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Cover Page Footnote

Adrian Rainer is a senior nursing student in the baccalaureate nursing program at St. Cloud State University. Thank you to Dr. Amy E. Hilleren-Listerud for the continued help and encouragement with this project, and to my mother, Susan Rainer, for instilling in me a childhood curiosity about medicine.

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Risk of Cardiovascular Disease and Events in Transgender Patients undergoing Hormone Therapy

Adrian T. Rainer

Transgender people are a greatly misunderstood population, both from a medical standpoint and from a societal perspective. With trans people often being the target of misinformed and inflammatory public discourse (Arlee et al., 2019), it can be easy to forget that these individuals are patients that have real and complex medical needs.

Gender dysphoria is the distressing incongruence between one's gender assigned at birth and their gender identity (American Psychiatric Association, 2020). This incongruence is typically what motivates trans people to physically transition. Over 80% percent of trans people pursue cross-sex hormone therapy as the primary treatment for their gender dysphoria (Nguyen et al., 2018). However, not all trans people experience gender dysphoria (particularly those who have positive social supports in place), and dysphoria is not considered a requirement to be transgender or to pursue gender transition (Dargie et al., 2014). Additionally, many trans people do not pursue CSHRT in any form and instead alleviate dysphoria using other means, including legally changing their name and gender, pursuing social transition, and/or undergoing surgical interventions (American Psychiatric Association, 2020).

The goal of CSHRT is to suppress endogenous sex hormones and achieve therapeutic levels of those hormones within the range of the gender the person identifies as. Transwomen (women who were assigned male at birth) usually take a daily set of pills consisting of estrogen preparations, along with antiandrogens and occasionally progesterone (Streed et al. 2017). Transmen (men who were assigned women at birth) typically are prescribed a weekly or bi-weekly intramuscular injection of testosterone (Streed et al. 2017). These are generalizations, as goals of CSHRT may vary from person to person.

The effects of administering cross-sex hormone replacement therapy (CSHRT) to transgender individuals are well-documented as being effective for alleviating mental distress and gender dysphoria (Nguyen et al., 2018). However, from a cardiovascular perspective, the long-term effects of CSHRT are not well understood. Most research regarding administration of sex hormones and cardiovascular health has been obtained from cisgender people (people whose gender identity aligns with what was assigned at birth), which is problematic due to marked differences in dosing, duration of therapy, and comorbidities between transgender and cisgender populations (Pyra et al., 2020). This lack of information may make it difficult for healthcare providers to administer safe and effective evidence-based practice to trans people. Healthcare providers have a responsibility to serve each population without judgement, and to understand risks associated with the medications that patients are prescribed. If the time is not taken to research and understand the full risks and benefits of CSHRT, healthcare providers may be unable to fulfill their duty as patient educators.

When trans people initiate CSHRT, they must sign informed consent paperwork indicating that they understand that the full medical effects and safety of CSHRT are not fully known (Schulz, 2017). Once initiated, most transgender individuals will continue taking CSHRT for the rest of their lives (Nguyen et al., 2018). This leaves the over 1,000,000 trans people currently taking hormone therapy uninformed as to the cardiovascular risks associated with these medications (Nguyen et al., 2018). Considering the potential for compounding negative effects over a lifetime

of taking the same medications, it is necessary for research on this topic to stay appropriately up to date. The purpose of this article is to analyze the cardiovascular risks associated with taking CSHRT.

Literature Review

Though there are many gaps in medical literature regarding transgender medical needs, the topic chosen to discuss in this paper is the risk of cardiovascular disease and acute events that come with undergoing cross-sex hormone therapy. Specifically, this paper seeks to answer the question of what the rate of cardiovascular disease is among transgender patients receiving CSHRT when compared to the general population who are not taking CSHRT.

I. Literature Search Strategy

A comprehensive literature search occurred during the month of September 2021 on the Cumulative Index of Nursing and Allied Health Literature (CINAHL) database. Due to the body of research on this topic being rather limited, relevant literature from any year of publication was accepted. Key terms included in the database search include transgender, male-to-female, female-to-male, transsexual, cardiovascular disease, heart disease, hypertension, HTN, venous thromboembolus, VTE, deep vein thromboembolus, DVT, thromboembolus, TE, risk of, chance, and probability. To be included in this review, literature had to be published in English. Literature had to include data on transmen and transwomen taking CSHRT; studies on cisgender men taking testosterone and cisgender women taking any female hormone preparations were excluded. Lastly, literature had to contain data related to cardiovascular disease, including but not limited to at least two of the following: hypertension (HTN), incidence of thromboemboli (including ischemic stroke and/or pulmonary embolus), myocardial infarcts, lipid levels, diabetes, and coronary heart disease. Under these constraints, five results met the criteria.

This review will categorize each piece of literature according to the Fineout-Overholt et al. (2010) hierarchy of evidence, which ranks literary evidence on a scale of 1-7. The highest level of evidence examined in this review is a level one, performed by Streed et al. (2017). Evidence levels two and three require controlled trials with placebo groups, and although these types of trials would be ideal to evaluate the effect of CSHRT on cardiovascular outcomes, withholding treatment to trans people render placebo groups unethical due to the known psychological benefits that CSHRT has on the transgender population (Streed, 2017). Thus, this review contains no level two or three evidence. Level four evidence consists of well-designed cohort studies, of which this review contains four (Pyra et al. 2020, Getahun et al. 2018, Caceres et al. 2019, Wierckx et al. 2013).

II. Level One Evidence

The study with a level one tier of evidence done by Streed et al. (2017) systematically reviewed 13 studies on the effects of CSHRT on the rates of cardiovascular disease (CVD) in transgender men and women. This study's goal was to highlight the key research on the relationship between transgender adults taking CSHRT and the incidence of CVD. This study's biggest strength is the fact that 13 different studies were included, giving us a better idea CVD risk in different populations of transgender individuals across the United States. The researchers systematically searched PubMed and EMBASE and extracted the relevant data from those studies to use in the systemic review.

This study found that transwomen who were taking high-dose oral estradiol were found to have a 20- to 45-fold increase in the incidence of thromboembolus (TE) when compared to ciswomen. Transwomen on transdermal hormones had significantly lower risks of TE (with rates nearly identical to ciswomen) than transwomen on the high-dose oral estradiol. Transwomen had a higher risk of MIs when compared to ciswomen of similar risk factors, but a similar risk of MI when compared to cismen. There were no studies that showed significant differences in the amount of high-density or low-density lipid levels in transwomen taking CSHRT.

In this review, the researchers found that transmen taking CSHRT didn't have a statistically significant increase in the risk of acute cardiovascular events (including TIAs, MIs, and TEs) when compared to cismen or ciswomen. The studies included in this systematic review also revealed conflicting results regarding the relationship between transmen on CSHRT and the rate of hypertension (HTN).

Of the 13 studies included in this review, six of them had sample sizes of less than 30 individuals. These small sample sizes, combined with the weak correlation between CSHRT and cardiovascular events and diseases in transmen, indicate that longitudinal studies with larger cohorts of various ages are needed to reach a more definitive answer to this question.

III. Level Four Evidence

The first level four piece of literature reviewed regarding this topic is an observational study by Pyra et al., published in 2020 in the journal Transgender Health. This study utilized a retrospective cohort at a Chicago health center of 6,512 transgender participants on CSHRT to examine the relationships between transgender individuals taking CSHRT and the incidence of HTN and TE. A strength of this study is the fact that this study has an exceptionally large sample size. This study adjusted for factors such as age, race, insurance type, HIV status, sexual orientation, body mass index, diabetes status, and smoking status, and time elapsed since first prescribed CSHRT. A limitation of the study is that surgical history data was not available, so endogenous hormone production (which may be a major factor in CVD risk) was not accounted for. Additionally, any data on cardiovascular drugs or hormones prescribed outside of the clinic was unable to be accessed by the researchers.

The results of this study showed that among transwomen, 0.8% (19) experienced a thromboembolism (TE). There were no associations between rate of TE and the blood levels of either estradiol or testosterone in transwomen. Transwomen who were recently prescribed progestin or medroxyprogesterone acetate had odds that increased nearly threefold of experiencing TE, after adjusting for the relevant risk factors. The sample size was too small for conclusions to be drawn, but TE is still regarded generally as being a rare event among transwomen, even among those taking progestin or medroxyprogesterone acetate. Hypertension in transwomen was experienced by 2.1% (49) of the cohort. The study found that a history of taking progestin was protective against development of HTN in transwomen, but that a history of oral use of estrogen appeared to increase rates of HTN.

Among transmen, only 0.2% of the cohort (3 participants) developed thromboembolism, thus no further association analyses were done as no meaningful conclusions would have been able to be drawn due to small sample size. The transmen in the study experienced HTN at a rate of 1.5% (28). There appeared to be no relationship between the levels of testosterone in the blood and the rate of HTN, thus no meaningful conclusions were able to be drawn.

The next piece of level four research was published by Emory University (Getahun et al. 2018). This study was done on a California-based cohort of 2842 transwomen and 2118 transmen,

and evaluated the relationship between CSHRT and TE, ischemic stroke, and myocardial infarction. These researchers utilized an electronic health record to identify transgender patients currently taking CSHRT, and then matched each individual transgender participant to 10 cisgender male and 10 cisgender female counterparts based on age, race, and geographic location. These cisgender counterparts were used as a comparison group for the transgender participants. The pairing of the transgender cohort with a total of 20 cisgender people per one transgender person is this study's biggest strength, as the cohort of transgender people is already exceptionally large at nearly 5,000 participants. As with the study by Pyra et al. (2020), this study was unable to control for hormones and medications prescribed outside of the clinic which the data was pulled from.

For transwomen taking estrogen, this study found an increased likelihood of TEs. When calculated as the number of cases per 1000 person-years, transwomen on estrogen had a 6.6 chance of acquiring a TE, compared to cisgender women at 3.2 and cisgender men at 2.5. This is over a twofold increase of TE risk when compared to cisgender individuals. For ischemic stroke, transwomen had an incidence rate of 6.6, whereas cisgender women had a rate of 3.2 and cisgender men had a rate of 2.9. Myocardial infarct rates were the only ones in which transgender women were at a lower risk than cisgender women. Transwomen had an incidence rate of 1.5, and cisgender women had an incidence rate of 2.4. Cisgender men had lower rates of myocardial infarct than cisgender or transgender women, at 1.0 case per 1000 person-years.

For transmen, this study found that those taking testosterone are at an increased risk of TE when compared both to cisgender men and cisgender women. Calculated as number of cases per 1000 person-years, transmen experienced VTE at rates of 3.1, whereas cisgender men and women experience VTE at rates of 1.6 and 1.1, respectively. Rates of myocardial infarct were higher among transmen taking testosterone (1.2) than in cisgender women (0.7) but were similar to rates observed among cisgender men (1.3). Lastly, this study shows that transmen had a nearly twofold risk for ischemic stroke (2.1) when compared both to cisgender men (1.1) and cisgender women (1.3).

The next piece of level four medical literature was published by Columbia University's School of Nursing (Caceres et al., 2019). The researchers used data from the Behavioral Risk Factor Surveillance System (BRFSS) to examine the relationship between cardiovascular disease and condition risk to gender identity in United States adults. This study is notable because the researchers surveyed the participants' health behaviors, as these are a major factor in the likelihood of developing cardiovascular disease or experiencing acute cardiac events. This study utilized both standard odds ratios and adjusted odds ratios. The adjusted odds ratios were based upon risk factors identified while surveying the participants' health behaviors, body mass index, age, employment and marital status, and medical coverage. The following description will include only the adjusted odds ratios.

This study found that transgender women were 38% more likely than cisgender men and 124% more likely than cisgender women to have any kind of cardiovascular disease (the researchers did not differentiate between any cardiovascular diseases). Transgender men were 3% less likely than cisgender men, but 60% more likely than cisgender women to develop cardiovascular disease. The odds of transgender men or women developing ischemic stroke were much different. Transgender women were 62% more likely than cisgender men and 88% more likely than cisgender women to have experienced an ischemic stroke. Transgender men, however, were 55% more likely than cisgender men and 80% more likely than cisgender women to have experienced an ischemic stroke. Overall, this study found that transgender women were the group at the highest risk to develop diabetes, coronary heart disease, stroke, myocardial infarct, and any

kind of cardiovascular disease when compared to cisgender men, cisgender women, and transgender men.

A limitation of this study is that it did not examine blood concentration levels of CSHRT, nor did it examine prescription dosage of CSHRT. This makes it difficult to draw definite conclusions upon the relationship between CSHRT and cardiovascular events and disease. If we assume that the transgender people in this study were taking CSHRT at similar dosages as the transgender people in other studies, then this study strongly suggests that taking exogenous estrogen is a risk factor for developing cardiovascular disease or experiencing cardiac events in transgender women. Lastly, this data is only cross-sectional and self-reported, meaning that lifetime behaviors are not being taken into account and that this study may be prone to bias on behalf of the participants.

The final level four study reviewed in this paper is one done by Wierckx et al. in 2013. This study utilized an electronic health record to identify people diagnosed with gender dysphoria who underwent at least three months of CSHRT, and then sent out an invitation to participate in the study by letter to the possible participants. This study received a 54% response rate, with a total of 352 transgender participants. Both cohorts of transgender people got age-matched to 10 female and 10 male counterparts to compare data with regarding cardiovascular disease. The data is presented in cases per 1000 persons.

This study revealed that transwomen had a relatively high incidence of TE (60.7), especially when compared with transmen (14.5). This study also revealed that transwomen had higher incidences of cardiovascular disease (23.4) when compared both to the group of control men (9.4) and control women (14.9). Additionally, the transmen in the study had zero cases of cardiovascular disease. Compared to the control men and women who both had the same number of cases per 1000 people (7.3), this is much lower. These findings suggest that oral estrogen preparations significantly raise an individual's risk of acquiring cardiovascular disease when compared to control groups, and that testosterone preparations do not significantly affect cardiovascular health outcomes.

A major strength of Wierckx et al.'s (2013) study is that they controlled for BMI, which many others did not. Furthermore, the median number of years that the participants had been taking CSHRT was approximately 10, giving us a better idea of the level of CVD risk after many years of CSHRT. However, only 54% of those invited to participate in the study participated, making selection bias on behalf of the volunteers a possibility. Lastly, the sample size of 352 people total was too small to determine an accurate prevalence of morbidity and mortality.

Synthesis

This literature review evaluated five different scientific studies examining the effect that CSHRT has upon the cardiovascular health of the transgender population. This examination revealed three main themes: Risk of TEs in transwomen, risk of TEs in transmen, and route of CSHRT administration in transwomen.

I. Rate of TEs in transwomen

Every article reviewed examined the general cardiovascular risk posed to transgender women taking CSHRT, but not every article recorded the instances of the same kinds of CVD; For example, although every piece of literature examined rates of TEs, only one studied rates of MI. Thus, this part of the synthesis will focus only the instance of TEs in transwomen, as that is

recorded in every study. The articles used many different methods of calculating risk of TE, including number of cases out of 1000 person-years (Getahun et al. 2018, Streed et al. 2017), adjusted odds ratios (Wierckx et al. 2013), and percentage points (Pyra et al. 2020, Caceres et al. 2019).

Pyra et al. (2020) found that 0.8% of the transwomen in their study had experienced a TE in the past. In the study done by Getahun et al. (2018), they found that 6.7 percent of transwomen experienced a TE at any point during their eight-year study (over twice as likely as any other group). Caceres et al. (2019) determined that transwomen were 62% more likely to experience a TE than cisgender men, and Wierckx et al. (2013) determined that transgender women had a 5.1% chance of experiencing a TE in their lifetime. The systematic review done by Streed et al. (2017) showed that the most conservative estimates determined transwomen to have a 5.1% rate of TEs in a lifetime. Despite having different methodologies and methods of calculating risk, every article agrees that transwomen are at the highest rates of TEs when compared to cisgender men, cisgender women, and transgender men.

II. Rate of TEs in Transmen

Because transmen have unique biological profiles when compared to cisgender men, cisgender women, and transgender women, they too were found to have experienced different rates of TE when compared to any of the above groups. Like above, the measures used to record rates of TE among transmen varied from study to study, however general takeaways can still be gleaned from the information presented in the studies regarding transmen and TEs.

In Pyra et al.'s study (2020), they found that only 0.2% (three participants) of the cohort developed a TE; because so few developed TEs, no meaningful conclusions could be drawn. However, it does show TEs not being a common occurrence among transmen. Getahun et al. (2018) found evidence to support that transgender men experienced TEs at about twice the rate of cisgender men and three times the rate of cisgender women. Caceres et al. (2019) showed that no differences in rates of TEs were observed between transmen and cisgender women, but that transgender men had a 45% higher rate of TEs than cisgender men.

In contrast, Wierckx et al. (2013) showed that transmen had a 1.4% chance of having a TE in their lifetime (compared to 6.07% of transwomen); However, this study did not examine rates of TE among their cisgender participants, so it is unknown exactly how this would have compared to cisgender men or women. Lastly, Streed et al. (2017) was not able to find convincing evidence in the systematic review that there was any statistically significant increase at all when looking at TEs in transmen. The evidence for transmen is less conclusive than that of transwomen, but this may be due to the generally smaller sample sizes for transmen when compared to the sample sizes for transwomen included in the studies.

III. Route of CSHRT Administration in Transwomen

The last common theme identified is the difference that CSHRT routes have on TE risk. Not all CSHRT is administered via the same route, and four of the five studies examined here distinguish between the routes of CSHRT administration and risk of developing TE. In the United States, the most common routes of administration of CSHRT for transwomen include intramuscular injections, transdermal patches, and oral preparations (Nguyen et al. 2018). For the purpose of this synthesis, "high-dose oral estrogen preparations" have been defined as any oral estrogen prescription equal or greater than 100mg daily. Transgender men overwhelmingly take

CSHRT via intramuscular injections (Streed et al. 2017), so there are no meaningful comparisons that can be made regarding route of CSHRT in transmen and the risk of TE.

Transwomen in Pyra et al.'s (2020) study who were taking oral progesterone (medroxyprogesterone acetate) experienced TEs at nearly three times the rate of transwomen not taking progesterone orally, or those who were not taking progesterone at all. Getahun et al. (2018) found that transwomen who were taking high-dose oral estrogen were twice as likely to get a TE when compared to cisgender women taking low-dose oral estrogen preparations. Wierckx et al. (2013) found that their rate of TE in 5.1% of the participants was lower than that of a similar study done in 1997 (Van Kesteren et al.), which showed transwomen having a 6.4% chance of acquiring a TE; Interestingly, proportionally fewer people in Wierckx et al.'s (2013) study were on high-dose oral estrogen when compared to Van Kesteren et al.'s (1997) study, leading these researchers to suggest that high-dose oral estrogen preparations are the reason for this difference. In the systematic review performed by Streed et al. (2017), one study was noted in which a cohort of 816 transwomen receiving CSHRT contained 36 participants who developed TEs; Of these 36 participants, 35 were taking high-dose oral estrogen preparations. However, it is very important to note that prescriptions of high-dose oral estrogen preparations for transwomen are not the norm, nor are they recommended practice due to this known risk of the development of TEs (Streed et al. 2017).

IV. Unanswered Questions

Because transgender people were systematically denied CSHRT administration from healthcare professionals until as recently as the 1980s, there is still much research to be done concerning the effects it has on the cardiovascular system (Naz Khan, 2016). For example, there are currently no studies able to be found on the risk of cardiovascular disease in older trans people taking CSHRT. Because cardiovascular risk increases with age in the cisgender population, it is important for elderly transgender people on CSHRT to know how and if these risks change with age. Additionally, it is unknown how long-term administration of CSHRT affects cardiovascular health. Because people are getting access to CSHRT at earlier ages, soon there may be people who are only in their mid-thirties who have been receiving CSHRT for over 20 years. It is unknown if, for these individuals, cardiovascular risks "level out" to rates closer to their cisgender counterparts, or if transgender individuals on CSHRT will always be at an increased risk.

V. Future Recommendations

Future studies on the topic of transgender cardiovascular health should focus on the risks associated with taking CSHRT over time, and on whether the potentially harmful cardiovascular effects of CSHRT compound over time. This can be achieved by designing a long-term observational study that observes the type and dose of CSHRT, the age at which CSHRT was initiated, and the current age of the participants, along with relevant cardiovascular risk factors. Were this review able to include many participants of diverse age, it may be able to answer the first two unanswered questions listed above. Lastly, more studies are necessary to analyze whether transgender people are aware of the risk to physical health that CSHRT can pose, and if they are aware that different medication regimens have different levels of cardiovascular risk associated with them.

Conclusion

This literature concludes that CSHRT may have some negative effects on the cardiovascular health of transwomen, and that current evidence is insufficient to declare what effect CSHRT may have on transmen. Healthcare providers should be aware that different dosages and formulations of CSHRT (namely high-dose oral estrogen) may put patients at higher risk of adverse cardiac outcomes. Although CSHRT may have some adverse effects on the cardiovascular system, the psychological benefits these individuals experience when utilizing CSHRT often outweigh the cardiovascular dangers. Patients should be educated on the cardiovascular risk factors associated with CSHRT prior to initiation. Lastly, it is important that in patients undergoing CSHRT, medical professionals prioritize monitoring for and educating on modifiable cardiovascular risk factors, such as smoking, physical inactivity, and high BMI to best maintain the health of these patients.

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