Safety and rapid efficacy of guideline-based gender-affirming hormone therapy: an analysis of 388 individuals diagnosed with gender dysphoria

Gesine Meyer[1], Moritz Mayer[1], Antonia Mondorf[1], Anna Katharina Flügel[1], Eva Herrmann[2] and **Joerg Bojunga[1]**

[1]Division of Endocrinology, Department of Internal Medicine 1, Goethe-University Hospital, Frankfurt, Germany and [2]Institut for Biostatistics and Mathematic Modelling, Goethe-University, Frankfurt, Germany

Correspondence should be addressed to G Meyer
Email
Gesine.Meyer@kgu.de

Abstract

Objective: Hormone treatment is an important part of gender reassignment therapy in gender dysphoria. Previous data about efficacy and safety are commonly based on small cohorts or they comprise former cohorts under meanwhile obsolete therapy regimes. Our objective was to investigate these topics in a large cohort of individuals under guideline-based treatment.
Design/methods: Cohort study of medical files of $n = 155$ male-to-female (transwomen) and $n = 233$ female-to-male transgender persons (transmen) of an Endocrine outpatient clinic between 2009 and 2017.
Results: Median time to reach amenorrhoea in transmen under testosterone monotherapy was 3 months, regardless of whether testosterone undecanoat or gel was used. Transmen with higher levels of hemoglobin 3–4 months after onset of GAHT had a greater chance to reach amenorrhea early, whereas testosterone levels showed no significant correlation (hemoglobin: HR: 1.639; 95% CI: 1.036–2.591, $P = 0.035$; testosterone: HR: 0.999; 95% CI: 0.998–1.001, $P = 0.490$). Estradiol levels (ρ −0.117; $P = 0.316$) had no significant influence on breast development in transwomen. Testosterone levels (ρ −0.398; $P < 0.001$) and FAI (ρ 0.346; $P = 0.004$) were significantly negatively correlated with reached Tanner stage. Liver values and blood lipids showed an alignment to reference range of the required sex in both groups. Relevant elevations of liver values were rare (2.44% in transmen, 4.23% in transwomen) and transient in most cases. Most relevant side effects were acne (44.8%), respectively erythrocytosis (up to 5.6%) in transmen and venous thrombembolism (1.9%) in transwomen.
Conclusions: Gender-affirming hormone therapy in accordance with current clinical practice guidelines is efficient and safe.

European Journal of Endocrinology
(2020) **182**, 149–156

Introduction

Gender dysphoria, previously most commonly termed as transsexualism, is defined as the affliction resulting from discrepancy between somatic and subjectively perceived sex. Gender-affirming hormone treatment (GAHT), formerly termed cross-sex hormone therapy, is an important part of gender reassignment therapy in individuals diagnosed with gender dysphoria. The main therapeutic goals are to suppress the undesirable physical characteristics of the somatic sex and to develop those of the affirmed sex as far as possible. The achievable effects of GAHT have been well known for a long time. Development of a female breast is one of the most eagerly awaited

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-19-0463

Published by Bioscientifica Ltd.

changes in transwomen (male-to-female transgender individuals) and was also of early scientific interest (1, 2). One of the most important clinical milestones in transmen (female-to-male transgender individuals) is menstrual cessation, though only very few studies pointed to this topic so far (3, 4). Data of correlations between hormone preparations used as well as serum hormone levels and temporal progression of desired effects are still limited.

The number of individuals affected, respectively, the number of individuals asking for medical treatment has markedly increased over the past years (5). As GAHT does usually mean a lifelong medication of physically healthy and often young individuals, adverse side effects have to be minimized. A relevant, since potentially life-threatening adverse side effect of GAHT in transwomen is venous thrombembolism. Former studies described a considerably increased risk (6, 7, 8, 9). The adverse side effect of erythrocytosis in transmen under testosterone substitution occurs in up to one-sixth of the individuals in a former study (8).

Another focus is on metabolic side effects under long-term therapy. Several previous studies examined the course of bodyweight, serum lipids as well as liver enzymes under GAHT. The results are summarized in a number of reviews (10, 11, 12, 13, 14). Most of the studies show an increase of body mass index (BMI) in transmen as well as transwomen (3, 15, 16). An unfavourable change of serum lipids with an increase of low-density lipoprotein cholesterol (LDL-C) and a decline of high-density lipoprotein cholesterol (HDL-C) was observed in transmen (3, 15, 16, 17). Under estradiol treatment of transwomen, an increase of triglycerides (TG) was described, but also a decline of LDL-C and an increase of HDL-C (15, 16, 18). A previous study indicated an increase of liver enzymes in a relevant proportion of transwomen as well as transmen under GAHT (6).

However, various of these data about efficacy and safety are based on small cohorts or they include former cohorts under meanwhile obsolete therapy regimes.

The first GAHT was implemented about 80 years ago. In the late 1970s the 'World Professional Association for Transgender Health' (WPATH) formulated first standards of care that have been revised regularly since then (19). Evidence-based clinical guidelines for endocrine treatment of gender dysphoric persons were first developed by the endocrine specialist society in 2009 and revised in 2017 (20, 21). In the last two decades, recommendations for hormone preparations and formulations used in GAHT have changed considerably. Reasons are alterations in preparations and formulations available and, particularly, a rising awareness of side effects. While 20 years ago, ethinyl estradiol was used regularly for treatment of transwomen, it is no longer recommended because of its increased risk of thrombembolic events. The currently recommended dosage of the antiandrogenic drug cyproterone acetate of 10–50 mg daily is less than half of the dosage used 10 years ago. Guidelines for testosterone substitution in transmen did not change to the same degree, though oral testosterone is rarely applied today (20, 21).

Our objective was to investigate the efficacy and safety of GAHT in a large cohort of individuals under guideline-based treatment. We hypothesised that GAHT is efficient, notably in the first year after onset, and that the risk for adverse metabolic side effects is low under professional treatment. A secondary objective was to define clinical and laboratory follow-up markers to optimise GAHT, in particular regarding menstrual cessation in transmen respectively breast development in transwomen.

Subjects and methods

Since its foundation in 2009 until March 2017, $n=536$ individuals presented in our Endocrine outpatient clinic for gender dysphoria. In $n=105$ individuals the psychological evaluation required for GAHT by a qualified psychologist was still outstanding at the time of inquiry. Data of $n=43$ individuals were incomplete and hence excluded, thereof $n=27$ solely due to recently initiated therapy and $n=16$ due to other reasons. Thus, data of $n=388$ individuals who started GAHT in our medical attendance were analysed. All data were collected retrospectively from medical documentation. The study was approved by the local ethical committee (permit no. 185/16).

For calculation of significant differences of clinical and laboratory data to different dates only individuals with complete datasets over the observation period were analysed using Wilcoxon-matched-pairs-test. Laboratory results are presented as median and interquartile range. Regarding latency to amenorrhoea in transmen, only data of individuals without a preceding or additional medication with progestins or GnRH agonists were considered. Median and confidence interval of latency to amenorrhoea were calculated using Kaplan–Meier estimates with Hall–Wellner interval. A multivariate Cox regression analysis was performed to investigate factors influencing latency to amenorrhoea. This analysis includes type of testosterone agent, testosterone serum levels, Free Androgen Index (FAI) as an indicator for biological relevant free testosterone, as well as haemoglobin and haematocrit,

both of which typically increase depending on the effect of testosterone on erythropoietin-responsive cells.

To compare the influence of different doses of cyproteronacetate on testosterone levels and free androgen index in transwomen, a Mann–Whitney *U*-test was performed. Possible influencing factors on breast development in transwomen (estradiol serum levels, testosterone levels and FAI) were analysed using Spearman's rank correlation, considering BMI and age at onset of GHAT as potential independent confounders.

Statistical analysis was performed using the statistical software BiAS 11.05. Statistical significance was accepted for P values of less than 0.05.

Results

Participants

In our cohort of 388 individuals $n=155$ were male-to-female and $n=233$ female-to-male transgender persons resulting in a sex ratio of transwomen to transmen from 1 to 1.5.

Median age at start of GAHT was significantly lower in transmen (median of 21 years, range: 15–52) compared to transwomen (median of 25 years, range: 15–61; $P<0.001$).

GAHT was implemented according to current clinical guidelines (19, 20) in all individuals. Dosages of all medications were adjusted based on clinical and laboratory results every 3–6 months.

In transmen, choice of testosterone preparation was made on the individual's preference. Testosterone undecanoat intramuscularly was used in 76.4% (dosage: 1000 mg every 10–17 weeks, median of 12 weeks), transdermal testosterone gel in 23.6% (dosage: 25–75 mg/day, median of 50 mg/day). In about ¼ of transmen a preceding or concomitant therapy with progestins or GnRH agonists was performed to assist menstrual cessation, 71.7% were treated with testosterone monotherapy.

Formulations of estradiol in transwomen were selected after informed consent dependent on the individual's cardiovascular and thrombembolic risk profile. Transdermal formulations of estradiol were applied in 52.9%, thereof transdermal gels in 89% (dosage: 1.5–6 mg/day, median of 2.25 mg/day) and transdermal patches in 11% (dosage: 0.1 mg/day). Oral formulations of estradiol valerate respectively hemihydrate (dosage: 3–10 mg/day, median of 6 mg/day) were used by 47.1% of transwomen. Antiandrogenic medication was established with cyproteronacetate in 71.5% (dosage: 10–50 mg/day, median of 25 mg/day). Based on own clinical experience, since 2014 mainly low dosages between 10 and 25 mg per day were used. Spironolactone was used in 5.6% (dosage: 50–100 mg/day, median of 100 mg/day) and combinations of both in 5.6%. 17.4% of transwomen refused to use antiandrogens. Antiandrogen medication was discontinued at the time of gonadectomy.

During the observation period, gonadectomy was performed in 24.5% of transmen and 29.8% of transwomen with a latency of 8–54 months (median of 18 months) in transmen, respectively 4–46 months (median of 20 months) in transwoman. After gonadectomy, dosage of estradiol was slightly reduced in 7.9% of transwomen. In transmen, gonadectomy leads to a reduction of the testosterone dosage in 19.7 and in 3.9% dosage of testosterone was increased after ovariectomy.

Efficacy

Female-to-male transgender persons

Serum levels of testosterone as well as Free Androgen Index (FAI) lay within the reference range for young men after 3–4 months of therapy (Table 1).

Median time to reach amenorrhoea in individuals under testosterone monotherapy was 3 months, regardless whether testosterone undecanoat or gel was used. In 3.8% of the individuals amenorrhoea was not reached 1 year after onset of therapy (Fig. 1).

FAI as well as haemoglobin levels were significantly correlated with menstrual cessation. Transmen who had higher levels of hemoglobin 3–4 months after onset of GAHT had a greater chance to reach amenorrhoea whithin the first months of therapy. Testosterone levels showed no significant correlation (fAI: HR 1.009; 95% CI 1.004–1.014, $P<0.001$; haemoglobin: HR 1.639; 95% CI 1.036–2.591, $P=0.035$; testosterone: HR 0.999; 95% CI 0.998–1.001, $P=0.490$).

Male-to-female transgender persons

After onset of hormone therapy, serum levels of estradiol increased within the first 3–4 months to the target for transwomen, corresponding to the levels for premenopausal females and remained stable over the observation period. Testosterone serum levels as well as FAI lay within the reference range for women after 3–4 months of therapy (Table 1).

In our cohort, we could not find any significant differences between testosterone level or FAI 3–4 months

Table 1 Efficacy of gender-affirming hormone treatment. Data shows laboratory and clinical changes over time.

	Baseline	3–4 months	10–14 months	3–4 years	Reference range
Testosterone (nmol/L)					
Transmen, *n*	197	208	169	71	
Median (IQR)	1.08 (0.66)	13.51 (11.08)	18.06 (10.66)	16.39 (10.31)	8.65–29.03
Transwomen, *n*	99	108	96	41	
Median (IQR)	14.82 (7.33)	0.63 (0.9)	0.63 (1.59)	0.48 (0.49)	0.28–1.67
fAI					
Transmen, *n*	194	204	168	71	
Median (IQR)	1.94 (2.3)	38.4 (33.9)	63.7 (39)	58.4 (34.9)	15–95
Transwomen, *n*	97	108	96	40	
Median (IQR)	45 (21.3)	1.3 (2.9)	1.4 (2.9)	0.8 (2)	<3.5
Estradiol (pmol/L)					
Transmen, *n*	198	206	167	65	
Median (IQR)	211.4 (387.8)	158.1 (139.7)	136.0 (73.5)	117.6 (91.9)	99.6–193
Transwomen, *n*	94	108	96	51	
Median (IQR)	80.9 (56.3)	367.6 (404.5)	430.1 (400.7)	341.9 (382.4)	98.2–1154.4
Breast-chest difference (cm)					
Transwomen, *n*		27	62	30	
Median (IQR)		8 (5)	8 (4)	8.5 (5)	
P			**0.004**	0.055	
Tanner stage					
Transwomen, *n*		71	84	38	
Median (IQR)		3 (1)	3 (1)	4 (1)	
P			**<0.001**	**<0.001**	

fAI, free androgen index; IQR, interquartile range.

after onset of GAHT and different starting doses of cyproteronacetate, neither comparing dosages of 25 vs 50 mg/day (testosterone: median difference (MD): 8.05, 95% CI: 14.06 to 30.16, P=0.468; fAI: MD: 0.12, 95% CI: 1.95 to 2.19, P=0.498), 10 vs 25 mg/day (testosterone: MD:13.63, 95% CI : 33.75 to 6.5, P=0.180; fAI: MD:1.13, 95% CI: 2.75 to 0.5, P=0.170), nor 10 vs 50 mg/day (testosterone: MD: 5.57, 95% CI: 19.54 to 8.39, P=0.427; fAI: MD: 1, 95% CI: 2.69 to 0.69, P=0.239).

Significant increment in breast-chest difference was observed in transwomen within the first year of GAHT but not in the later course of treatment (Table 1). After the first year of hormone therapy, nearly half the individuals (48.4%) presented with a bra cup size of less than AAA (defined as a breast-chest difference of less than 8 cm), 22.6% reached an AAA cup (breast-chest difference 8 to less than 10 cm), 16.1% an AA cup (10 to less than 12 cm) and 6.5% an A cup (12 to less than 14 cm). Only 6.5% gained a bra cup size of B (1.6%) or C (4.8%). Development of breast shape determined by Tanner stages showed a significant progress within the first year as well as after 3–4 years of hormone treatment (Table 1). Estradiol levels, BMI as well as age at onset of GAHT had no significant influence on breast development (estradiol: Spearman correlation (ρ)=–0.117, P=0.316; BMI: ρ=0.189, P=0.104; age: ρ=–0.103, P=0.376). Testosterone levels and FAI were significantly negatively correlated with the level of tanner stage (testosterone: ρ=–0.398, P<0.001; fAI: ρ=0.346, P=0.004).

Safety

The most frequent side effect in transmen was acne, which affected 44.8%, whereby the manifestation was only mild in 84.6% of these individuals. The choice of testosterone

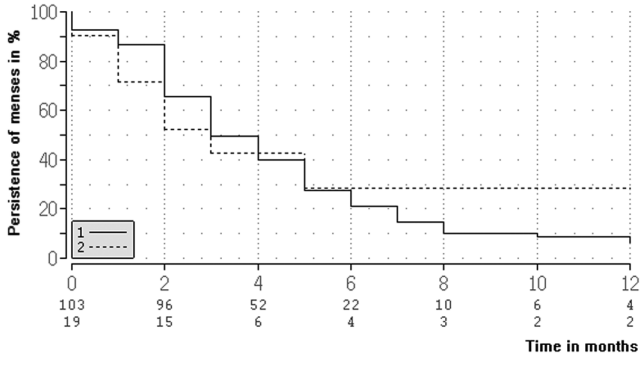

Figure 1
Persistence of menstrual bleeding in % of transmen after onset of GAHT with testosterone undecanoat (1) or transdermal testosterone gel (2). Numbers at risk under treatment with testosterone undecanoat (upper line) resp. transdermal testosterone gel (lower line). Median time to reach amenorrhoea amounts to 3 months in both groups.

preparation had no significant influence on the prevalence of this side effect (45.5 vs 43.6% under medication with testosterone undecanoat vs gel, $P=0.320$). Erythrocytosis, defined as haemoglobin level > 10.86 mmol/L, was observed in up to 5.6% of transmen. A haematocrit above 50% was observed in up to 14.3%. This side effect occurred with a peak after several years of testosterone therapy and did not correlate with serum testosterone levels above the upper limit in any of the affected persons (Table 2).

Venous thrombembolisms occured in $n=3$ (1.9%) of transwomen during the observation period. In two of the cases pulmonary embolism was diagnosed directly after gender-affirming surgery. Age at onset of GAHT (29; 51; 51 years) as well as BMI (26.6; 30.7; 38.4 kg/m^2) were higher in individuals affected compared to the overall transwomen study cohort. Transdermal estradiol formulations were used in two and oral estradiol valerate in one of the affected individuals. In the youngest person affected hereditary thrombophilia (heterozygous prothrombin mutation) was diagnosed. In transmen, deep vein thrombosis was observed in $n=1$ individual (0.4%) related to gender-affirming surgery, obesity (BMI 32.5 kg/m^2)

Table 2 Safety of gender-affirming hormone treatment. Table shows laboratory and clinical changes over time.

	Baseline	3–4 months	10–14 months	3–4 years	Reference range
GGT (U/L)					
Transmen, *n*	195	203	166	71	
Median (IQR)	12 (7)	14 (9)	15.5 (8.25)	18 (14)	<60
Transwomen, *n*	100	106	94	52	
Median (IQR)	19 (13.5)	18 (15)	19 (15.25)	15.5 (11)	<40
ALT (U/L)					
Transmen, *n*	160	147	112	31	
Median (IQR)	16 (9.5)	18 (10)	19 (14)	21 (20)	<50
Transwomen, *n*	89	88	69	37	
Median (IQR)	21 (14)	19 (15.75)	19 (17)	18 (9)	<35
AST (U/L)					
Transmen, *n*	194	206	164	69	
Median (IQR)	20 (6)	22 (7)	22 (8)	24 (10)	<40
Transwomen, *n*	100	106	95	51	
Median (IQR)	24.5 (7)	21 (6)	20 (5)	20 (6)	<35
LDL-C (mmol/L)					
Transmen, *n*	195	204	148	65	
Median (IQR)	2.28 (0.92)	2.29 (0.92)	2.51 (1.34)	2.82 (1.37)	<2.97
Transwomen, *n*	95	107	81	48	
Median (IQR)	2.43 (1.24)	2.2 (0.96)	2.28 (0.94)	2.3 (0.89)	<2.97
HDL-C (mmol/L)					
Transmen, *n*	195	205	150	68	
Median (IQR)	1.56 (0.49)	1.4 (0.45)	1.29 (0.47)	1.3 (0.4)	>1.03
Transwomen, *n*	97	107	81	48	
Median (IQR)	1.39 (0.56)	1.35 (0.6)	1.34 (0.52)	1.45 (0.65)	>1.29
TG (mmol/L)					
Transmen, *n*	196	206	150	68	
Median (IQR)	0.83 (0.39)	0.9 (0.54)	1.03 (0.6)	1.23 (0.92)	<2.29
Transwomen, *n*	97	107	81	48	
Median (IQR)	1.03 (0.9)	0.86 (0.53)	0.86 (0.59)	0.89 (0.76)	<2.29
BMI (kg/m^2)					
Transmen, *n*	201	176	159	69	
Median (IQR)	23.7 (6.5)	24.8 (5.8)	25.2 (6.3)	24.8 (7.5)	<25
P		**<0.001**	**<0.001**	0.962	
Transwomen, *n*	102	94	83	49	
Median (IQR)	22.4 (6.2)	22.45 (5.6)	23.5 (5.4)	25 (8.7)	<25
P		0.393	**<0.001**	**<0.001**	
Hb >10.86 mmol/L					
Transmen, %	0	0	0.6	5.56	
Hct >50%					
Transmen, %	0	1.5	3.6	14.3	

BMI, body mass index; Hb, hemoglobin; Hct, hematocrit; HDL-C, high-densitiy lipoprotein-cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides.

and previously unknown hereditary thrombophilia as additional risk factors.

BMI increased significantly in transmen as wells as in transwomen, but median BMI remained in or slightly above the upper normal range in both groups (Table 2).

Liver enzymes (AST, ALT, GGT) showed an alignment to reference range of the required sex in both groups (Table 2). Relevant elevations of liver values to more than two-times the upper limit of the reference range were rare (5 out of 205, 2.44% in transmen, respectively 3 out of 71, 4.23% in transwomen) and transient in three of the five transmen, respectively in two of the three transwomen. Chronic viral hepatitis was excluded prior to the initiation of hormone treatment in all individuals. An adaption to the specific reference range of required gender in both groups was also seen regarding blood lipids (LDL, HDL, triglycerides) (Table 2).

Discussion

Our study provides important data about the efficacy and safety of GAHT according to current clinical guidelines in a large cohort of 388 individuals with gender dysphoria.

Levels of sex hormones lay within the reference range of the intended gender within a few months after onset of GAHT and before gonadectomy in transmen and in transwomen.

Our data indicate that small doses of 10-25 mg cyproteronacetate, less as recommended in the current clinical guidelines, are sufficient to suppress androgens in a majority of transwomen. This result is certainly limited by the retrospective approach of our study. However, it strengthens our clinical impression and could be an interesting question for prospective studies.

We can register a rapid and satisfying clinical impact of therapy, particularly in our cohort of transmen. Amenorrhoea is one of the most important clinical milestones for transmen. The few studies on this subject available reveal a wide range of few to 41 weeks in median till amenorrhoea is reached (3, 4). A prospective comparison of different testosterone formulations in small groups of 15 individuals each showed no differences regarding menstrual cessation (3). In our cohort, median time to reach amenorrhoea under testosterone monotherapy was 3 months, regardless whether testosterone undecanoat or gel was used and irrespectively of the level of testosterone within the male reference range. However, transmen with higher levels of haemoglobin 3–4 months after onset of GAHT were more likely to reach amenorrhoea within the first months of therapy. Increase of haemoglobin due to the effect of testosterone on erythropoietin-responsive cells was observed simultaneous or even before the onset of amenorrhoea, making a relevant effect of menstrual cessation on haemoglobin levels unlikely. Therefore, we evaluate haemoglobin as an important laboratory marker of testosterone action in transmen.

One of the most eagerly awaited clinical impacts of GAHT in transwomen is the development of a female breast. Our data confirm the results of a recent prospective study showing an only moderate effect of hormone therapy in general and a significant increment in breast-chest difference only within the first year of therapy (22). The vast majority (87.1%) of our transwomen did not reach a breast-chest difference corresponding to a bra cup size A, a result very similar to that of the prospective study mentioned (22). Breast shape determined by Tanner stages showed a significant progress even 3–4 years after onset of hormone therapy in our cohort. In accordance to previous studies (22, 23), we could not find any correlation between breast development and estradiol levels measured. However, regarding the level of Tanner stage, we observed a significant negative correlation between testosterone levels as well as FAI. Therefore, an efficient suppression of androgens to the normal female range seems to have an impact on breast development in transwomen.

The results of our study indicate that the risk for adverse metabolic side effects of GAHT is low under professional treatment using modern therapy regimes. Former studies observed an unfavourable change of serum lipids therapy especially in transmen (3, 15, 16, 17), raising the question of a potentially increased cardiovascular risk under testosterone treatment (9, 24). In transwomen an increase of triglycerides has been reported (15, 16, 18). Using a therapy according to latest guidelines, we observed an alignment of blood lipids to the specific reference range of required gender in transmen as well as in tranwomen. A similar effect was seen regarding liver enzymes. Whereas a former study including individuals under therapy with ethinyl estradiol and higher doses of antiandrogens in transwomen as well as oral testosterone formulations in transmen that revealed an at least moderate increase of liver enzymes in about 10–15% of individuals (6), we observe rather an adaption of liver enzymes to the reference range of the affirmed gender in both groups. Relevant elevations of liver enzymes to more than two times of the upper limit of the reference range are rare and transient in most cases. Similar results were seen in prospective studies with small cohorts using modern therapy regimes (18, 25, 26).

The most frequent side effect in our cohort of transmen was predominantly mild acne, comparable to former investigations (27, 28). An erythrocytosis was observed in up to 5.6% (defined as a haemoglobin level above the upper limit of the reference value) respectively 14.3% (defined as a haematocrit above the upper limit of the reference value) of our individuals with raising frequency over time. Interestingly, a correlation to supraphysiological testosterone levels could not be seen in our cohort; yet, testosterone doses were adapted if serum levels increased to the upper normal range under treatment. Again, elder studies reported higher rates of erythrocytosis (8), whereas current data indicate a decline under modern therapy regimes (29). Nevertheless, this serious side effect should be considered notably in the long-time follow-up of virilizing hormone therapy.

Venous thrombembolisms remain serious adverse events of feminizing hormone therapy in transwomen, especially in individuals with additional risk factors like higher age, obesity, smoking and in the context of gender-affirming surgery. In comparison to incidences reported under meanwhile obsolete therapies including ethinyl estradiol (6, 7), a decline can be observed under modern therapy regimes (14, 30, 31), as well as in our study.

Our data, raised in a valid cohort of gender dysphoric individuals, confirm a decreasing risk of side effects using a modern, guideline-based GAHT. Especially, incidences like metabolic side effects and erythrocytosis in transmen and venous thrombembolisms in transwomen are impressively declining compared to former data.

GAHT in accordance with current clinical practice guidelines can be designated as efficient and safe.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

1 Orentreich N & Durr NP. Proceedings: mammogenesis in transsexuals. *Journal of Investigative Dermatology* 1974 **63** 142–146. (https://doi.org/10.1111/1523-1747.ep12678272)

2 Meyer 3rd WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B & Walker PA. Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Archives of Sexual Behavior* 1986 **15** 121–138. (https://doi.org/10.1007/bf01542220)

3 Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S & Meriggiola MC. Effects of three different testosterone formulations in female-to-male transsexual persons. *Journal of Sexual Medicine* 2014 **11** 3002–3011. (https://doi.org/10.1111/jsm.12698)

4 Mueller A, Haeberle L, Zollver H, Claassen T, Kronawitter D, Oppelt PG, Cupisti S, Beckmann MW & Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *Journal of Sexual Medicine* 2010 **7** 3190–3198. (https://doi.org/10.1111/j.1743-6109.2010.01912.x)

5 Wiepjes CM, Nota NM, de Blok CJM, Klaver M, de Vries ALC, Wensing-Kruger SA, de Jongh RT, Bouman MB, Steensma TD, Cohen-Kettenis P *et al*. The Amsterdam cohort of gender Dysphoria Study (1972–2015): trends in prevalence, treatment, and regrets. *Journal of Sexual Medicine* 2018 **15** 582–590. (https://doi.org/10.1016/j.jsxm.2018.01.016)

6 van Kesteren PJM, Asscheman H, Megens JAJ & Gooren LJG. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clinical Endocrinology* 1997 **47** 337–342. (https://doi.org/10.1046/j.1365-2265.1997.2601068.x)

7 Asscheman H, Gooren LJG & Eklund PLE. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. *Metabolism: Clinical and Experimental* 1989 **38** 869–873. (https://doi.org/10.1016/0026-0495(89)90233-3)

8 Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G & T'Sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. *Journal of Sexual Medicine* 2012 **9** 2641–2651. (https://doi.org/10.1111/j.1743-6109.2012.02876.x)

9 Getahun D, Nash R, Flanders WD, Baird TC, Becerra-Culqui TA, Cromwell L, Hunkeler E, Lash TL, Millman A, Quinn VP *et al*. Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. *Annals of Internal Medicine* 2018 **169** 205–213. (https://doi.org/10.7326/M17-2785)

10 Moore E, Wisniewski A & Dobs A. Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 3467–3473. (https://doi.org/10.1210/jc.2002-021967)

11 Elamin MB, Garcia MZ, Murad MH, Erwin PJ & Montori VM. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clinical Endocrinology* 2010 **72** 1–10. (https://doi.org/10.1111/j.1365-2265.2009.03632.x)

12 Seal LJ. A review of the physical and metabolic effects of cross-sex hormonal therapy in the treatment of gender dysphoria. *Annals of Clinical Biochemistry* 2016 **53** 10–20. (https://doi.org/10.1177/0004563215587763)

13 Velho I, Fighera TM, Ziegelmann PK & Spritzer PM. Effects of testosterone therapy on BMI, blood pressure, and laboratory profile of transgender men: a systematic review. *Andrology* 2017 **5** 881–888. (https://doi.org/10.1111/andr.12382)

14 Defreyne J, Van de Bruaene LDL, Rietzschel E, Van Schuylenbergh J & T'Sjoen GGR. Effects of gender-affirming hormones on lipid, metabolic, and cardiac surrogate blood markers in transgender persons. *Clinical Chemistry* 2019 **65** 119–134. (https://doi.org/10.1373/clinchem.2018.288241)

15 Gooren LJ & Giltay EJ. Men and women, so different, so similar: observations from cross-sex hormone treatment of transsexual subjects. *Andrologia* 2014 **46** 570–575. (https://doi.org/10.1111/and.12111)

16 Deutsch MB, Bhakri V & Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. *Obstetrics and Gynecology* 2015 **125** 605–610. (https://doi.org/10.1097/AOG.0000000000000692)

17 Goh HH, Loke DFM & Ratnam SS. The impact of long-term testosterone replacement therapy on lipid and lipoprotein profiles in women. *Maturitas* 1995 **21** 65–70. (https://doi.org/10.1016/0378-5122(94)00861-z)

18 Wierckx K, Van Caenegem E, Schreiner T, Haraldsen I, Fisher AD, Toye K, Kaufman JM & T'Sjoen G. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. *Journal of Sexual Medicine* 2014 **11** 1999–2011. (https://doi.org/10.1111/jsm.12571)
19 Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, Cuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ *et al*. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *International Journal of Transgenderism* 2012 **13** 165–232. (https://doi.org/10.1080/15532739.2011.700873)
20 Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer 3rd WJ, Spack NP, Tangpricha V, Montori VM & Endocrine Society. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 3132–3154. (https://doi.org/10.1210/jc.2009-0345)
21 Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V & T'Sjoen GG. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 3869–3903. (https://doi.org/10.1210/jc.2017-01658)
22 De Blok CJM, Klaver M, Wiepjes CM, Nota NM, Heijboer AC, Fisher AD, Schreiner T, T'Sjoen G & Den Heijer M. Breast development in transwomen after 1 year of cross-sex hormone therapy: results of a prospective multicenter study. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 532–538. (https://doi.org/10.1210/jc.2017-01927)
23 Wierckx K, Gooren L & T'Sjoen G. Clinical review: breast development in trans women receiving cross-sex hormones. *Journal of Sexual Medicine* 2014 **11** 1240–1247. (https://doi.org/10.1111/jsm.12487)
24 Nota NM, Wiepjes CM, De Blok CJM, Gooren LJG, Kreukels BPC & Den Heijer M. Occurrence of acute cardiovascular events in transgender individuals receiving hormone therapy. *Circulation* 2019 **139** 1461–1462. (https://doi.org/10.1161/CIRCULATIONAHA.118.038584)
25 Mueller A, Kiesewetter F, Binder H, Beckmann MW & Dittrich R. Long-term administration of testosterone undecanoate every 3 months for testosterone supplementation in female-to-male transsexuals. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 3470–3475. (https://doi.org/10.1210/jc.2007-0746)
26 Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann MW & Mueller A. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. *Experimental and Clinical Endocrinology and Diabetes* 2005 **113** 586–592. (https://doi.org/10.1055/s-2005-865900)
27 Giltay EJ & Gooren LJG. Effects of sex steroid deprivation/administration on hair growth and skin sebum production in transsexual males and females. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 2913–2921. (https://doi.org/10.1210/jcem.85.8.6710)
28 Wierckx K, Van de Peer F, Verhaeghe E, Dedecker D, Van Caenegem E, Toye K, Kaufman JM &T'Sjoen G. Short- and long-term clinical skin effects of testosterone treatment in trans men. *Journal of Sexual Medicine* 2014 **11** 222–229. (https://doi.org/10.1111/jsm.12366)
29 Defreyne J, Vantomme B, Van Caenegem E, Wierckx K, De Blok CJM, Klaver M, Nota NM, Van Dijk D, Wiepjes CM, Den Heijer M *et al*. Prospective evaluation of hematocrit in gender-affirming hormone treatment: results from European Network for the investigation of gender incongruence. *Andrology* 2018 **6** 446–454. (https://doi.org/10.1111/andr.12485)
30 Arnold JD, Sarkodie EP, Coleman ME & Goldstein DA. Incidence of venous thromboembolism in transgender women receiving oral estradiol. *Journal of Sexual Medicine* 2016 **13** 1773–1777. (https://doi.org/10.1016/j.jsxm.2016.09.001)
31 Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola MC, Mueller A, Kuhn A, Dhejne C, Morel-Journel N & Gooren LJ. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia* 2014 **46** 791–795. (https://doi.org/10.1111/and.12150)

Received 21 June 2019
Revised version received 12 November 2019
Accepted 15 November 2019