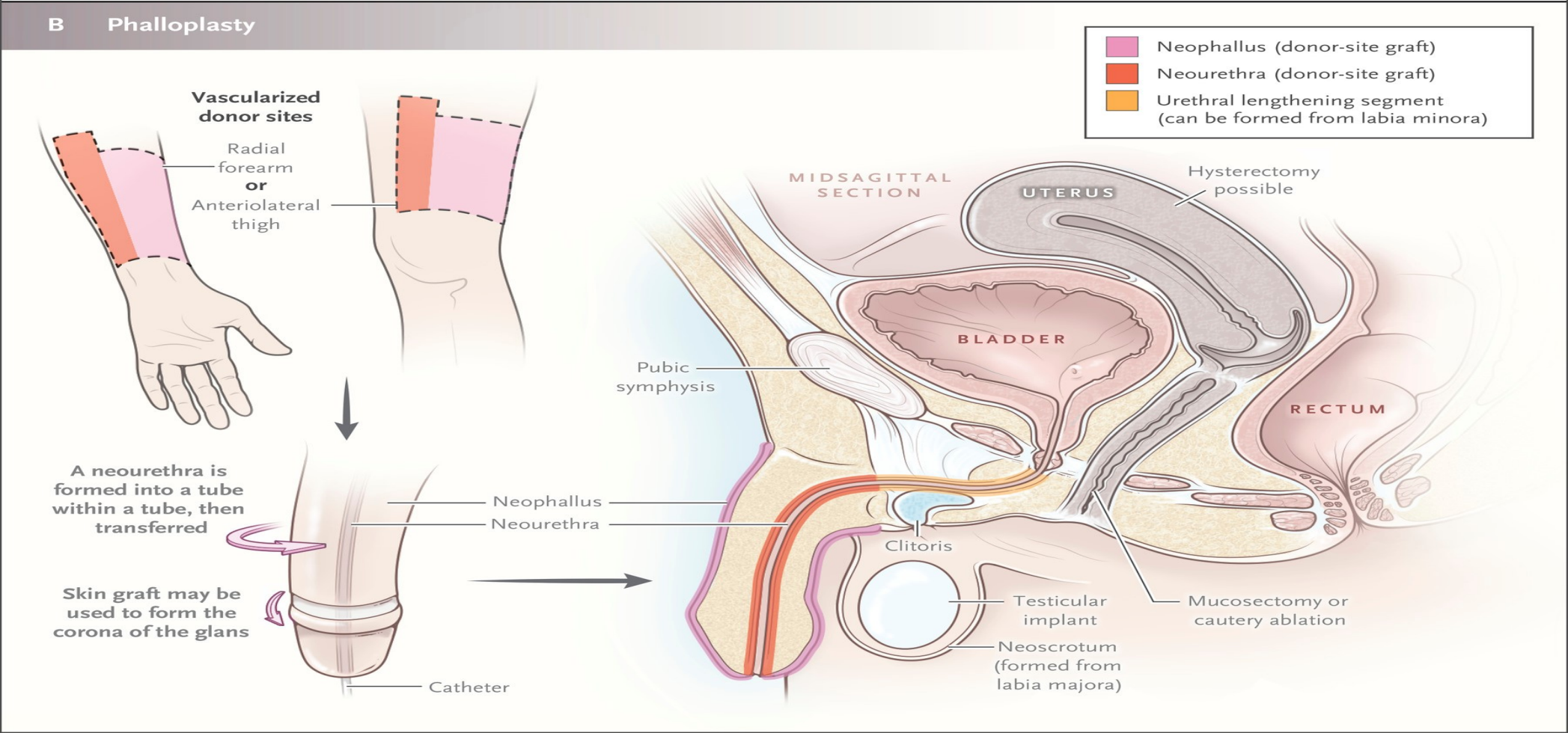
Gender Affirmation Surgery in Transfeminine Individuals





Gender Affirmation Surgery in Transmasculine Individuals

Using the
Free Flap
Technique



Potential Adverse Effects of Transfeminine Hormone Therapy

- Infertility
- Thromboembolism
- Weight gain (increased adiposity)
- Hyperkalemia (those on spironolactone)
- Hyperprolactinemia (more in those on cyproterone)
- CVA or MI, uncertain at this point
- Increased triglycerides

Potential Adverse Effects of Transmasculine Hormone Therapy

- Infertility
- Erythrocytosis
- Weight gain
- Acne
- Male pattern hair loss
- CVA or MI, uncertain at this point
- Increased LDL, lower HDL

Summary

Transgender and gender diverse individuals represent a growing segment of the population. Transgender face many barriers to care including access to knowledgeable health care professionals.

Guidelines exist to aid healthcare professionals in the diagnosis, treatment, and monitoring of long-term health concerns of transgender patients.

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Summary



This learning activity will improve competence and skill in the diagnosis of people with a transgender identity and provide appropriate treatment for these patients. By incorporating the recommendations made in this activity, the patients' providers will be able to diagnose and deliver treatment accordingly.

Increasing the skill level of a wide range of clinicians in the management of transgender individuals decrease barriers to access of care and will lead to improvement of health outcomes of transgender people.