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Parenteral Estrogen versus Combined Androgen Deprivation in the Treatment of Metastatic Prostatic Cancer

Scandinavian Prostatic Cancer Group (SPCG) Study No. 5

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Objective: In the mid-1980s, interest in parenteral estrogen therapy for prostate cancer was renewed when it was found that it influenced liver metabolism only marginally and had very few cardiovascular side-effects. In this study high-dose polyestradiol phosphate (PEP; Estradurin®) was compared to combined androgen deprivation (CAD) for the treatment of patients with metastatic prostate cancer. The aim of the study was to compare anticancer efficacy and adverse events, especially cardiovascular side-effects.

Material and Methods: A total of 917 patients with T0–4, NX, M1, G1-3 prostate cancer and an Eastern Cooperative Oncology Group performance status of 0–2 were randomized to treatment with either PEP 240 mg i.m. twice a month for 2 months and thereafter once a month or flutamide (Eulexin®) 250 mg t.i.d. per os in combination with either triptorelin (Decapeptyl®) 3.75 mg per month i.m. or, on an optional basis, bilateral orchidectomy. A total of 556 patients had died at the time of this analysis.

Results: There was no difference between the treatment arms in terms of time to biochemical or clinical progression and overall or disease-specific survival. There was no increase in cardiovascular mortality in the PEP arm. The PEP group had a higher prevalence of cardiovascular disease prior to the study and a significantly higher incidence of non-fatal ischemic heart events and heart decompensation during the study.

Conclusions: PEP has an equal anticancer efficacy to CAD and does not increase cardiovascular mortality. Final evaluation of cardiovascular morbidity is awaiting further analysis and follow-up. PEP is considerably cheaper than CAD.

Key words: advanced disease, cardiovascular complications, combined androgen deprivation, hormone treatment, multicenter study, parenteral estrogen, prostate cancer.

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Oral estrogen treatment, once the commonest method for hormone manipulation of prostate cancer in the Nordic countries, was largely abandoned in the 1970s due its significant cardiovascular toxicity. In the mid-1980s, interest in estrogen therapy was renewed when it was found that estrogen administered parenterally did not induce these side-effects. The significant changes in liver metabolism and grave deviations in blood levels of coagulation factors seen after oral therapy were reported to be absent or only marginally present after parenteral therapy (1). Two Finnish studies showed that polyestradiol phosphate (PEP; Estradurin®, Pharmacia AB, Sweden) given at a dose of 160 mg i.m. per month did not lead to higher cardiovascular morbidity or mortality than bilateral orchidectomy (2) or gonadotrophin-releasing hormone analog therapy (3). This dose of PEP did however have

*A complete list of the members of the SPCG-5 study group is given in the Appendix.

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inferior anticancer efficacy, measured in terms of progression-free survival. This may be explained by the fact that 160 mg of PEP per month does not decrease serum testosterone to castration levels (4). In a Swedish pilot study it was found that PEP given at a dose of 240 mg per month decreased serum testosterone to castration levels, and that this was most rapidly achieved by giving PEP 240 mg every second week during the first 2 months (5). In an open study of 40 prostate cancer patients, no increase in cardiovascular toxicity was noted during the first 3 years of this therapy (6).

The aim of the present study was to compare PEP with combined androgen deprivation (CAD), with overall survival as the primary endpoint. Secondary objectives were to compare time to biochemical and clinical progression, cancer-specific survival, cardiovascular toxicity, other adverse events and quality of life. Some data from the first evaluation have previously been published (7). The present paper gives a more comprehensive presentation of the design and initial results.

MATERIAL AND METHODS

Between December 1992 and June 1997, 917 men with hormone-naive, T0–4, NX, M1, G1–3 prostate cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 were randomized to receive treatment with either PEP or CAD. All patients had skeletal metastases as evaluated from bone scans supplemented with X-rays when needed. The primary tumor was staged by means of digital rectal examination according to the TNM classification of 1987 and graded according to the World Health Organization (WHO) system, either as a result of fine-needle aspiration cytology (8) or histologically from transurethral resection of the prostate specimens (9). The extent of bone disease was calculated from pretreatment bone scans according to a modified Soloway score as follows: score 1, the total area of hot spots is less than three bodies of a lumbar vertebra; score 2, the total area of hot spots is larger than that of score 1, but <75% of the total scan; and score 3, superscan (10).

Exclusion criteria were as follows: patients who had received previous systemic treatment for prostate cancer or with a malignancy of any other kind, with the exception of basal cell carcinoma of the skin; patients who had suffered myocardial or cerebral infarction $\leq$1 month before the start of the study; patients with previous or current liver disease with a bilirubin or alanine aminotransferase value above the upper limit of normal; and patients who it was felt would not be able to comply with the study protocol. The patients were given oral and written information about the study and gave their oral consent to participate.

Patients were stratified according to country (with Iceland being included in the Norwegian group), ECOG performance status 0–1 vs 2, alkaline phosphatase level under or over 1.25$\times$ the upper limit of normal and whether or not they had a previous or current history of cardiovascular disease. Randomization was done by the Oncologic Center of the Karolinska Hospital, Stockholm, at which the eligibility of the patients was initially checked. Patients were allocated to treatment according to their position on the stratification list.

Polyestradiol phosphate (Estradurin) was given as i.m. injections of 240 mg twice a month for 2 months (total of five doses), and thereafter once every month. CAD was given as flutamide tablets (Eulexin®, Schering-Plough AB, Stockholm, Sweden), 250 mg t.i.d., in combination with either triptorelin (Decapeptyl®, Ferring AB, Malmö, Sweden), 3.75 mg i.m. per month, or, on an optional basis, bilateral orchidectomy. Flutamide treatment was started 1 week before the first triptorelin injection. Irradiation of the breasts prior to therapy was optional.

The patients were followed by visits to the trialist 1, 3 and 6 months after the start of the study and thereafter every 6 months until clinical progression was clearly established. Between these visits, prostate-specific antigen (PSA) values were determined in every patient, so that the PSA was measured every 3 months. If required, patients could request more detailed examinations. At every visit patients were questioned and evaluated with regard to symptoms or signs of disease progression and adverse events. Blood pressure, body weight, performance status and pain and analgesic scores (see Table II) were noted and levels of hemoglobin, creatinine, PSA and liver enzymes, including alkaline phosphatase, were measured. Digital rectal examination, bone scan or X-rays were not done regularly and only if considered necessary for evaluation of the disease status. The evaluation of clinical progression was based on clinical signs and symptoms. When clinical progression was definitively established, treatment and follow-up of the patient were at the discretion of the individual trialist. The time and cause of death were recorded.

Monitoring was done by research nurses or monitoring specialists by means of visits to the trialist at least once a year for the first 5 years. After the fifth year, monitoring was done only by means of telephone conversations and correspondence. Some centers with many patients in the study were monitored more closely. To check compliance with medication the patients had to bring their empty vials of Eulexin at their visits to the trialist and charts were also kept on

which the nurses noted all injections of Estradurin or Decapeptyl. A statement from the trialist regarding compliance was included in the case report form (CRF) for clinical progression.

Definition and analysis of endpoints

Time to biochemical progression was calculated from randomization to the time when the first rise in PSA was observed, followed by a continuous rise in consecutive measurements. Time to clinical progression was defined as the time from randomization to the first suspicion of clinical deterioration of the disease, which could be supported by further clinical deterioration in consecutive evaluations. Clinical deterioration was thus based on symptoms, most commonly pain or decreased performance status, but also in a few cases on micturition problems, lymph edema or uremia. The evaluation of biochemical and clinical progression was done according to the retrospective sequential method (11). Overall survival was the time from randomization to death from any cause. Analysis of cancer-specific survival included deaths from prostate cancer or deaths from another disease with significant contribution to the prostatic malignancy, i.e. in these patients clinical progression had occurred before death (11).

Evaluation of adverse events

Strict criteria for different cardiovascular events were established as follows.

Heart decompensation. Signs of pulmonary crepitations or rales, stasis of pulmonary vessels on X-ray or a third heart sound should be registered. Use of diuretics, angiotensin-converting enzyme inhibitors or digitalis should be needed.

Ischemic heart disease. Myocardial infarction according to the WHO criteria or unstable angina with progression to stable angina with frequent attacks or a long-lasting attack (>15 min), with newly developed ST-change or T-inversion.

Cerebral ischemic event. Cerebral infarction seen on computerized tomography or transient ischemic attacks with clear neurological symptoms from regions of the internal carotid or vertebral arteries.

Intermittent claudication. Only severe intermittent claudication at a maximum walking distance of 200 m to be counted.

Venous thromboembolism. Thromboses to be diagnosed using phlebography, pletysmography, ^{125}I fibrinogen scanning or thermography. Pulmonary embolism to be verified by means of combined perfusion and ventilatory scintigraphies or angiography. A non-fatal event was only counted once in a patient even if the same category of event happened several times. If such an event was ultimately the cause of death it was counted again in the cause-of-death table.

Evaluation of cardiovascular toxicity: the blind observer

In order to optimize the evaluation of cardiovascular events, all such events were evaluated by a blind observer, a cardiologist with a special interest in cardiovascular side-effects of estrogen treatment. When a cardiovascular event was suspected, the patient's file, blinded as to the treatment that the patient had received for prostate cancer, was sent to the blind observer, who decided whether the event qualified as a cardiovascular event or not, according to the criteria of the trial. This was also done for the categorization of the cause of death if death was not obviously caused by the malignant disease. The blind observer was also to be contacted if there was any uncertainty at stratification as to whether a patient's disease prior to enrollment in the trial could be counted as a cardiovascular disease according to the criteria of the trial.

Evaluation of other toxicity

Gastrointestinal and liver toxicity, as well as allergic or cutaneous manifestations, were graded according to the WHO scale (12). Hot flushes were evaluated in terms of frequency and annoyance according to Frödin et al. (13). The extent of gynecomastia was recorded as follows: slight, only involving the mammary gland and nipple; moderate, involving the mammary gland and including lipomastia; or severe, area of the breast involved larger than the patient's fist.

Data were continuously collected in a data bank. Prior to locking the data after the death of the patient, a final check of all CRFs was done by a Data Quality Committee, consisting of 10 experienced urologists, two each from Denmark, Finland and Norway and four from Sweden.

The trial was analyzed on an intent-to-treat basis. The study was performed in accordance with the recommendations of the Helsinki Declaration (World Medical Assembly, Helsinki, 1964; amended in Tokyo, 1975, Venice, 1983 and Hong Kong, 1989). The study was approved by the Ethical Committee of the Karolinska Institute, Stockholm and by the local ethical committees of the participating centers.

Statistical methods

The aim of the study, according to the protocol, was to show that PEP treatment was equally effective as CAD in terms of overall median survival by testing the

Table I. *Parameters of stratification*

Parameter	PEP ($n = 455$)	CAD ($n = 455$)
Country		
Denmark	106	107
Finland	46	44
Norway and Iceland	51	51
Sweden	254	255
Performance status		
ECOG 0–1	375	384
ECOG 2	80	71
Alkaline phosphatase level		
Low	232	233
High	225	222
Previous cardiovascular disease	78	66
Ischemic heart disease	46	40
Heart decompensation	13	12
Ischemic cerebral disease	6	4
Venous thromboembolism	11	8
Intermittent claudication	2	2

Table II. *Other demographic characteristics at entry*

Characteristic	PEP	CAD
Age (years)[a]	71.9 (71.2–72.6)	72.2 (71.5–72.9)
Body weight (kg)[a]	75.2 (74.4–76.0)	76.2 (75.4–77.0)
Pain score[b]		
0	192	185
1	137	145
2	94	98
3	29	24
4	3	3
T stage		
T0	1	4
T1	14	19
T2	68	78
T3	244	249
T4	110	98
Grade of malignancy		
1	67	69
2	211	203
3	163	177
Soloway category of bone metastases		
1	152	167
2	250	233
3	49	49
Pretreatment irradiation of the breasts	234	67
B-hemoglobin(g/l)[a]	92 (86–98)	91 (86–99)
S-creatinine μl/l[a]	98 (94–102)	102 (97–106)
S-testosterone nmol/l[a]	14 (13–14)	14 (13–15)
S-PSA μg/l[a]	823 (632–1014)	719 (597–841)

[a] Mean and 95% confidence interval.
[b] 0 = no pain; 1 = slight pain, non-opioid analgesics occasionally; 2 = moderate pain, non-opioid analgesics regularly; 3 = severe pain, opioids occasionally; 4 = intolerable pain, opioids regularly.

hypothesis using two one-sided level alpha-tests (14). A difference in time to death of <20% was not considered clinically significant. To demonstrate an equivalence in median survival with a power of 80% and at an alpha level of 5%, 371 deaths were needed per group. A total of 900 randomized patients were recommended in order to obtain the necessary number of deaths.

A total of 917 patients were included in the study. The analyses of overall and cancer-specific survival and of the time to progression were based on the events in the 556 deceased patients for whom data were examined by the Data Quality Committee. Survival was measured from the date of randomization to the date of death by any cause for overall survival or to the date of death by prostate cancer for cancer-specific survival or to the most recent follow-up available in the database. The deaths of the 556 deceased patients occurred between March 1993 and December 1999. The most recent date of follow-up for the remaining patients ranged between January 1995 and May 2000. Time to progression, clinically or biologically, was determined from the date of randomization to the date of progression, death or most recent follow-up.

A Cox proportional hazard regression model was used to estimate the relative effects of treatments with regard to overall survival. The hypothesis stated in the protocol (assuming a constant hazard) corresponds to a relative hazard expressed as $e^B = \lambda_{PEP}(t)/\lambda_{CAD}(t) < 1.25$, where B was estimated from Cox regression. Kaplan–Meier plots were performed for overall and cancer-specific survival and time to progression. Differences between the two treatment groups in terms of time to progression were tested using the log rank test. A p-value of 0.05 was considered significant.

Analyses for adverse events were based on information obtained from the total available material from all randomized patients. Fisher's exact test was used in comparisons between the two treatment groups. The software used for all analyses was SPSS for Windows (SPSS Inc., Cary, NC).

RESULTS

In the present evaluation the median follow-up was 27.1 months for the PEP group and 27.4 months for the CAD patients. A total of 556 patients (61%) had died. Three patients were found to be non-eligible as they had a ECOG performance status of 3 at randomization, leaving 914 patients available for evaluation. Only 901 of these had at least one follow-up documentation. In the CAD group, 159 patients (35%) underwent orchidectomy and 298 (65%) were treated with triptorelin. The parameters of stratification are listed in Table I. The different forms of previous cardiovascular disease are included although stratification was performed only on the basis of whether or not the patient had a history of cardiovascular disease. As is apparent from Table I, there were some differences between the groups with regard to cardiovascular

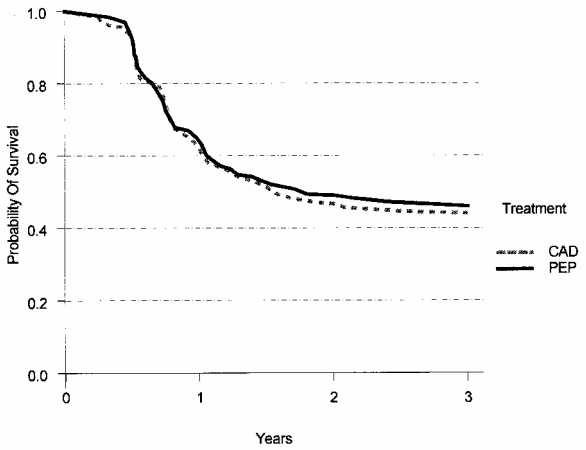

Fig. 1. Kaplan–Meier estimates of biochemical progression; $p = 0.58$ (log rank test). Median time to biochemical progression: PEP 10.2 (9.4–11.0), CAD 10.1 (9.3–10.9) months.

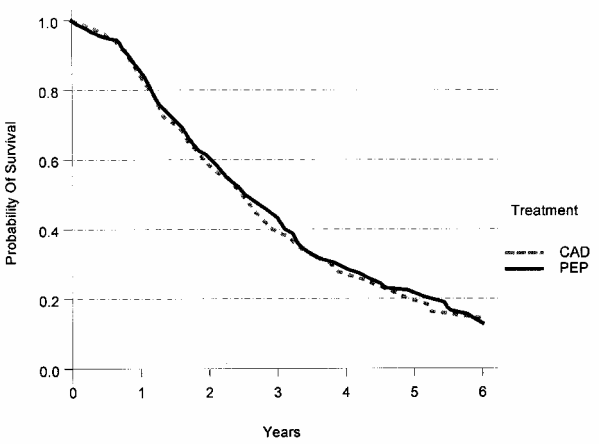

Fig. 3. Kaplan–Meier estimates of overall survival.

morbidity. As shown in Table II, other baseline characteristics were well balanced.

Time to biochemical and clinical progression for the 556 patients that had died is shown in Figs 1 and 2. There were no significant differences between the two treatments: $p = 0.58$ and 0.87, respectively. Patients who died of another disease without having progressed ($n = 50$), patients who progressed rapidly and died of prostate cancer without having been registered for a period of progression in the 6-month interval between the routine follow-up visits ($n = 20$), patients who died from unknown causes ($n = 13$) or those for whom PSA values were missing ($n = 14$) were censored. Clinical progression was first seen as recurrence of pain and decline in performance status in most patients but in 43/556 patients lymph edema, micturition problems or uremia were the reasons for assessing the condition as clinical progression.

Overall and disease-specific survival are shown in Figs 3 and 4. The calculated hazard ratio for overall survival was 0.96, with a 95% confidence interval of 0.82–1.12. The corresponding figures for cancer-specific survival were 0.91 and 0.77–1.08. The PEP and CAD treatments were equally effective in terms of median overall survival: $p = 0.001$.

Cause of death is shown in Table III. There was no difference between the two groups. Patients who were found dead at home and in whom no post-mortem investigation was done were considered to have died from unknown causes. Causes of death other than prostatic malignancy, with and without contribution of prostatic cancer, are shown in Table IV. There was no significant difference between the two treatment arms.

Non-fatal cardiovascular events are shown in Table V. There was significantly more ischemic heart disease and heart decompensation in the PEP group, with other

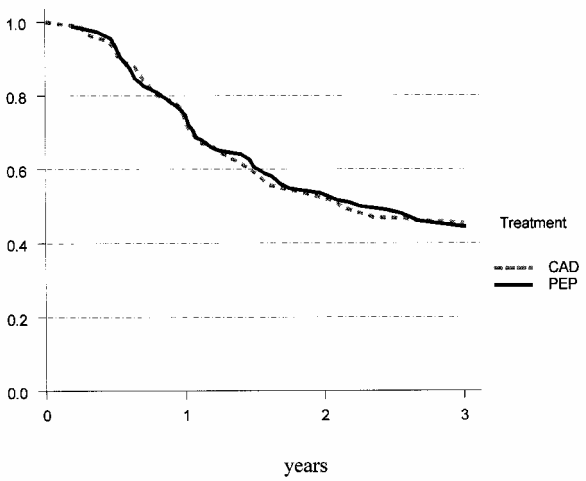

Fig. 2. Kaplan–Meier estimates of clinical progression; $p = 0.87$ (log rank test). Median time to clinical progression: PEP 13.7 (12.5–14.9), CAD 13.5 (12.4–14.6) months.

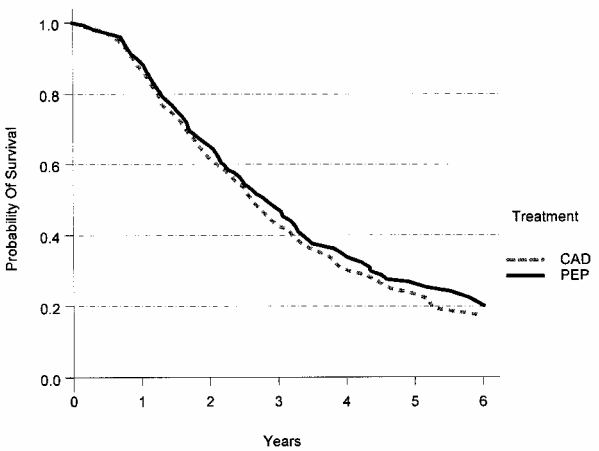

Fig. 4. Kaplan–Meier estimates of cancer-specific survival.

Table III. *Causes of death*

	PEP	CAD	*p*
Prostate cancer	223	223	
Other disease with contribution of prostate cancer	16	29	NS
Other disease without contribution of prostate cancer	29	21	NS
Unknown	9	6	

NS = not significant ($p > 0.05$).

Table IV. *Causes of death other than prostate cancer*[a]

	With contribution of prostate cancer		Without contribution of prostate cancer	
	PEP	CAD	PEP	CAD
Ischemic heart disease	2	3	5	3
Heart decompensation	2	3	7	2
Ischemic cerebral disease	4	3	2	5
Venous thromboembolism	0	0	1	1
Cerebral hemorrhage	0	1	0	2
Other malignancy	2	2	9	3
Septicemia	1	1	2	1
Suicide	1	0	0	1
Trauma	0	1	0	1
Other non-malignant disease[b]	4	1	3	2

[a] The groups are too small for calculation of any significant differences.
[b] Heterogeneous group.

Table V. *Non-fatal cardiovascular events*

	PEP ($n = 455$)	CAD ($n = 455$)	*p*
Ischemic heart disease	17	5	0.009
Heart decompensation	20	9	0.035
Ischemic cerebral disease	9	10	NS
Venous thromboembolism	9	9	NS
Intermittent claudication	2	3	NS

NS = not significant ($p > 0.05$).

Table VII. *Temporary or persistent dose reduction/termination of therapy due to adverse events*

	PEP	Flutamide	Triptorelin
Nausea/diarrhea		13/20	
Increase in liver enzymes		7/11	
Cardiovascular events	1/10		
Cutaneous (allergy)	0/2	0/2	
Pain of injections	0/3		
Flush			0/2
Impotence			0/2
Gynecomastia	0/1		
Fatigue, depression	0/2		0/2
Misunderstanding	2/1		
Miscellaneous	0/4		

cardiovascular events being equally distributed. The principal trial investigator advised the trialist to stop PEP treatment in 4 patients who suffered a myocardial infarction during treatment, as this was considered to be in the interests of the patients. Other non-fatal events are shown in Table VI. Temporary or persistent reduction of the dosage or cessation of therapy occurred in 85 patients, the reasons for which are shown in Table VII.

DISCUSSION

This study shows that the PEP regimen, which is considerably cheaper than CAD, has an anticancer efficacy equal to that of CAD when evaluated in terms of time to biochemical and clinical progression and overall and disease-specific survival. The patient material represents many patients with a large tumor burden, as can be seen from the pretreatment PSA values and Soloway scores. The periods of disease-free survival were relatively short in the present study, indicating that many patients progressed and died rapidly.

Table VI. *Other non-fatal events stratified by severity and presented as percentages of the groups as follows: PEP* (n = *446)/CAD* (n = *451)*

	Severity				
	0	1	2	3	4
Nausea	80.5/74.9	14.8/17.5	3.8/5.3	0.9/2.0	0.0/0.2
Diarrhea[a]	90.4/74.3	7.6/10.9	1.6/7.1	0.4/7.3	0.0/0.4
Cutaneous[b]	96.4/94.9	2.2/2.4	0.9/2.4	0.2/0.2	0.2/0.0
Flush frequency[c]	69.5/25.7	27.6/40.4	2.9/25.5	0.0/8.4	0.0/0.0
Flush bother[d]	74.0/33.5	20.6/29.7	4.7/29.0	0.7/7.8	0.0/0.0
Gynecomastia(%)					
Prophylactic irradiation	40.7/52.3	47.8/44.6	9.6/3.0	1.7/0.0	
No irradiation	15.5/63.9	52.6/30.9	27.6/4.8	4.2/0.2	
Pain after drug injections[e]	93.5/100.0	2.8/0.0	1.0/0.0		

[a] 0 = none; 1 = slight; 2 = moderate; 3 = severe, requiring therapy; 4 = intolerable.
[b] 0 = none; 1 = erythema; 2 = dry desquamation/pruritus; 3 = ulceration; 4 = exfoliative dermatitis.
[c] 0 = none; 1 = 1–3/day; 2 = 4–10/day; 3 = >10/day
[d] 0 = not; 1 = slightly; 2 = moderately; 3 = greatly.
[e] Only for the 556 patients who died. For other definitions, see Material and Methods.

No significant increase in cardiovascular mortality with PEP was observed. There was, however, a significant increase in non-fatal ischemic heart disease and heart decompensation. These results are in accordance with those of the Finnprost study no. 6, where treatment with the same dose of PEP was compared to orchidectomy in 440 patients (15). The final implication of our finding must, however, await further follow-up and analysis owing to the discrepancy between the mortality and morbidity data and the higher prevalence of cardiovascular disease prior to the study in the PEP group.

It is well known that oral estrogen treatment induces grave deviations in liver metabolism leading to an increase in coagulation factors VII and X, a decrease in antithrombin III and changes in the fibrinolytic system, all of which are supposed to contribute to cardiovascular toxicity. It has been postulated that the increase in factor VII is strongly related to myocardial ischemia as the increase is directly proportional to the depression of the ST-segment on the electrocardiogram (16). However, after parenteral estrogen therapy, factor VII was only slightly and insignificantly elevated and antithrombin III decreased slightly (1). It has also been found that elderly men with advanced prostatic malignancy are already in a hypercoagulable state before therapy, with increased levels of coagulation factor V, fibrinogen, fibrinogen degradation products and plasminogen inhibitors (17).

When the present study was designed much interest was focused on the evaluation of cardiovascular side-effects. Only very few patients were excluded from randomization due to previous cardiovascular morbidity, i.e. those who had suffered a myocardial or cerebral ischemic event within 1 month of the date of randomization. A total of 142 patients with previous cardiovascular disease according to the strictly defined protocol criteria were included in the study. In addition, patients with non-protocol-defined cardiovascular conditions, such as hypertension and atrial fibrillation, were also included. It is well known that previous cardiovascular disease is a strong risk factor for cardiovascular complications during oral estrogen therapy (18).

The blind observer was consulted on 255 occasions and her evaluation of cardiovascular event reports proved to be of great importance. It can easily happen that a patient with leg edema or a patient who reports some dyspnea on uphill walking can be incorrectly registered with heart decompensation, especially if the CRFs contain questions and boxes where this can be ticked and especially if the patient is on estrogen treatment. Also, pain in the legs or thorax may be misinterpreted as intermittent claudication or myocardial ischemia, respectively, which may turn out to be metastatic pain on closer evaluation and with knowledge of the further development of the disease in the patient. It has been shown that ischemic complications of oral estrogen treatment can be reduced by prophylaxis with aspirin (19). In a Finnish study this prophylaxis was given to patients treated with 160 mg of PEP per month (2). No cardiovascular complications occurred in the PEP group, but the anticancer effect was inferior to that of orchidectomy. No data are available concerning the efficacy of aspirin prophylaxis or any other anticoagulant therapy during treatment with 240 mg of PEP per month. A detailed analysis of the patients who were receiving anticoagulant therapy at the start of this trial will be done separately. The incidence of cardiovascular events encountered in the PEP group was very much lower than that registered in earlier studies in which oral estrogen treatment was administered (18) and can be considered a modest problem. Despite stratification, the PEP group contained more patients with previous cardiovascular disease and a more detailed evaluation of cardiovascular adverse events and pre-trial cardiovascular disease will be done separately when a more complete follow-up is available. It is important that the urologist prescribing PEP is aware of the cardiovascular risk involved, monitors the situation closely and can interfere if symptoms and signs occur.

The treatment arms showed well-known differences with regard to other side-effects (Table VI). It may seem surprising that so many PEP patients experienced slight or moderate nausea and diarrhea. It was also unexpected that so many PEP patients reported slight hot flushes, as estrogen is often used to alleviate flushes in castrated patients. This phenomenon, which has also been reported in other trials (3, 20, 21), is dealt with in a separate publication from this study (22). Irradiation of the breasts seemed to have a more pronounced effect in PEP patients than in the CAD group. Dose reduction or termination of therapy was most frequent in flutamide-treated patients. In most patients with increased liver enzymes the increase was very modest and no critical cases were seen during the trial. It is likely that registration of side-effects was relatively complete in this study as, instead of registering side-effects only after questioning the patient regarding whether there were any problems overall, the CRFs contained separate boxes that could be ticked for nausea, diarrhea, cutaneous, anaphylactic, gynecomastia, flush frequency, flush bother, ischemic heart, ischemic cerebral, venous thromboembolism, intermittent claudication, heart decompensation and others. It is probable that the pain associated with PEP injections is more frequent than was reported. From personal experience, slight pain during the day is rather common even if the injections are given with care.

A quality-of-life analysis using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire C-30, with the addition of special questions for prostate cancer, will be published later. It is of interest to see whether the two forms of castration studied, one involving the addition of female steroid hormones and the other involving emptying the body of male steroids, will have different effects on male psychology and quality of life.

In summary, the PEP regimen used in this study had an equal anticancer efficacy to that of CAD. Furthermore, PEP treatment was not associated with any increase in cardiovascular mortality. Significantly more non-fatal ischemic heart disease and heart decompensation events occurred in the PEP group which unfortunately had a higher prevalence of cardiovascular disease prior to the study despite the stratified randomization. Until a more comprehensive analysis of the cardiovascular data obtained in this study is done we are not able to identify any risk factors for cardiovascular complications attributable to this PEP regimen.

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APPENDIX

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Iceland

Borgarspitalinn Hospital: Gudmundur Geirsson.

Norway

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Sweden

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