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Hot flushes in prostatic cancer patients during androgen deprivation therapy with monthly degarelix or leuprolide

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Short title: Hot flushes in men during ADT

ABSTRACT

The aim of the study was to compare the onset, incidence, and frequency/intensity of hot flushes during androgen deprivation therapy with a GnRH blocker versus an agonist using data from a randomized Phase 3 clinical trial. Six hundred ten prostate cancer patients received monthly degarelix (sc, 240 mg/80 mg, n=207, or 240/160 mg, n=202) or leuprolide (im, 7.5 mg, n=201) for 12 months. Data on hot flushes was collected as self-reported adverse events and in a subgroup of 254 patients with electronic diaries. The onset of hot flushes was faster on degarelix versus leuprolide and was accompanied by higher median hot flush scores during the first 3 months. However, there were no significant differences in overall incidence rates and median hot flush scores over the entire 12 months. Beyond the third month incidence rates dropped below 6%, whilst prevalence rates remained constant in all 3 treatment arms. In multivariate analysis, body weight and heart rate at baseline were independent predictors of hot flushes ($p < 0.05$). Except for a more rapid onset with the GnRH antagonist, there were no major differences in the overall pattern of hot flushes between treatment options. Weight control may help to minimise the incidence of hot flushes.

Keywords: Hot flushes, testosterone, degarelix, leuprolide, modifiable risk factors

INTRODUCTION

Androgen deprivation therapy (ADT) is the mainstay treatment of advanced prostate cancer (PCa) (1). GnRH agonists are currently the standard medical therapy to suppress androgen production (2). These agents initially bring about strong stimulation of GnRH receptors, which in turn results in an initial surge of testosterone, and microsurgers upon repeated injections (3,4). In contrast, GnRH blockers (antagonists) immediately block pituitary GnRH receptors, thereby causing rapid and pronounced testosterone suppression devoid of the initial surge and subsequent microsurgers (5,6). These differences in the mechanism of action warrant further exploration with respect to the onset, incidence, and severity of their ADT-related side effects.

Vasomotor symptoms have been reported as common adverse effects of ADT, but the variation in their reported incidence has been large, ranging from 3 to 100% (7-9). Hot flushes in men have received little attention in the medical literature, possibly because these events were initially considered as infrequent, transitory, and of little bother to the patient. However, according to some reports up to 27% of men experiencing hot flushes reports these as the most debilitating treatment-related side effect (10-12). Since this side effect can pose long-lasting impairment of quality of life (13), it may also impact on patients' compliance and ultimately on the overall efficacy of ADT.

When considering different alternatives of ADT, it is important to know whether the onset, frequency, and severity of hot flushes differ depending on the choice. In this context, the faster and somewhat more pronounced direct effect of GnRH blockers on the cognate receptors and thereby on serum testosterone may theoretically pose an increased risk for hot flushes as compared with the slower action of agonists. Although the Phase 3 pivotal trials of abarelix were leuprolide-controlled, no details on hot flushes have been reported (14-16). **From the leuprolide-controlled pivotal Phase 3 trial**

of degarelix, including 610 patients treated with these agents for 12 months, only the elementary safety data, including overall incidence rates of hot flushes, has been reported (17). In the present study, we have undertaken a more focused and elaborate analysis of hot flushes and compared the speed of onset, overall and quarterly incidence rates, frequencies and severities (hot flush scores) during the 12-month treatment period. In addition, we attempted to identify subpopulations with increased risk for hot flushes by investigating associations between baseline patient characteristics and hot flushes. Importantly, while the pivotal trial investigated two dosing regimens of degarelix, only the lower dose (240/80 mg) became approved by both FDA and EMA for the treatment of advanced prostate cancer (18).

PATIENTS AND METHODS

Subjects and treatment

The trial design and the patient population have been previously described in detail (17). Patients were randomly allocated to receive treatment with either degarelix using a starting dose of 240 mg followed by monthly maintenance doses of either 80 mg (240/80 mg, n=207) or 160 mg (240/160 mg, n=202), or with leuprolide 7.5 mg monthly (n=201). Concomitant short anti-androgen therapy could be given to patients in the leuprolide group for flare protection at the discretion of the investigator, and 22 patients received such supplementary therapy in the beginning of the trial.

The trial was performed in accordance with the Declaration of Helsinki II and Good Clinical Practice Guidelines. The study protocol was approved by independent Ethics Committees and institutional review boards.

Baseline characteristics

Baseline characterization included data on age, race, body weight and height, blood pressure and heart rate, the ECOG performance score, serum levels of FSH, LH, testosterone, and PSA, medical history and concomitant medications.

Reporting of hot flushes

Patient informed consents informed participants about the possible risk of hot flushes during the therapy. Hot flushes were collected as patient-reported adverse events to standard non-leading question of "How have you been since the last visit" on Day 1, 3, 7, 14, 28 and monthly thereafter. Targeted prospective assessment of hot flushes was undertaken in a subgroup of 254 patients; 89 in the degarelix 240/80 mg, 74 in the degarelix 240/160 mg, and 89 in the leuprolide arm (50 patients per arm is

recommended for Phase 3 trials (19)). These patients were equipped with a hot flushes diary developed and validated by the North Central Cancer Treatment Group and Mayo Clinic (20). This instrument collected data on a patient's daily assessment of hot flush frequency and severity (rated on a scale from 1='mild' to 4='very severe') enabling calculation of a daily hot flush score as frequency multiplied by severity (19). Within each time period the mean number of hot flushes or average hot flush score for each patient is used for calculating the treatment group summaries. This diary has been used in over 1,700 patients in ten randomised controlled trials and analysis of data from 968 patients has provided evidence of its validity and reliability (19). A validated eDiary was used to transfer the information from the hot flush diary to database.

Statistical methods

Demographic and other baseline characteristics, annual incidence and quarterly incidence and prevalence rates and the daily hot flush score are summarized descriptively. Onset of hot flushes addressed by comparing incidence rates to the first dose of leuprolide or degarelix was done by conventional two-sided Fisher Exact test. Trend tests of hot flushes across tertiles of the continuous covariates were carried out using the partial likelihood ratio test for the log hazard ratio. The Pearson-correlation coefficients between testosterone and both body weight and BMI at baseline were assessed, and corresponding t-test for association was performed. Independent predictors of hot flushes were explored by a Cox proportional hazard model. A similar model for time to castration was used to investigate whether explanatory baseline characteristics for increased hot flush incidence also yielded faster testosterone suppression. The significance level in all performed analyses was conventional $\alpha=0.05$ level.

RESULTS

Baseline characteristics

The comparable baseline characteristics of the patient population stratified according to treatment arms are illustrated by Table 1.

Daily hot flush score

The median daily number of hot flushes (Fig. 1, upper) and the median daily hot flush scores (Fig. 1, lower) had in general low values when summarized for the different time periods. During Days 1-28 and 29-84, the median numbers of hot flushes and the daily hot flush scores were higher in degarelix versus leuprolide-treated patients, in line with the more rapid suppression of testosterone by the GnRH blocker. **Of the 22 leuprolide-treated patients that received antiandrogens for flare protection, 11 had e-Diary reporting and their scores were statistically not different from those taking leuprolide without antiandrogens.** Subsequently, degarelix-treated patients seemed to reach a plateau, whereas leuprolide-treated patients tended to display increases in both scores. However, over the whole treatment period (Days 1-364), median scores were comparable between the three treatment arms.

The majority of reported events were mild or moderate, with only very few patients (n=6) reporting severe hot flushes. **Eight patients received some form of medical treatment for their hot flushes.** There were only two patients who chose to discontinue medication due to the burden of hot flushes; one in the degarelix 240/160 mg and another in the leuprolide 7.5 mg treatment arm.

Incidence rates of hot flush (yes/no) obtained by e-Diary vs. non-leading question

As highlighted by Fig.1, the incidence rates of hot flushes were comparable when collecting this qualitative information by a simple non-leading question (after warning patients for this potential AE) or a more sophisticated and quantitative e-Diary. For this reason, the following analysis, using hot flushes as a discriminative variable only, (yes/no) are conducted based on the total population.

Annual and periodic incidence and prevalence rates of hot flushes

The annual incidence was numerically but not significantly higher in the degarelix 240/80 mg (27%, $p=0.15$) and degarelix 240/160 mg (25%, $p=0.56$) groups compared with the leuprolide group (21%).

During the first month, more degarelix-treated patients reported hot flushes compared with leuprolide-treated patients (14.9% vs. 8.5%, $p<0.05$). The earlier rise of hot flushes in degarelix-treated patients is illustrated graphically in Fig. 2. Incidence during the first 3 months were identical (17%) in the degarelix 240/80 mg and the leuprolide groups, and slightly higher (22%, $p>0.1$) in the degarelix 240/160 mg group.

Only a few patients reported the start of hot flushes beyond the third month of therapy (Fig. 3, upper panel), whilst prevalence rates remained sustained (Fig. 3, lower panel), indicating that hot flushes were largely confined to a subpopulation.

Association with patient characteristics at baseline

Incidence rates of hot flushes were not associated with age, smoking habits, ECOG score, serum testosterone, LH or FSH at baseline (Table 2). However, hot flushes were more frequent in regular drinkers compared with never-drinkers, but the differences did not reach statistical significance. In contrast, body weight at baseline and the incidence of hot flushes showed a significant association ($P=0.03$); hot flushes were more frequent among patients with higher body weights. Interestingly, in corresponding

tertiles, incidence rates were consistently higher in degarelix versus leuprolide-treated patients. Moreover, when using BMI - a more accurate surrogate of obesity - the trend remained significant for degarelix ($p=0.03$), but not for leuprolide ($P=0.23$).

We found consistent negative association between heart rate at baseline and the incidence of hot flushes ($P=0.04$).

Of the two variables, heart rate showed no significant correlation either with baseline testosterone levels ($r=-0.064$, $p=0.11$) or with the velocity of reaching castration level (data not shown). Neither did the heart rate show any significant changes in any of the treatment arms at any time point during therapy. **Furthermore, the association could not be attributed to the use of β -blockers ($n=120$), as Kaplan-Meier plots of hot flushes stratified according to the use of β -blockers did not indicate statistically significant differences in incidence rates, which observation was true both for degarelix (log-rank $p=0.44$) and leuprolide-treated patients (log-rank $p=0.95$).**

In contrast, body weight as well as BMI were both negatively associated with baseline testosterone levels ($r=-0.21$, $P<0.0001$). In addition, there were numerically more patients reaching castration levels in the highest tertile (Table 3), suggesting faster castration effect in overweight/obese patients.

Independent predictors of hot flushes

In a multivariate model, heart rate and body weight at baseline remained independent predictors of hot flushes (Table 4). Concretely, a 12 beats per minute (inter-quartile range) increase in heart rate was associated with a 20% lower risk and a 16.2 kg (inter-quartile range) increase in weight was associated with 23% higher risk of hot flushes. According to the model, there were no significant differences in the relative risk of hot flushes between the two different doses of degarelix and leuprolide.

DISCUSSION

This is the first report providing a detailed comparison of hot flushes induced by a GnRH blocker versus an agonist in a large randomized trial. The main findings were as follows: 1) In the early phase of the treatment, median number of hot flushes and daily hot flush scores were higher in degarelix versus leuprolide-treated patients – in line with the more rapid suppression of testosterone by the GnRH antagonist (17) - no differences were noted in overall median scores (Day 1-364), 2) Although the onset of hot flushes was significantly faster upon degarelix treatment, the quarterly incidence rates accompanying leuprolide and the approved dose of degarelix were comparable, 3) Hot flushes were mild/moderate in intensity, 4) Those that had not experienced hot flushes during the first 3 months of therapy had very low risk of facing this side effect thereafter, 5) Of the different baseline characteristics addressed, low heart rate and high body weight were the main independent predictors of hot flushes.

A literature review on hot flushes in PCa patients treated with GnRH agonists reveals a large variability in incidence rates. Four randomized clinical trials reviewed by Spetz et al (7) found an average incidence rate of 42%, but ranging from 12% to 65%. A similar very broad range of incidence rates (3% to 100%) was reported in surgically castrated patients (7). Likely reasons for the large variability include differences in the demographic characteristics of patient populations, cultural differences in the reporting of adverse events, and differences in data collection (24,25). In our study, incidence rates fall in the middle of the range seen with GnRH agonists and was comparable whether collected by a non-leading question or the electronic hot flush diary.

Prevalence rates of hot flushes were fairly sustained throughout the treatment period regardless of the therapy given, suggesting a subpopulation of men being

susceptible to this side-effect and experiencing it for a prolonged time. In a retrospective study (13) 68% of the subjects reported hot flushes following castration treatment, which was still 48% 5 years later, and 40% 8 years later. Most of these men reported that their current symptoms had the same frequency and duration as when they started. Collectively, these observations emphasize that in risk patients, hot flushes may be a long-lasting bystander of ADT and therefore the issue deserves due attention by treating physicians.

Our analysis identified a significant association between incidence rate of hot flushes and patients' body weight at baseline. In men, overweight/obesity is predominantly manifesting in central fat deposition. Interestingly, women with predominant abdominal obesity are also more likely to report hot flushes during the rapid decreases of circulating estrogens accompanying the menopause (29). The current observations suggest that the explanation to the higher incidence of hot flushes in patients with overweight/obesity lies in a combination of having lower circulating testosterone levels and a higher velocity of testosterone suppression (30). **This is in line with the currently held notion that the velocity of testosterone suppression has a greater impact on the thermoregulatory centre than the absolute level of the hormone (8).**

Another apparently independent predictor of hot flushes was the heart rate. The negative association of heart rate with hot flushes did not involve testosterone (or use of β -blockers), but was due to another confounding factor not addressed in the present study. Thyroid dysfunction may influence the propagation of hot flushes (31,32). Øverlie et al (33) found that during the menopause high level of TSH (as a result of decreased thyroid function) is associated with vasomotor complaints. Thyroid hormones are modulators of the heart rate; lower thyroid function in the elderly, particularly if combined with coronary conditions may be accompanied by a 10-20 beats per minute

slower heart rate compared with normal conditions. In our study population, the incidence of manifest hypothyreosis was low (<3%) but about one quarter of the patients in each arm had manifest ischemic heart disease. Although we did not measure thyroid and thyrotropic hormones, it seems reasonable to speculate that the negative association between heart rate and the risk of hot flushes could reflect subclinical hypothyreosis of the elderly, which in turn can influence the function of the thermoregulatory zone via increased TSH levels. Further investigations are needed to verify this plausible hypothesis.

In summary, hot flushes, although relatively common, pose only mild to moderate bother to patients undergoing ADT. Although the higher velocity of testosterone suppression with degarelix seems to play a role in the faster onset and greater frequency/severity of hot flushes in the early phase, the overall incidence rate and hot flush score generated by degarelix and leuprolide were comparable. Since hot flushes seem to pose a long-lasting side effect of ADT in an affected subpopulation of patients, their thorough characterization is warranted to better understand the modifiable risk factors involved. Our initial efforts highlight body weight and to a lesser extent alcohol consumption as modifiable risk factors, which, if adequately controlled, may diminish the bother of hot flushes during ADT.

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CONFLICT OF INTEREST

The authors have no competing financial interest in relation to the manuscript. Drs. Karup, van der Meulen, and Tankó are full-time employees of Ferring Pharmaceuticals.

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TABLES

Table 1. Baseline characteristics of the patient population stratified into treatment groups.

	Degarelix 240/80 mg (n=202)	Degarelix 240/160 mg (n=207)	Leuprolide 7.5 mg (n=201)
Age (years)	71.6 (8.1)	72.1 (8.4)	72.5 (8.8)
Body height (m)	1.73 (0.06)	1.72 (0.07)	1.72 (0.07)
Body weight (kg)	79.8 (14.9)	78.7 (13.0)	78.4 (12.2)
Body mass index (kg/m²)	26.7 (4.2)	26.6 (3.7)	26.9 (3.9)
Blood pressure (mmHg)			
Systolic	135 (17)	136 (17)	135 (16)
Diastolic	77 (9)	78 (10)	78 (10)
Heart rate (bps)	70 (9)	71 (10)	71 (10)
Alcohol	118 (57%)	106 (52%)	106 (53%)
Smoking	27 (13%)	25 (12%)	27 (13%)
Hypertension	111 (54%)	106 (52%)	101 (50%)
Diabetes mellitus type 2	31 (15%)	20 (10%)	22 (11%)
Ischemic heart disease	52 (26%)	58 (28%)	51 (25%)
Hypercholesterolemia	35 (17%)	27 (13%)	33 (16%)
ECOG score			
Fully active	158 (76%)	143 (71%)	148 (74%)
Restricted	37 (18%)	48 (24%)	42 (21%)
Unable to work	12 (6%)	11 (5%)	11 (5%)
Testosterone (ng/ml)	4.34 (1.77)	4.02 (1.70)	4.05 (1.65)
FSH (IU/L)	11.4 (11.1)	12.6 (13.3)	13.2 (13.4)
LH (IU/L)	7.12 (4.51)	7.69 (7.53)	7.85 (5.95)
PSA (pg/ml)	112 (375)	268 (1345)	218 (903)

Numbers are mean (SD) or number of patients (%).

Table 2. Incidence of hot flushes according to tertiles (T) of baseline parameters of interest

TERTILES OF	Degarelix-treated patients (n=409)			Leuprolide-treated patients (n=201)			p
	T1	T2	T3	T1	T2	T3	
Age	27 % 38/142	29 % 40/137	22 % 28/130	18 % 11/61	23 % 15/66	24 % 18/74	NS
Weight	21 % 30/141	27 % 37/136	30 % 39/132	13 % 8/62	25 % 17/67	26 % 19/72	0.03
BMI	23% 32/140	25% 34/135	30% 40/134	25% 16/63	21% 14/68	20% 14/70	0.04 *
Heart rate	32 % 44/136	23 % 32/137	22% 30/136	31 % 21/67	15 % 10/66	19 % 13/68	0.04
Testosterone	26 % 34/132	25 % 34/135	27 % 39/132	20 % 14/71	21 % 14/68	26 % 16/62	NS
LH	23 % 33/141	31 % 42/135	23 % 31/133	21 % 13/62	24 % 16/68	21 % 15/71	NS
FSH	26 % 38/146	29 % 37/129	23 % 31/134	21 % 12/57	19 % 14/74	16 % 18/70	NS
CATEGORIES OF	No	Yes	No	Yes			
Alcohol consumption	21% 39/185	30% 67/224	19% 18/95	25% 26/106	NS		
Smoking	26% 92/357	27% 14/52	22% 38/174	22% 6/27	NS		
ECOG (Unable to work)	26% 77/131	27% 29/108	23% 34/148	19% 10/53	NS		

NS, statistically non-significant (p>0.05)

* for degarelix only

Table 3. Baseline testosterone and incidence of testosterone suppression below castration level (0.5 ng/ml) at Day 1 (degarelix) and Day 14 (leuprolide) in tertiles (T) of baseline body weight

	Tertiles of baseline body weight						p
	Degarelix treated patients (n=409)			Leuprolide treated patients (n=201)			
	T1	T2	T3	T1	T2	T3	
Means ± SD of body weight at baseline	65.4 (5.7)	77.8 (3.4)	94.4 (10.8)	66.8 (5.2)	78.1 (3.6)	92.9 (7.9)	
Means ± SEM of baseline testosterone	4.7 (0.16)	4.0 (0.14)	3.8 (0.13)	4.1 (0.22)	4.3 (0.20)	3.7 (0.18)	<0.001
% with castration (i.e. T<0.5 ng/ml) at Day 1	43% 60/141	49% 67/136	53% 70/132				NS
% with castration (i.e. T<0.5 ng/ml) at Day 14				15% 9/62	15% 10/67	25% 18/72	NS

NS, statistically non-significant ($p>0.05$)

Table 4. Independent predictors of hot flush in prostate cancer patients (Cox proportional hazards model)

	Class level	Reference	HR (95% CI)	P
Heart Rate		per 12 beat/min (IQR)	0.80 (0.65-0.98)	0.038
Weight		per 16.2 kg (IQR)	1.23 (1.02-1.50)	0.030
Treatment	Degarelix 240/80 mg	Leuprolide 7.5 mg	1.33 (0.89-1.98)	0.15
	Dearelix 240/160 mg		1.13 (0.75-1.69)	0.56

Continuous variables standardized per their inter-quartile range (IQR).

Other baseline covariates included in the model were age, height, race, smoking, alcohol consumption, ECOG performance score, testosterone, LH, and FSH. **Use of β -blockers did not affect the hazard ratio and hence was excluded from the multivariate model.**

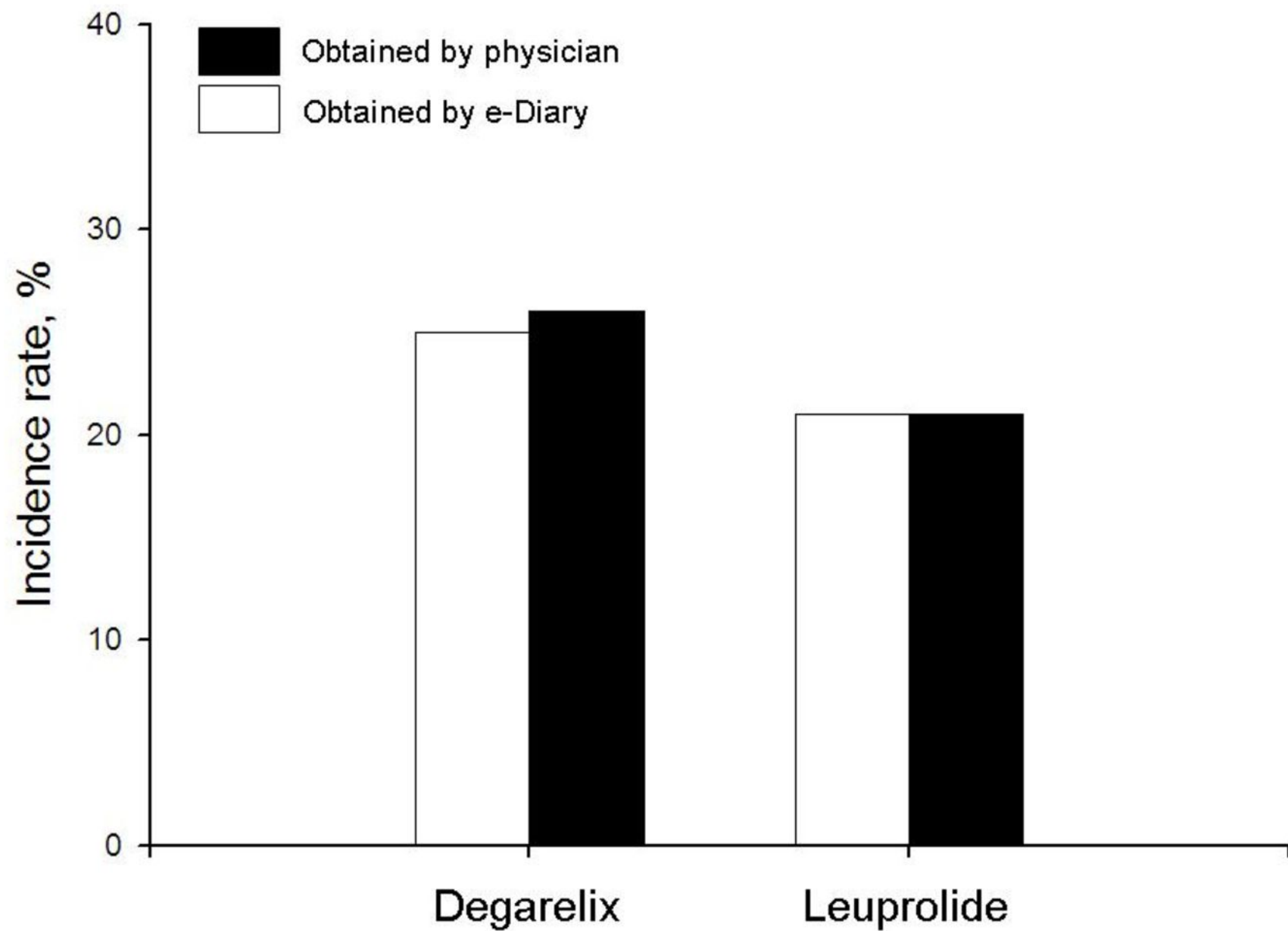
LEGEND TO FIGURES

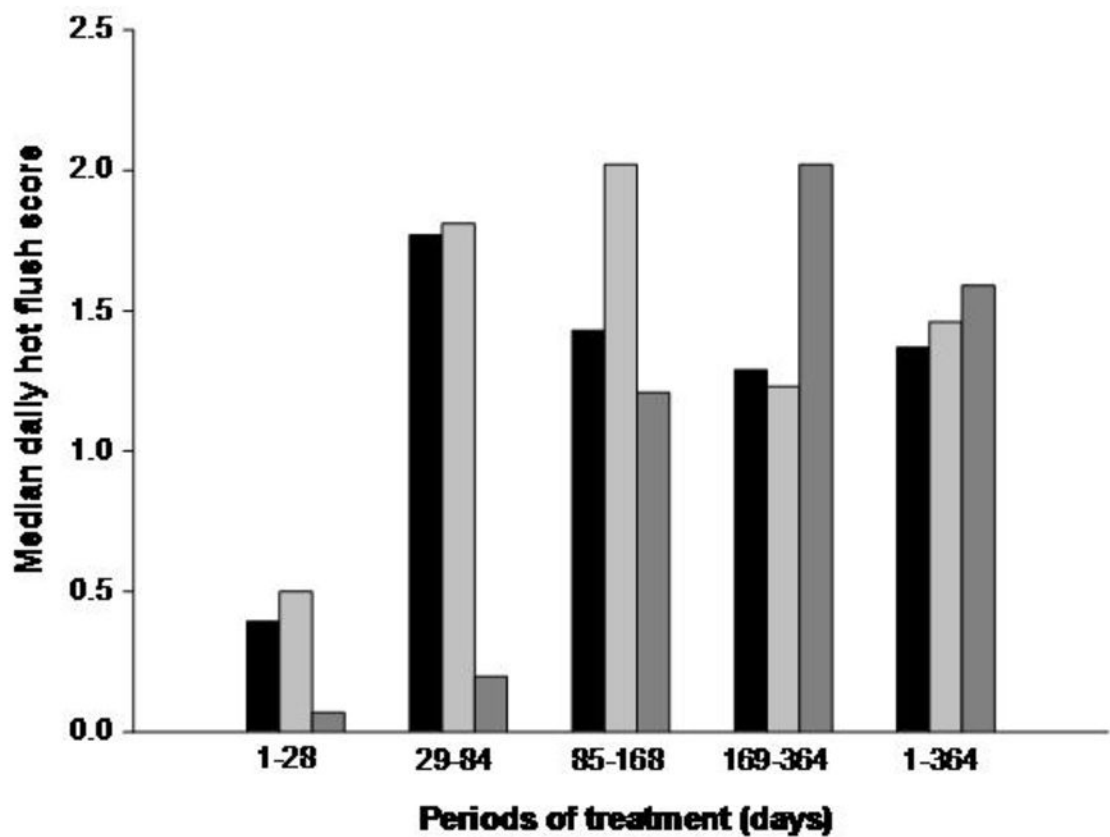
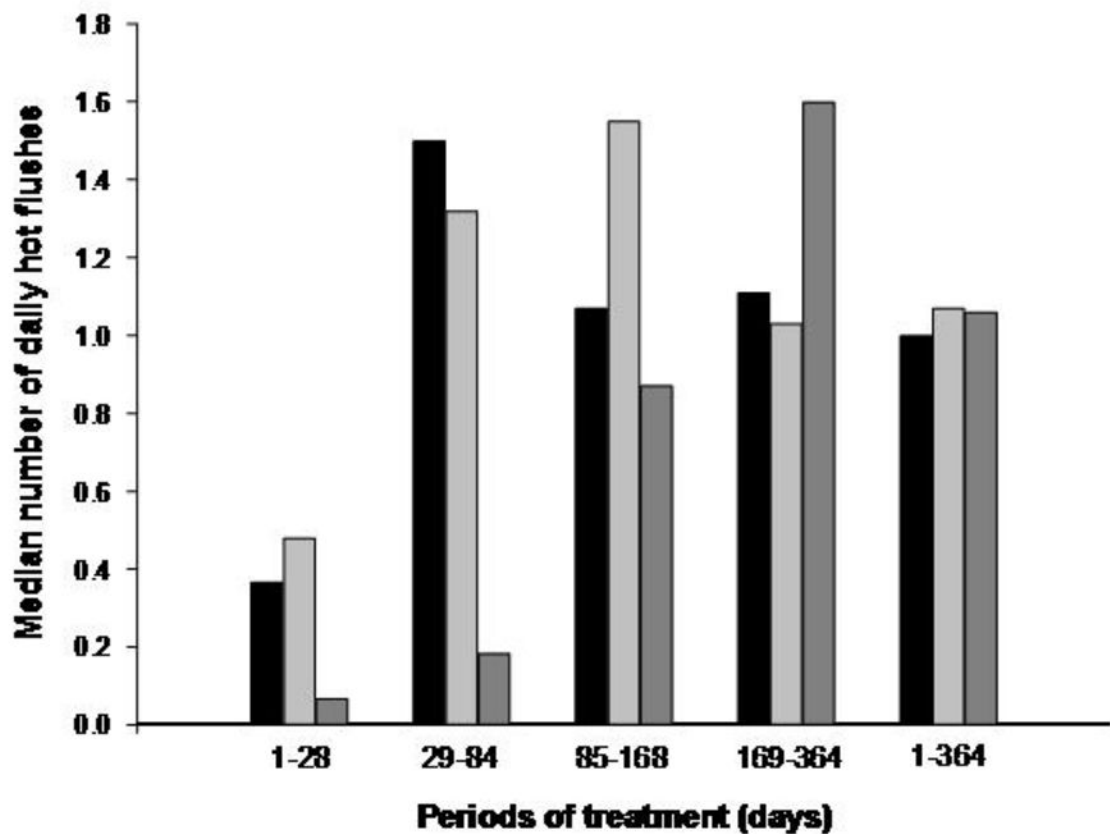
Figure 1. Incidence rate of hot flushes as derived from data collected by electronic hot flush diary and in response to a non-leading question by the treating physician, following information about this possible adverse effect of androgen deprivation therapy in the written informed consent.

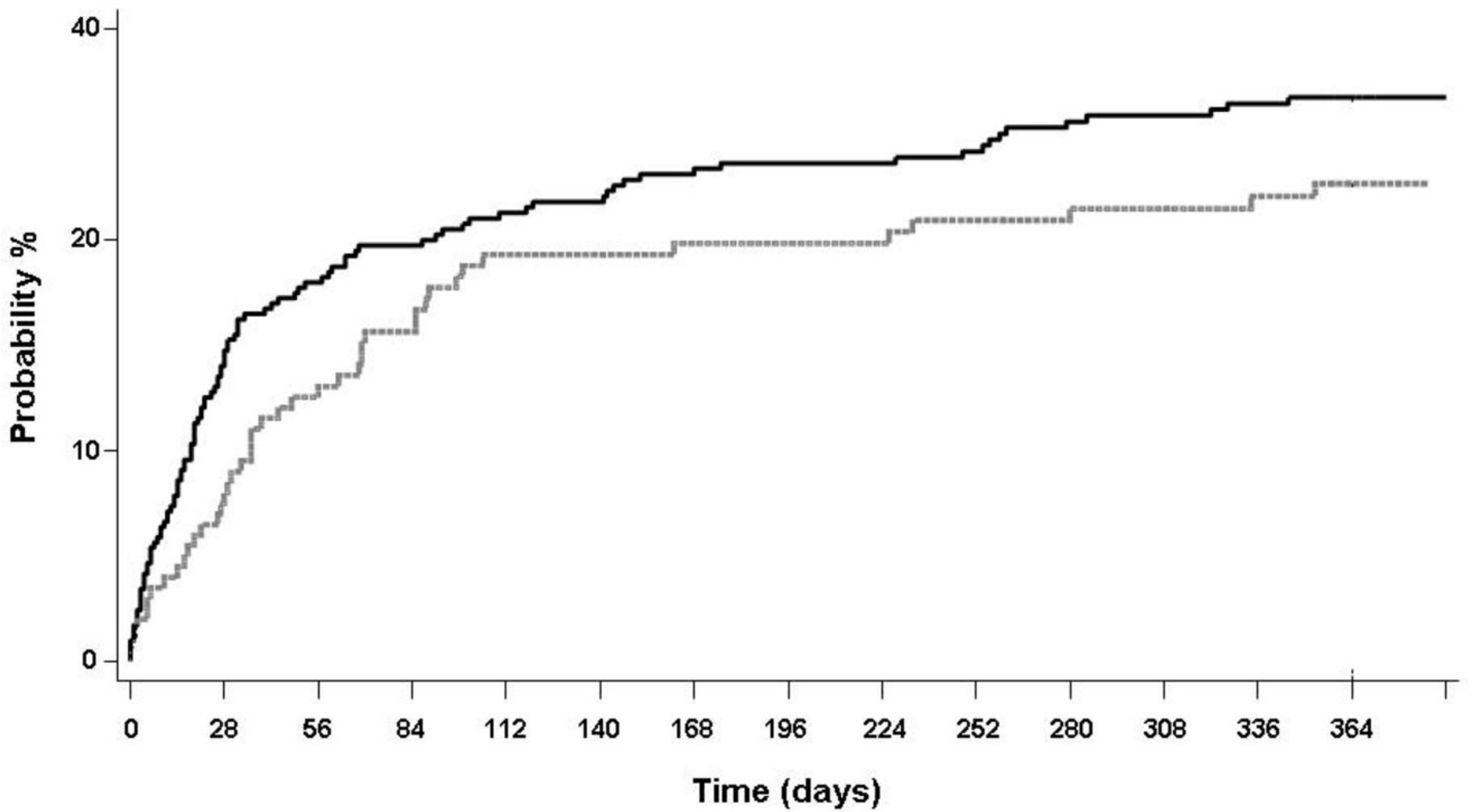
Figure 2. Median number of hot flushes (upper panel) and median daily hot flush score (lower panel) in patients treated with monthly doses of degarelix or leuprolide at different time intervals of the therapy. Black bars indicate degarelix 240/80 mg, light grey bars degarelix 240/160 mg, and the dark grey bars the leuprolide group. Note the higher values in degarelix-treated compared with leuprolide-treated patients in the early phase of the therapy (1-28 and 29-84 days), and the virtually equal values when compared over the entire treatment period (1-364 days).

Figure 3. Kaplan-Meier plots of time to first patient-reported hot flush adverse events in prostate cancer patients receiving androgen deprivation therapy with monthly degarelix (black line) or leuprolide (grey line). Although the onset of hot flushes to the starting dose of degarelix (240 mg) was faster during the first month, overall there were no statistically significant differences in event rates (log-rank $p=0.22$). The numbers below the figure indicate patients at risk as a function of time in the degarelix versus the leuprolide arm.

Figure 4. Incidence (upper panel) and prevalence (lower panel) of self-reported hot flush adverse events in prostate cancer patient treated with monthly leuprolide or degarelix in the four quartiles (each 3 month) of the treatment year. Black bars indicate degarelix 240/80 mg, light grey bars degarelix 240/160 mg, and the dark grey bars the leuprolide group. Differences in incidence and prevalence rates between treatment arms at the different time-points did not reach statistical significance.







Time (days)	Degorelix	Leuprolide 7.5 mg
0	409	201
28	349	184
56	330	173
84	318	162
112	307	162
140	299	154
168	291	151
196	286	150
224	280	147
252	273	145
280	262	142
308	258	138
336	251	133
364	192	92
End	1	

