

Parenteral Oestrogens for
Prostate Cancer: A Systematic
Review of Clinical Effectiveness
and Dose Response

Parenteral oestrogens for prostate cancer: A systematic review of clinical effectiveness and dose response

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Table of Contents

Executive Summary.....	v
1. Introduction.....	1
2. Review Questions.....	3
3. Methods.....	4
4. Results.....	8
5. Discussion.....	31
6. Conclusions.....	34
References.....	35
Appendix 1: Search Strategies.....	38
Appendix 2: Data Extraction Form.....	58
Appendix 3: Quality Assessment Proforma.....	59
Appendix 4: List of Abbreviations.....	60
Appendix 5: Stages and Grades.....	61
Appendix 6: List of Excluded Studies... ..	63
Appendix 7: Data Extraction Tables.....	66

List of Tables

Table 1: Interventions and comparators.....	9
Table 2: Summary of studies using parenteral oestrogen and reporting survival data.....	17
Table 3: Summary of studies using parenteral oestrogen in combination and reporting survival data.....	20
Table 4: Cardiovascular events and deaths reported in studies employing parenteral oestrogen.....	23
Table 5: Cardiovascular events and deaths reported in studies employing parenteral oestrogen in combination.....	26
Table 6: Summary of studies using parenteral oestrogen and reporting testosterone data.....	28
Table 7: Summary of study using parenteral oestrogen in combination and reporting testosterone data.....	30

List of Figures

Figure 1: Summary of study identification, retrieval and inclusion/exclusion.....	8/9
Figure 2: Overall mortality in trials employing parenteral oestrogen alone in which data were fully reported.....	18
Figure 3: Prostate cancer mortality in trials employing parenteral oestrogen alone in which data were fully reported.....	18
Figure 4: Overall survival in trials using parenteral oestrogens in combination with oral oestrogens in which data were fully reported.....	21
Figure 5: Cancer mortality in trials using parenteral oestrogens in combination with oral oestrogens for which data could reliably be extracted.....	21
Figure 6: Cardiovascular mortality in trials involving parenteral oestrogen alone for which data were fully reported.....	24
Figure 7: Cardiovascular morbidity in trials involving parenteral oestrogen alone for which data were fully reported.....	24
Figure 8: Cardiovascular mortality in trials using parenteral oestrogens in combination with oral oestrogens in which data were fully reported.....	27
Figure 9: Cardiovascular morbidity in trials using parenteral oestrogens in combination with oral oestrogens in which data were fully reported.....	27

Executive Summary

Objectives

This review was undertaken to inform the design of a clinical trial using transdermal oestrogen patches in prostate cancer. The main objectives were:

1. To examine the clinical effectiveness and safety of parenteral oestrogen therapy in prostate cancer.
2. To examine the relationship between dose and efficacy and safety of parenteral oestrogen in prostate cancer.
3. To compare the safety profile of oestrogen given transdermally with other routes of administration, in males or male-to-female transsexuals with any condition.

Methods

Search strategy

Eighteen electronic databases including EMBASE and MEDLINE were searched from inception to March 2004. Appropriate paper and internet resources were also searched.

Inclusion/exclusion criteria

Objective 1: Randomised controlled trials of parenteral oestrogen compared with any treatment in patients diagnosed with prostate cancer. Included studies had to report at least one of the following outcomes: disease progression; disease-free survival; overall survival; adverse events (limited to cardiovascular morbidity and mortality, osteoporosis, hot flushes, gynaecomastia and cognitive dysfunction); quality of life; and economic costs.

Objective 2: Studies of any design which compared the efficacy or safety of different doses of parenteral oestrogen in patients diagnosed with prostate cancer, and reported at least one of the outcomes listed for objective 1 above.

Objective 3. Randomised controlled trials of parenteral oestrogen compared with oestrogen administered by other routes in males, or male to female transsexuals, with any condition, which reported adverse events, limited to cardiovascular events, second primary cancers and osteoporosis in conjunction with effectiveness outcomes.

Data extraction and quality assessment strategy

Data on settings, populations, interventions, outcomes and analysis were extracted by one reviewer and independently checked for accuracy by a second reviewer. Laboratory data on hormonal outcomes were also reported where relevant. Studies with data spread across multiple publications were extracted and reported as a single study. Two reviewers independently assessed the methodological quality and reporting of the individual studies. Disagreements were resolved through consensus, and a third reviewer was consulted where necessary. No attempt was made to contact authors for missing data on content and quality.

Methods of analysis

The results of the data extraction and quality assessment for each study of clinical effectiveness are presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings are discussed. Heterogeneity between the included studies was assessed by considering differences in (a) study population, (b) intervention, (c) outcome measures and (d) study quality. Due to the high level of clinical heterogeneity between studies, it was not statistically or clinically meaningful to pool studies in a meta-analysis.

Results

Quality and quantity of evidence

The evidence was heterogeneous and largely of low or uncertain methodological quality. There was little evidence on the relationships of dose with efficacy or safety from trials which

compared different doses. There was no randomised evidence on the safety of transdermal oestrogen in males with conditions other than prostate cancer. There was only one small study on the use of transdermal oestrogen in prostate cancer, and this used cream rather than patches as the mode of administration. The great majority of the evidence comes from studies using intramuscular (i.m.) polyestradiol phosphate (PEP). There was no evidence as to the cost-effectiveness of parenteral oestrogen.

Results of studies

1. The evidence on the use of parenteral oestrogen in prostate cancer was heterogeneous and largely of low or uncertain methodological quality. There is therefore insufficient evidence to draw definitive conclusions on its safety and efficacy.

Randomised controlled trials of i.m. PEP in doses not sufficient to produce castrate levels of testosterone, such as 160mg/month, suggest that PEP at these doses may not be as effective as orchidectomy or luteinising-hormone releasing hormone (LHRH) in controlling prostate cancer as measured by tumour response. Overall survival appeared comparable between the groups.

Randomised controlled trials of i.m. PEP at 240mg/month, a dose sufficient to produce castrate levels of testosterone, suggest that the use of i.m. PEP at these doses may be as effective as orchidectomy and LHRH in controlling prostate cancer as measured by disease-free and overall survival.

The use of parenteral oestrogen in the form of i.m. PEP (both at 160mg and 240mg) appears to be associated with increased cardiovascular morbidity when compared to conventional hormonal treatments for prostate cancer. The level of cardiovascular morbidity was, however, lower than that previously seen with oral oestrogen. In contrast there was no evidence of such differences between i.m. PEP and conventional hormone therapy in terms of cardiovascular mortality. The disparity between cardiovascular morbidity and mortality might be real, or it might be because the mortality data are relatively sparse or because of the relatively short follow-up on most of the studies.

5. In randomised controlled trials i.m. PEP given at 80mg/month in combination with oral oestrogen appears to be as effective as comparison treatments (orchidectomy, estramustine phosphate or radiotherapy) in controlling prostate cancer. However, the levels of both cardiovascular mortality and morbidity were higher for combination oestrogen treatment than for these comparator treatments.

Conclusions and research recommendations

The studies included in this review do not provide sufficient evidence to allow a clear conclusion to be reached on the effectiveness and safety of parenteral oestrogen in prostate cancer. The great majority of evidence was concerned with i.m. PEP, but was largely of poor quality or was poorly reported. None of the trials in the review reported in any detail on long-term serious adverse events such as osteoporosis, and the largest and highest quality trials included in the review do not provide long-term survival data. No studies of cost-effectiveness were found.

The available evidence suggests that parenteral oestrogen administered alone, in adequate dosage, may be an effective therapeutic option for men with prostate cancer. Cardiovascular, cancer-specific and overall mortality appeared similar to orchidectomy or LHRH, although an excess of cardiovascular morbidity was associated with the use of parenteral oestrogen. The nature and severity of this excess cardiovascular morbidity is not clear from the available evidence. In the light of these results, and of the limited quality and quantity of the evidence available, further well-designed trials should address both efficacy and safety, particularly cardiovascular effects, osteoporosis and cognitive function, hot flushes and quality of life, and provide long-term follow-up data. A full economic evaluation of the cost-effectiveness of parenteral oestrogen therapy should also be undertaken.

The available evidence on parenteral oestrogen in combination with oral oestrogens suggests that cardiovascular mortality and morbidity may be considerably elevated by their use. It is therefore more difficult to justify further research into this combined therapy.

1. Introduction

1.1 Objectives

The purpose of this review was to examine the literature on the use of parenteral oestrogens (e.g. administered intravenously, intramuscularly, subcutaneously or transdermally) in prostate cancer, in order to inform the design of a randomised clinical trial. A small pilot study had been conducted on the use of oestrogen patches in patients with prostate cancer.¹ Twenty patients with locally advanced or metastatic prostate cancer, were treated with oestrogen patches. All patients had tolerated the patches well and achieved castrate levels of luteinising hormone (LH), follicle stimulating hormone (FSH) and testosterone within three weeks (for a full list of abbreviations see Appendix 4). One patient had experienced fluid retention and was withdrawn from trial medication, but no coronary heart disease, cerebral ischemic events or thromboembolic complications were seen. Bone mineral densities of the lumbar spine and the hip were maintained or significantly improved, such that four patients had improved WHO classification of osteoporotic risk and no patients had hot flushes.² Oestrone-oestradiol ratios and sex-hormone binding globulin (SHBG) were not affected by transdermal oestrogen administration indicating that hepatic metabolism had not been induced.³

In order to extend this work on oestrogen patches as a form of androgen suppression (AS) therapy for prostate cancer it was felt that a systematic review of parenteral oestrogen in prostate cancer should be undertaken, to ascertain whether a similar approach had been investigated previously, and to assess any potential toxicities or disadvantages associated with this approach, as well as its efficacy. The review also aimed to examine the relationship between the dose of parenteral oestrogen employed, and the effectiveness and safety of therapy.

1.2 Background

Prostate cancer is the second most common cause of male cancer deaths. In the UK approximately 25,000 men are diagnosed with prostate cancer each year.^{4,5} Over 30% of patients present with disease that is not confined to the prostate gland (see Appendix 5 for summary of staging of prostate cancers) and, therefore, radical surgery or radiotherapy with curative intent is not feasible. The primary treatment for patients with extra-prostatic disease is AS therapy achieved either with luteinising hormone releasing hormone (LHRH) analogues (with or without oral anti-androgens) or surgically with bilateral orchidectomy.

Such AS therapy is being increasingly employed as a therapeutic option. It is used as adjuvant and neo-adjuvant therapy in men undergoing radical surgery or radiotherapy for localised carcinoma of the prostate, and as primary treatment for the 30% of men who present with extra-prostatic disease, and also for those with a rising prostate specific antigen (PSA) but no other evidence of disease.⁶ The increased use of PSA monitoring, as well as the tendency for men to receive treatment for extra-prostatic disease earlier in the natural course of the disease, mean that some men may receive LHRH analogues for ten years or more. Responses are seen in up to 83% of patients, but osteoporosis and symptoms of the andropause are significant side effects.

The increasing and prolonged use of AS therapy, particularly LHRH analogues, has focussed attention on their long-term toxicity. A recent longitudinal study has shown that 45% of men who receive AS therapy for more than two years will have at least one skeletal fracture in the first seven years of treatment.⁷ There are a number of clinical trials in progress addressing the question as to whether adding a bone-strengthening agent such as a bisphosphonate to LHRH therapy would decrease the incidence of osteoporosis and skeletal-related events. These approaches may require patients to take up to three agents (LHRH + anti-androgen + bisphosphonate) and are expensive. An alternative approach is to evaluate agents that are potentially as effective (or more effective) than LHRH analogues, have fewer side effects and can be used as single agents.

Oral oestrogen (e.g. Stilboestrol (DES)) was used originally as a method of AS and is as effective as orchidectomy or LHRH analogues in producing castrate levels of testosterone. It also avoids some of the side effects associated with other hormonal therapies such as osteoporosis, osteoporotic fractures

and hot flushes but it is not used routinely as first-line therapy because of the increased incidence (30-35%) of cardiovascular system (CVS) complications, including mortality, observed at higher doses.⁸

The CVS effects of oral oestrogen have been attributed to first pass hepatic metabolism. Exposure of the liver to high doses of oestrogen via the hepatic portal circulation alters the metabolism of hormones, coagulation proteins and lipids. Activation of coagulation factors increases the risk of venous thrombosis, and disruption of the physiological ratios of hormones is thought to be responsible for short and long-term CVS events.^{9,10} In contrast, parenteral oestrogen avoids first pass metabolism in the hepatic circulation and is not expected to be associated with the same incidence of CVS toxicity as oral oestrogen. Proteins that have been shown to be modified by oral oestrogen but not transdermal oestrogen include angiotensin precursor, c-reactive protein and growth-hormone-induced IGF-1 which affect cardiovascular risk, as well as serum binding proteins which affect hormone bioavailability and activated protein C which is associated with coagulation.¹¹

2. Review Questions

Q1 Effectiveness and safety:

Is parenteral oestrogen therapy more effective in prolonging failure-free survival and overall survival in patients with prostate cancer than

- a. conventional hormone therapy (LHRH analogues, orchidectomy), or
- b. oral oestrogen.

What are the CVS morbidity and mortality rates of parenteral oestrogen compared with conventional hormone therapy or oral oestrogen in patients with prostate cancer?

Q2 Dose:

How do different doses of parenteral oestrogen affect efficacy and adverse events, including where they are given in combination with other treatment?

Q3 Adverse events:

What is the adult side effect profile of transdermal oestrogen compared with oestrogen given by other routes, with particular reference to CVS and thromboembolytic events, osteoporosis, cognitive impairment, and hot flushes, in relation to effectiveness outcomes?

Only randomised controlled trials (RCTs) of parenteral oestrogen - alone or in combination – were eligible for inclusion in the review of efficacy. The review of dose response includes data from a broad range of study designs as well as RCTs. RCTs comparing the adverse effects of transdermal oestrogen versus any treatment were eligible for the review of adverse events, which was not restricted to prostate cancer.

3.1 Search Strategy

Q1 (Effectiveness and safety) & Q2 (Dose)

The search strategy was first developed on MEDLINE. Appropriate MeSH headings were found and clinical experts were consulted over search terms selected and their suggestions added to the strategy. Drug trade names were found by consulting the British National Formulary,¹² Martindale's Drug Reference¹³ and the Federal Drug Agency web site.¹⁴ This strategy was then adapted to run on the other databases.

Q3 (Adverse events)

The question required the search to concentrate on parenteral oestrogens administered to either men or transsexuals. The strategy was developed on MEDLINE using the parenteral oestrogen terms for questions 1 and 2. These were combined with the MeSH headings Men and Transsexualism. Males could not be searched for in titles or abstracts because of the large number of irrelevant records retrieved. Transsexual textwords were included because the size of the literature for this group is very small. A filter to limit the results to RCTs was applied to the strategy where possible. The strategy was adapted to run on the other databases.

For all questions, a range of databases and other information resources were searched to locate details of both published and unpublished studies. All resources were searched from their inception to the most recent date available. There was no restriction by country of origin, language or publication date. The databases searched were:

- CINAHL
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews on the Cochrane Library
- Database of Abstracts of Reviews of Effects (DARE)
- EMBASE
- Health Technology Assessment Database (HTA)
- MEDLINE
- NHS Economic Evaluation Database (NHS EED)
- PreMEDLINE
- Science Citation Index (SCI)

Ongoing and recently completed research

- Current Controlled Trials
- ClinicalTrials.gov
- National Research Register (NRR)
- International Cancer Research Portfolio (ICRP)

Conference proceedings

- Index to Scientific and Technical proceedings (ISTP)

Reports, dissertations and other grey literature

- Index to Theses
- SIGLE

- HMIC

Paper resources

- Clinical Evidence
- British National Formulary (BNF)
- ABPI Medicines Compendium 2003
- Martindale: the complete drug reference 2002

Internet resources

- National Drug Code Directory Database – Federal Drug Agency website
www.fda.gov/cder/ndc/database

Full details of the search strategy for each source are given in Appendix 1.

3.2 Inclusion and exclusion criteria

Two reviewers at the Centre for Reviews and Dissemination (CRD) independently screened all titles and abstracts. Full paper manuscripts of any titles and/or abstracts that were potentially relevant were obtained, where possible, and the relevance of each study assessed according to the following criteria. Studies that did not meet all of the criteria were excluded and their bibliographic details listed with reasons for exclusion. Any discrepancies were resolved by consensus and, if necessary, a third reviewer was consulted. Additionally, the reference lists of all eligible articles identified in any of the above sources were checked for additional studies.

Q1 Effectiveness and safety of parenteral oestrogens in prostate cancer

Study design RCTs.

Participants Adult males diagnosed with prostate cancer.

Outcomes Data on at least one of the following outcome measures:

- Disease progression including complete response, partial response, stable disease and progressive disease.
- Disease-free survival.
- Overall survival including survival with prostate cancer that is (a) non-metastatic, or (b) metastatic.
- Adverse events (limited to cardiovascular morbidity and mortality, osteoporosis, hot flushes, gynaecomastia and cognitive dysfunction).
- Quality of life.
- Economic costs.

Following consultation with clinicians, the protocol was amended to include data on laboratory assays of hormonal levels. These were reported briefly where at least one of the preceding outcomes was also reported. Studies reporting only hormonal data were not eligible for inclusion.

Following this protocol amendment, other non-hormonal outcomes such as cholesterol levels or side effects other than those listed above were noted when reported, but data were not extracted for the review.

Interventions All parenteral oestrogens (intravenous, intramuscular, subcutaneous, transdermal) alone or in combination with any treatment and compared with any treatment, including, but not limited to LHRH, orchidectomy, oral oestrogens, radiotherapy, non-hormonal chemotherapy, and no treatment.

Q2 Parenteral oestrogen dose response in prostate cancer

Study design Studies of any design including RCTs, non-randomised controlled studies, cohort studies, case-controlled-studies, and case series.

Participants Adult males diagnosed with prostate cancer.

Outcomes Data on at least one of the following outcome measures:

- Disease progression including complete response, partial response, stable disease and progressive disease.
- Disease-free survival.
- Overall survival including survival with prostate cancer that is (a) non-metastatic, or (b) metastatic.
- Adverse events (limited to cardiovascular morbidity and mortality, osteoporosis, hot flushes, gynaecomastia and cognitive dysfunction).
- Quality of life.
- Economic costs.

Following consultation with clinicians, the protocol was amended to include data on laboratory assays of hormonal levels. These were reported briefly where at least one of the preceding outcomes was also reported. Studies reporting only hormonal data were not eligible for inclusion.

Following this protocol amendment, other non-hormonal outcomes were noted when reported, but data were not extracted for the review.

Interventions All parenteral oestrogens (intravenous, intramuscular, subcutaneous, transdermal) alone or in combination with any treatment comparing different doses of the same intervention for the treatment of prostate cancer.

Q3 Side effects and toxicity of transdermal parenteral oestrogens

Study design RCTs.

Participants Adult men or male-to-female transsexuals given treatment for any reason (including contraception).

Outcomes CVS events, second primary cancers and osteoporosis were eligible for inclusion if reported in conjunction with effectiveness outcomes. Studies that only listed adverse events in isolation were excluded from the review.

Interventions Therapeutic or prophylactic transdermal oestrogens compared with any treatment.

3.4 Data extraction

Study content: Data on settings, populations, interventions, outcomes, and analysis were extracted by one reviewer and independently checked for accuracy by a second reviewer (see Appendix 2). Disagreements were resolved through consensus, and a third reviewer was consulted where

necessary. Studies with data spread across multiple publications were extracted and reported as a single study.

Quality assessment: Two reviewers independently assessed the methodological quality and reporting of the individual studies using a proforma (see Appendix 3). Disagreements were resolved through consensus, and a third reviewer was consulted when necessary.

No attempt was made to contact authors for missing data on content and quality.

3.5 Methods of analysis/synthesis

The results of the data extraction and quality assessment for each study of clinical effectiveness are presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings are discussed. Studies were grouped according to the intervention which parenteral oestrogen treatment was compared to. Heterogeneity between the included studies was assessed by considering differences in (a) study population, (b) intervention, (c) outcome measures, and (d) study quality. Insufficient data were available to allow treatment effects to be presented as relative risks, weighted mean differences or hazard ratios. Due to the high level of clinical heterogeneity between studies, it was not statistically or clinically meaningful to pool studies statistically. Consequently, statistical χ^2 tests of heterogeneity were not performed. Due to this high level of clinical heterogeneity and the small number of studies in each intervention category, the possibility of publication bias was not explored with funnel plots or Egger's test.

4. Results

The literature searches for Q1 (efficacy and safety) and Q2 (dose) produced 935 citations of which 75 potentially relevant papers were ordered (see Fig. 1a). After full assessment, and removal of duplicate reports, 17 papers were accepted for Q1,¹⁵⁻³¹ and further details of four of the studies accepted for Q1 were obtained from five related publications found in the search.³²⁻³⁶ Three papers were accepted for Q2³⁷⁻³⁹ (see Fig. 1a). The literature search for Q3 (adverse events) yielded 1679 citations of which five potentially relevant papers were ordered. None met our inclusion criteria (see Fig. 1b). In addition, all citations for Q3 were rescreened for Q1 and Q2, and all citations found for Q1 and Q2 were rescreened for Q3, but no further potentially relevant papers were found. A list of excluded studies is provided in Appendix 6.

Populations

Q.1 The 17 RCTs included 3,627 (range 30 – 917) patients.

Q.2 The 3 studies included 82 (range 17 – 38) patients.

Q.3 No studies were included.

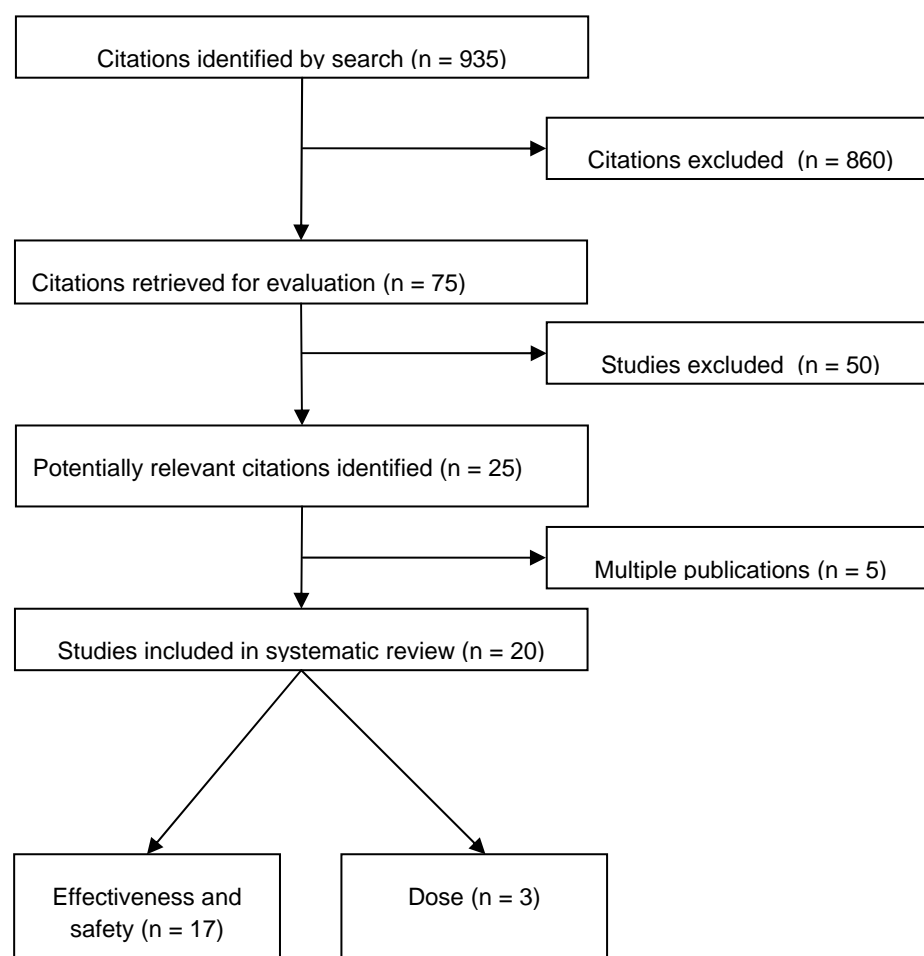


Figure 1a: Summary of study identification, retrieval and inclusion/exclusion for Q1 (effectiveness and safety) and Q2 (dose).

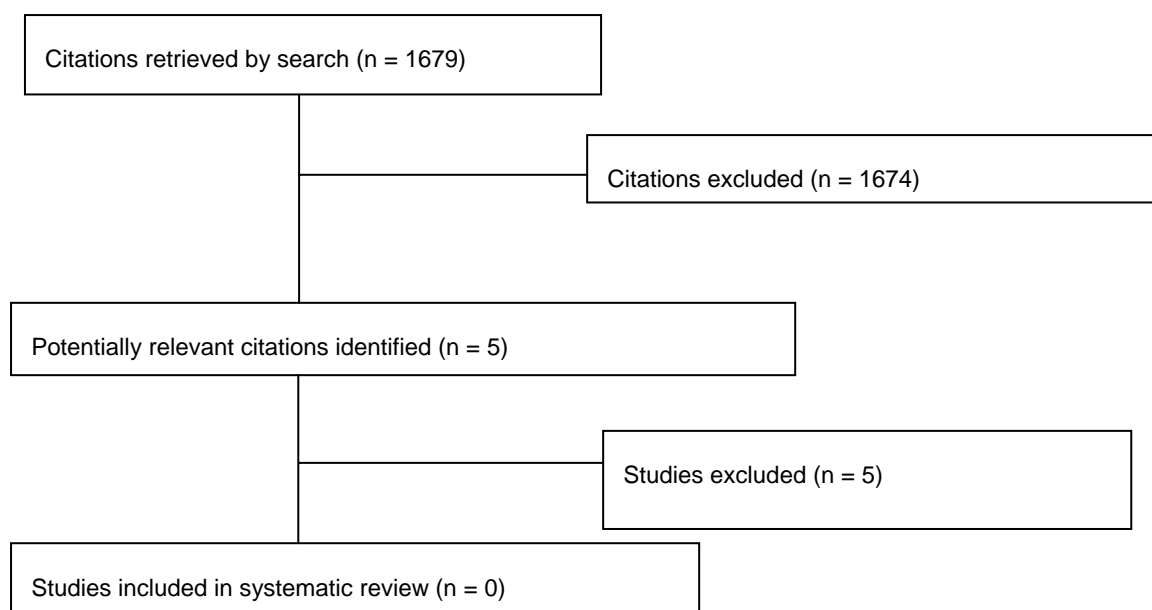


Figure 1b: Summary of study identification, retrieval and inclusion/exclusion for Q3 (adverse events).

Table 1. Interventions and comparators

Intervention	Comparator 1	Comparator 2	Number of trials	
Parenteral oestrogen alone				9
PEP	orchidectomy	—	4	
PEP	LHRH	—	2	
PEP	LHRH or orchidectomy	—	1	
estradiol undecylate	anti androgen	—	1	
beta-diethyl-estradiol	oral oestrogen	—	1	
Parenteral oestrogen in combination				8
PEP + oral oestrogen	orchidectomy	—	3	
PEP + oral oestrogen	orchidectomy	radiotherapy	1	
PEP + oral oestrogen	orchidectomy	estramustine phosphate	1	
PEP + oral oestrogen	estramustine phosphate	—	1	
PEP + oral oestrogen	estramustine phosphate	surveillance	1	
stilboestrol + doxorubicin	doxorubicin	—	1	

4.1 Interventions

Q1 Efficacy and safety

Parenteral oestrogen was given alone in 9 studies,¹⁵⁻²³ and combined with another drug (usually oral oestrogen) in 8 studies (parenteral oestrogen+).²⁴⁻³¹ In each study the parenteral oestrogen was polyestradiol phosphate (PEP) injected intramuscularly, with the exception of intravenous DES,³¹ intramuscular estradiol undecylate¹⁵ and topical 17-beta estradiol.¹⁶ The most common comparator intervention was orchidectomy, used in nine studies, as shown in Table 1. The table does not include details of non-parenteral oestrogen comparisons e.g. orchidectomy versus LHRH.

Q2 Dose

PEP given alone was evaluated in different dosages in three studies.³⁷⁻³⁹

4.2 Methodological quality

None of the included papers met all of the quality criteria listed in Appendix 3.

Q1 Effectiveness and safety

The majority of studies were more than 15 years old, most stating only that the study was randomised without specifying how. Insecure methods of randomization were reported in four studies: assignment by birthdate,^{26,28,29} and coded envelopes delivered to different sites.¹⁸ Two reports contained enough detail to confirm that the method of randomization was appropriate,^{19,23} and one of these also reported that assignment was concealed.¹⁹ Although the wide dissimilarities between comparison interventions would have made comprehensive patient and clinician blinding unfeasible in most studies, outcomes were assessed by a cardiologist blinded to interventions only in the most recently conducted trial.²³ Handling of patient withdrawals and dropouts were adequately specified in ten reports.^{16,22-28,30,31}

Q2 Dose

All 3 studies were more than 15 years old, and comprised two RCTs,^{38,39} and one controlled study that gave no details of assignment to treatment.³⁷ None of the studies mentioned blinding of patients, clinicians or evaluation. Attrition was not mentioned.

4.3 Details of studies

Full evidence tables for each study are given in Appendix 7.

4.3.1 Q1 Effects of parenteral oestrogens alone

Parenteral oestrogens given alone were compared with another treatment or treatments in nine RCTs.¹⁵⁻²³ The parenteral oestrogens evaluated were PEP (7 RCTs),¹⁷⁻²³ 17-beta-diethyl-estradiol (1 RCT),¹⁶ and estradiol undecylate (1 RCT).¹⁵ In several studies of parenteral oestrogen alone, PEP was given at a dose which many clinicians would consider too low to achieve full efficacy.¹⁷⁻²⁰ There were no trials which used oestrogen patches for transdermal administration, and only one which employed transdermal oestrogen.¹⁶ This section of the discussion is grouped by the comparator interventions of orchidectomy, LHRH, anti-androgen, and oral oestrogen.

Parenteral oestrogen vs. LHRH or orchidectomy (1 study)

One multicentric study in five Scandinavian countries (n = 917) randomised patients with histologically proven prostate cancer to PEP 240mg every 2 weeks for 2 months, and every month thereafter.²³ This study was of high methodological quality, and included blinded assessment of outcomes, although it was not clear whether appropriate measures were employed to ensure allocation

concealment. Patients in the control arm received either combined androgen ablation (CAD including the LHRH agonist triptorelin and flutamide (n = 298) or, optionally, orchidectomy (n = 159)). There were no significant differences in median time to clinical progression (p = 0.87). No significant differences in mortality were found, whether cancer-specific (PEP: 53%, LHRH/orchidectomy: 55%), overall (PEP: 61%, LHRH/orchidectomy: 61%) or CVS related (PEP: 5%, LHRH/orchidectomy: 5%). However, non-fatal CVS morbidity was higher in the PEP arm (PEP: 13%, LHRH/orchidectomy: 8%), significantly so for ischemic heart disease (p < 0.01) and heart decompensation (p = 0.035).

Parenteral oestrogen versus orchidectomy (4 studies)

In a British study (n = 117), patients with advanced prostatic carcinoma were randomised to PEP 160mg every month or orchidectomy.¹⁷ It was not clear from the reporting of this study whether appropriate methodological procedures had been followed. After at least three months in the PEP arm, unresponsive or relapsing patients were given orchidectomy. Local disease nonresponse was more pronounced in the PEP patients (28% vs 11%). Reduction of skeletal pain from bone metastases was slightly more noticeable in the PEP arm. Similar levels of CVS mortality were observed, although nonfatal CVS events were seen only in the PEP arm.

A study (n = 200) undertaken as part of Finnprostate II, one of a series of national multicentre trials directed by the Finnprostate research group, compared PEP 160mg with orchidectomy for newly diagnosed prostate cancer.¹⁸ Quality concerns with this study included an insecure method of randomisation. At two-year follow-up, combined disease progression and disease-specific mortality was significantly worse in the PEP group (p = 0.004). PEP patients were additionally randomized to daily low dose aspirin or placebo during the first six months of drug treatment in order to evaluate the effect on possible CVS complications, although the results are combined here as this reflects the authors' reporting in the primary publication.

The effect of an initial dose of PEP 320mg followed by 240mg monthly on locally advanced or metastasized disease was compared with orchidectomy in a study (n = 444) linked to Finnprostate VI.²¹ It was not clear from the reporting of this study whether appropriate methodological procedures had been followed. No significant differences were seen in disease progression (PEP: 28%, orchidectomy: 30%) at two-year follow-up, although CVS deaths and complications were significantly more common in the PEP arm (p < 0.05 for all CVS adverse incidents).

In a Swedish study patients (n = 33) with advanced disease were randomized to orchidectomy or PEP 240mg every two weeks for two months, and every month thereafter.²² While there was an adequate description of withdrawals from the study, on other measures of quality there was insufficient detail to determine whether appropriate procedures had been employed. PEP patients also received a single irradiative pre-treatment (dose unspecified) to the breast. At two-year follow-up, disease response (PEP: 82%, orchidectomy: 75%) and all cause mortality (PEP: 0%, orchidectomy: 6%) were similar in both groups. CVS events were markedly fewer in the PEP arm (PEP: 6%, orchidectomy: 25%), and all except two events occurred in patients with a CVS history. Testosterone levels decreased more rapidly in the orchidectomy arm, but mean levels below or close to the level of determination (17 pmol/l) were maintained after up to six weeks in the PEP arm.

Parenteral oestrogen vs. LHRH (2 studies)

A multicentric study (Finnprostate IV) (n = 147) compared PEP 160mg monthly with the LHRH agonist buserelin.¹⁹ Appropriate methods of randomisation and allocation concealment were employed, but it was unclear how withdrawals and dropouts were dealt with in the analysis. PEP patients also received irradiative pre-treatment to the breast. The unadjusted non-progression rate at three years favoured buserelin (PEP: 0.53, LHRH: 0.70), although CVS mortality (PEP: 6%, LHRH: 5%) and CVS complications (PEP: 1%, LHRH: 3%) were similar in both arms.

PEP 160mg was compared with the LHRH agonist goserelin acetate (Zoladex) in a multicentric Finnish study (n = 236).²⁰ It was not clear from the reporting of this study whether appropriate methodological procedures had been followed. Data on disease progression were presented only as graphs, significantly favouring goserelin (P < 0.001), while objective response also favoured LHRH (PEP: 47%, LHRH: 65%). Mortality was similar in both groups (PEP: 12%, LHRH: 11%). CVS events favoured LHRH (PEP: 15%, LHRH: 3%). Hot flushes were experienced by 85% of LHRH patients (PEP: 28%), and gynaecomastia was evident in 63% of PEP patients (LHRH: 6%). Serum

testosterone levels declined more rapidly in the LHRH arm, reaching equivalence in the PEP arm only after 144 weeks.

Parenteral oestrogen vs. anti-androgen (1 study)

Patients with histologically proven prostatic adenocarcinoma (n = 42) were randomized to intramuscular estradiol undecylate 100mg monthly or cyproterone acetate in a German study.¹⁵ It was not clear from the reporting of this study whether appropriate methodological procedures had been followed. Tumour regression was less noticeable in the parenteral oestrogen arm (estradiol: 52%, cyproterone: 76%). CVS mortality and CVS morbidity favoured the cyproterone arm (parenteral oestrogen: 2 deaths, 14 adverse CVS events, cyproterone: 0 for both). Gynaecomastia was experienced by more patients receiving estradiol (parenteral oestrogen: 21, cyproterone: 2). Testosterone levels were three times higher in parenteral oestrogen patients at 24 weeks (parenteral oestrogen: 2.9 ng/ml, cyproterone: 1 ng/ml).

Parenteral oestrogen vs. oral oestrogen (1 study)

Uniquely, parenteral oestrogen was applied transdermally in a French study published over 20 years ago.¹⁶ Withdrawals and dropouts were dealt with appropriately but it was not clear whether appropriate procedures were employed in dealing with other measures of study quality. Patients (n = 56) were randomized to receive 17-beta-diethyl-estradiol 5mg applied twice daily as a topical ointment, or DES 1mg daily orally. Clinical response (urinary function, prostatic volume, intravenous urography) was significantly worse in the parenteral oestrogen arm (parenteral oestrogen: 34%, DES: 63%, p < 0.05). CVS adverse events were significantly better in the parenteral oestrogen arm (parenteral oestrogen: 0%, DES: 19%, p < 0.05).

4.3.2 Q1 Effects of parenteral oestrogens combined with other treatments

Parenteral oestrogens were combined with other oestrogens (typically oral DES) for comparison with another treatment or treatments in eight RCTs.²⁴⁻³¹ The parenteral oestrogens evaluated were intramuscular PEP (7 RCTs),²⁴⁻³⁰ and intravenous DES (1 RCT).³¹ In the following discussion the term "parenteral oestrogen+" is used to denote parenteral oestrogen combined with another treatment. The discussion is primarily grouped by the comparator interventions of orchidectomy,²⁵⁻²⁹ estramustine phosphate,^{24,25,30} and doxorubicin.³¹ Three trials had two comparator arms, one compared parenteral oestrogen+ to orchidectomy and to estramustine,²⁵ one compared it to orchidectomy and to radiotherapy²⁸ and a third compared it to estramustine phosphate and to surveillance.³⁰ There were no trials using transdermal oestrogen in combination with another treatment, and no trials which compared combined treatments with parenteral oestrogen alone. One trial terminated recruitment to the parenteral oestrogen+ arm and instead randomised subsequent patients to a parenteral oestrogen alone arm, but data for these patients were not reported.³⁰

Parenteral oestrogen+ vs. orchidectomy (5 studies)

A multicentric Finnish study assigned patients (n = 277) to parenteral oestrogen+ (PEP 160mg monthly reducing to 80mg plus oral ethinyl estradiol 1mg/d for 2 weeks then 150µg/d) or orchidectomy.²⁶ Methodological concerns include inappropriate randomisation (by birth date), although withdrawals and dropouts were adequately specified. All cause mortality was similar between groups (parenteral oestrogen+: 69%, orchidectomy: 66%) at five-year follow-up. Cancer-specific mortality was lower under parenteral oestrogen+ treatment (parenteral oestrogen+: 31%, orchidectomy: 36%), while CVS mortality was higher (parenteral oestrogen+: 24%, orchidectomy: 18%).

Patients (n = 30) with newly diagnosed disease were assigned either to PEP 80mg i.m. combined with oral ethinyl estradiol 50µg t.i.d., bilateral orchidectomy, or estramustine in a Swedish single-site study.²⁵ Withdrawals and dropouts were adequately specified but on other measures there was insufficient information for study quality to be determined. At six months follow-up there had been one death (from coronary thrombosis, in the estramustine arm), and two DVTs (parenteral oestrogen+, estramustine). Testosterone levels declined similarly in the drug arms, and most steeply after orchidectomy.

A single-site Swedish study assigned patients (randomised $n = 91/100$: 9 patients either chose or were non-randomly assigned to treatment groups) to parenteral oestrogen+ (PEP 160mg monthly for three months reducing to 80mg plus oral ethinyl estradiol 1mg/d for 2 weeks then 150 μ g/d) or orchidectomy.²⁷ Methodological concerns include grouping of 91 randomised and nine non-randomised patients together. Cardiovascular events occurred at a much higher rate in the parenteral oestrogen+ arm than in the orchidectomy arm (13 of 53 in parenteral oestrogen+ arm; 0 of 47 in orchidectomy arm; $p < 0.001$).

A Swedish single-site study assigned patients ($n = 150$) with locally advanced disease or metastases to either PEP 80mg i.m. combined with oral ethinyl estradiol 150 μ g/d or bilateral total orchidectomy.²⁹ Methodological concerns include inappropriate randomisation (by birth date). At five years, fewer hormonally-treated patients showed progression (parenteral oestrogen+: 36%, orchidectomy: 51%), and the progression-free survival rate favoured parenteral oestrogen+ after univariate and multivariate adjustment. Time to disease-specific death was not significantly different between the two arms. All cause mortality from parenteral oestrogen+ was equivalent to orchidectomy, but CVS mortality was higher (parenteral oestrogen+: 18%, orchidectomy: 12%). CVS adverse events were significantly more frequent in the parenteral oestrogen+ arm (31%) than in the orchidectomy arm (5%).

Patients with locally advanced disease and no acute thromboembolic episodes in the previous six months ($n = 151$) were assigned to PEP 160mg monthly reducing to 80mg plus oral ethinyl estradiol 1mg/d for 2 weeks then 150 μ g/d, or orchidectomy, or megavoltage radiotherapy in a multicentric Finnish study.²⁸ Methodological concerns include inappropriate randomisation (by birth date), although withdrawals and dropouts were adequately specified. There were no significant differences in disease progression or CVS mortality rates between groups at four years. CVS complications were experienced most often in the oestrogen arm (parenteral oestrogen+: 26%, orchidectomy: 13%, radiotherapy: 7%).

Parenteral oestrogen+ vs. estramustine phosphate (3 studies)

In a multicentric Swedish study, patients ($n = 263$) with moderately to well-differentiated carcinoma (stages II to IV) were randomised to PEP 80mg i.m. plus oral 17- α -ethinyl estradiol 2mg/d for 2 weeks then 150 μ g/d or estramustine.²⁴ Withdrawals and dropouts were adequately specified but on other measures there was insufficient information for study quality to be determined. At two months follow-up reduction of the primary tumour was seen in 53% of the patients in the parenteral oestrogen+ arm and 64% of those in the estramustine arm. There appear to have been a large number of withdrawals (from progressive disease and adverse reactions among other reasons) and only a subgroup of those randomised to the trial are included in the interim report.

In another multicentric Swedish study, patients ($n = 285$) with moderately or well-differentiated carcinoma (stages I to III) were randomised to PEP 80mg i.m. plus oral ethinyl estradiol 50 μ g t.i.d., estramustine, or surveillance with delayed endocrine treatment (LHRH or orchidectomy) at progression.³⁰ Withdrawals and dropouts were adequately specified but on other measures there was insufficient information for study quality to be determined. Significantly more surveillance patients experienced progression leading to withdrawal from the trial (parenteral oestrogen+: 3%, estramustine: 8%, surveillance: 43%). There was no significant difference in time to metastasis between groups. All cause mortality was not significantly different between groups for the 228 patients who remained in the trial. CVS mortality (parenteral oestrogen+: 21%, estramustine: 15%, surveillance: 16%), and CVS morbidity leading to withdrawal (parenteral oestrogen+: 56%, estramustine: 41%, surveillance: 13%), was higher for parenteral oestrogen+ patients although not significantly so. In the light of large numbers of CVS events in the parenteral oestrogen+ arm, later in the trial patients were randomised to a new arm receiving PEP alone, although treatment was continued for those already in the original parenteral oestrogen+ arm.

As described above, patients ($n = 30$) with newly diagnosed disease were assigned either to PEP 80mg i.m. combined with oral ethinyl estradiol 50 μ g t.i.d., bilateral orchidectomy, or estramustine in a Swedish single-site study.²⁵ Withdrawals and dropouts were adequately specified but on other measures there was insufficient information for study quality to be determined. At six months follow-up there had been one death (from coronary thrombosis, in the estramustine arm), and two DVTs (parenteral oestrogen+, estramustine). Testosterone levels declined similarly in the drug arms, and most steeply after orchidectomy.

Parenteral oestrogen+ vs. doxorubicin (1 study)

Following bilateral orchidectomy and/or oestrogen therapy for confirmed prostatic cancer, patients with evidence of progressive metastatic disease (n = 188) were randomized to i.v. DES plus doxorubicin, or doxorubicin.³¹ Withdrawals and dropouts were adequately specified but on other measures there was insufficient information for study quality to be determined. Clinical improvement, reductions in bone lesions and overall survival at five-year follow-up were not significantly different between groups, although failure-free survival favoured parenteral oestrogen+ (p = 0.012). Serious cardiac events (including death) were significantly more common in the parenteral oestrogen+ group (14%) than the doxorubicin group (1%, p = 0.0041), while superficial and deep vein thrombosis, and pulmonary embolism were seen only in the parenteral oestrogen+ arm.

4.4 Specific outcomes

This section is grouped by specific outcomes of interest for trials involving parenteral oestrogen and parenteral oestrogen+. Within these broad categories, trials are grouped by the main comparator.

4.4.1 Tumour response

Trials involving parenteral oestrogen alone

One multicentric Scandinavian study (n = 917) compared parenteral oestrogen to either LHRH or orchidectomy and reported median time to clinical progression. There were no significant differences between the groups on this measure (PEP 13.7 mon (95% CI 12.5, 14.9), LHRH/orchidectomy 13.5 mon(95% CI 12.4, 14.6), p = 0.87).²³

Four studies compared parenteral oestrogen with orchidectomy.^{17,18,21,22} One study compared parental oestrogen with LHRH.²³ All reported outcomes related to tumour response. In the British study (n = 117), patients randomised to PEP 160mg/month were more likely to show local disease nonresponse after three months than those randomised to orchidectomy (28% vs 11%).¹⁷ A study linked to Finnprostate II (n = 200), compared PEP 160mg with orchidectomy in newly diagnosed prostate cancer and reported combined disease progression and disease-specific mortality at two-year follow-up.¹⁸ This was significantly worse in the PEP group (p = 0.004). Another study linked to Finnprostate 6 (n = 444), compared an initial dose of PEP 320mg followed by 240mg monthly with orchidectomy in patients with locally advanced or metastasized disease.²¹ No significant differences were seen in disease progression (PEP: 28%, orchidectomy: 30%) at two-year follow-up. In the Swedish study (n = 33) patients with advanced disease were randomized to orchidectomy or PEP 240mg every two weeks for two months, and every month thereafter.²² At two-year follow-up, disease response (PEP: 82%, orchidectomy: 75%) was similar in both groups.

Of the two multicentric studies which compared parenteral oestrogen with LHRH,^{19,20} one assessed objective response which favoured LHRH (PEP: 47%, LHRH: 65%).²⁰ Both studies reported disease progression favouring LHRH. One study (Finnprostate IV) (n = 147) compared PEP 160mg with the LHRH agonist buserelin and found that the unadjusted non-progression rate at three years favoured buserelin (PEP: 0.53, LHRH: 0.70).¹⁹ The other study (n = 236) compared PEP 160mg with the LHRH agonist goserelin acetate (Zoladex), data on disease progression were presented only as graphs, but showed a significant benefit for goserelin (p < 0.001).²⁰

One German study compared parenteral oestrogen with an anti-androgen.¹⁵ Patients with prostatic adenocarcinoma were randomised to intramuscular estradiol undecylate 100mg monthly or cyproterone acetate. Tumour regression occurred in a smaller proportion of patients in the parenteral oestrogen arm (estradiol: 52%, cyproterone: 76%).

The French study which compared parenteral oestrogen with oral oestrogen, where patients (n = 56) were randomised to receive 17-beta-diethyl-estradiol 5mg applied twice daily as a topical ointment, or DES 1mg daily orally used surrogate measures for tumour response.¹⁶ Clinical response (urinary function, prostatic volume, intravenous urography) was significantly worse in the parenteral oestrogen arm (parenteral oestrogen: 34%, DES: 64%, p < 0.05).

Trials involving parenteral oestrogen in combination (parenteral oestrogen+)

Of the five studies which compared parenteral oestrogen+ with orchidectomy,²⁵⁻²⁹ three reported outcomes related to disease progression.^{26,28,29} One multicentric Finnish study (n = 277) which compared parenteral oestrogen+ (PEP 160mg monthly reducing to 80mg plus oral oestrogen) to orchidectomy found disease progression at 5 year follow-up had occurred in a smaller percentage of patients assigned to parenteral oestrogen+ compared to those assigned to orchidectomy (17% vs. 37%, P < 0.05), with the effect more pronounced in patients with metastatic disease.²⁶ Mortality from prostate cancer did not differ between the two groups at five years (45 vs 47 deaths). The second multicentric Finnish study (n = 151) compared parenteral oestrogen+ with orchidectomy and megavoltage radiotherapy, and found no significant difference between the cumulative non-progression rates for the three groups.²⁸ Although a higher percentage of patients in the orchidectomy arm with tumours classified as grade 3 progressed than did such patients in the parenteral oestrogen+ or radiotherapy arms, the study was not sufficiently powered to enable conclusions to be drawn from these data. The Swedish single-site study assigned patients (n = 150) with locally advanced disease or metastases to either PEP 80mg i.m. combined with oral ethinyl estradiol or bilateral total orchidectomy.²⁹ At five years, fewer patients in the parenteral oestrogen+ arm showed progression (parenteral oestrogen+: 36%, orchidectomy: 51%), and the progression-free survival rate favoured parenteral oestrogen+ after univariate and multivariate adjustment. Time to disease-specific death was not significantly different between the two arms.

Three studies compared parenteral oestrogen+ with estramustine phosphate^{24,25,30} and two reported outcomes related to tumour response.^{24,30} The multicentric Swedish study (n = 263) randomised patients, with moderately to well differentiated carcinoma, (stages II to IV) to PEP 80mg i.m. plus oral oestrogen or estramustine.²⁴ After 2 months a reduction was observed in 53% of patients in the parenteral oestrogen+ arm and 64% of those in the estramustine arm. Of those patients considered in remission after 2 months, approximately 50% of patients in both arms were still in remission after 2 years. In a second multicentric Swedish study, patients (n = 285) with moderately or well-differentiated carcinoma (stages I to III) were randomised to PEP 80mg i.m. plus oral oestrogen, estramustine, or surveillance with delayed endocrine treatment (LHRH or orchidectomy) at progression.³⁰ Significantly more surveillance patients experienced progression leading to withdrawal from the trial (parenteral oestrogen+: 3%, estramustine: 8%, surveillance: 43%). There was no significant difference in time to metastasis between groups.

One study (n = 188) compared parenteral oestrogen+ (intravenous DES plus doxorubicin) with doxorubicin in patients with evidence of progressive metastatic disease following previous orchidectomy or oestrogen treatment.⁴⁰ Clinical improvement, reductions in bone lesions and overall survival at five-year follow-up were not significantly different between groups, although failure-free survival favoured parenteral oestrogen+ (p = 0.012).

4.4.2 Survival

Progression-free survival has been regarded as primarily an adjunct of tumour response and is accordingly dealt with above. The primary outcomes of interest are all cause mortality and length of survival, although where information on cause of death is available this is also reported. Cardiovascular mortality is dealt with in the section on adverse effects below.

Trials involving parenteral oestrogen alone

A recent multicentric study in five Scandinavian countries (n = 917) randomised patients with histologically proven prostate cancer to PEP 240mg every two weeks for two months, and every month thereafter.²³ Patients in the control arm received either combined androgen ablation including LHRH agonist triptorelin and flutamide (n = 298) or, optionally, orchidectomy (n = 159). No significant differences in mortality were found, whether cancer-specific (PEP: 53%, LHRH/orchidectomy: 55%), CVS related (PEP: 5%, LHRH/orchidectomy: 5%) or overall (PEP: 61%, LHRH/orchidectomy: 61%).

A summary of trials reporting survival data is provided in Table 2. Prostate cancer mortality and tumour response are also summarised. The overall mortality and prostate cancer mortality from the trials for which full data could reliably be extracted are shown in figures 2 and 3.^{21,23} In these and subsequent figures the forest plots do not present data which are suitable for pooling, as there is a considerable degree of clinical heterogeneity between trials. The relative size of data points is

representative of study sample size. Differences in parenteral oestrogen and comparator employed are indicated in the figures, however there were additional differences in factors such as patient population (e.g. disease stage and cardiovascular risk), adjuvant treatments and follow-up times for which data were available.

Four studies compared parenteral oestrogen with orchidectomy.^{17,18,21,22} One did not report survival data, although CVS mortality was reported (see below, adverse effects).¹⁷ The Swedish study, which randomised patients (n = 33) with advanced disease to orchidectomy or PEP 240mg every two weeks for two months, and every month thereafter found all cause mortality was similar in both groups (PEP: 0 in 17 patients (0%), orchidectomy: 1 in 16 patients (6%)).²² The study linked to Finnprostate II compared PEP 160mg with orchidectomy for patients with newly diagnosed prostate cancer (n = 200).¹⁸ When reported deaths from prostate cancer, CVS events and other causes at two-year follow-up were combined, all cause mortality was similar in the two groups (PEP 10%, orchidectomy 8%). The study linked to Finnprostate VI, compared an initial dose of PEP 320mg followed by 240mg monthly with orchidectomy in patients with locally advanced or metastatic cancer (n = 444).²¹ When reported deaths from prostate cancer, CVS events and other causes at two-year follow-up were combined, all cause mortality was similar in the two groups (PEP: 12%, orchidectomy: 11%).

Two studies compared parenteral oestrogen with LHRH.^{19,20} A multicentric study (Finnprostate IV) (n = 147) compared PEP 160mg with the LHRH agonist buserelin, but did not report overall survival.¹⁹ PEP 160mg was compared with the LHRH agonist goserelin acetate (Zoladex) in a second multicentric Finnish study (n = 236).²⁰ Mortality was similar in both groups (PEP: 12%, LHRH: 11%).

One German study compared parenteral oestrogen with an anti-androgen, but overall survival was not reported.¹⁵

A French study compared parenteral oestrogen applied transdermally with oral DES, but overall survival was not reported.¹⁶

Table 2: Summary of studies using parenteral oestrogen and reporting survival data.

			All cause mortality		Prostate cancer mortality		Tumour response	
Study	Follow-up period	Comparator	PEP	Comparator	PEP	Comparator	PEP	Comparator
PEP 240mg								
Hedlund, 2002 ²³	PEP median: 27.1 mon LHRH median: 27.4 mon	LHRH or orchidectomy	277 in 455	279 in 455	239 in 455	252 in 455	Time to progression: 13.7 mon	Time to progression: 13.5 mon
Mikkola, 1998 ²¹	1 and 2 yrs	Orchidectomy	27 in 227	23 in 217	6 in 227 at 1 yr 2 in 176 at 2 yrs	4 in 217 at 1yr 3 in 176 at 2 yrs	Disease progression: 33 in 227 at 1 yr 31 in 176 at 2 yrs	Disease progression: 32 in 217 at 1 yr 33 in 176 at 2 yrs
Henriksson, 1999 ²²	2 yrs	Orchidectomy	0 in 17	1 in 16	Not reported	Not reported	Response to therapy: 14 in 17	Response to therapy: 12 in 16
PEP 160mg								
Haapiainen, 1990 ¹⁸	2 yrs	Orchidectomy	12 in 125	6 in 75	6 in 125	5 in 75	Disease progression: 51 in 125	Disease progression: 16 in 75
Lukkarinen, 1994 ²⁰	PEP mean: 23 mon LHRH mean: 26 mon	LHRH	13 in 107	14 in 129	3 in 107	3 in 129	Objective response: 50 in 107	Objective response: 84 in 129

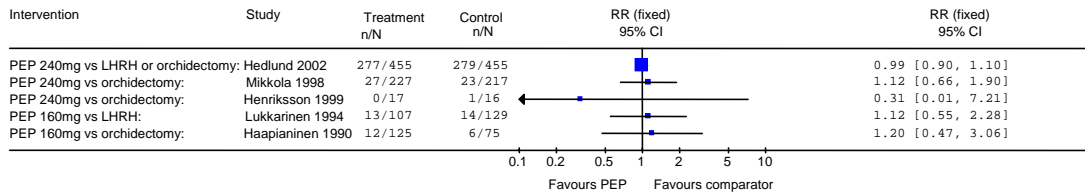


Figure 2: Overall mortality in trials employing PEP alone in which data were fully reported

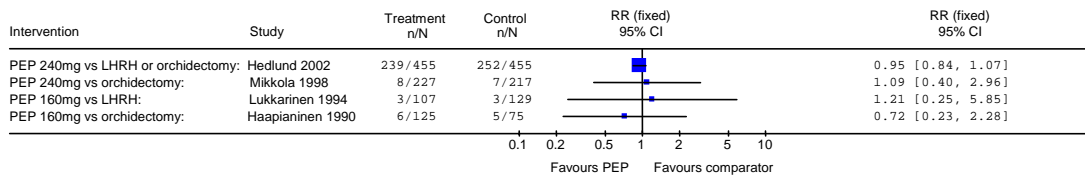


Figure 3: Prostate cancer mortality in trials employing PEP alone in which data were fully reported

Trials involving parenteral oestrogen in combination (parenteral oestrogen+)

A summary of trials reporting survival data is provided in Table 3. Prostate cancer mortality and tumour response are also summarised. The overall mortality and prostate cancer mortality for the parenteral oestrogen+ and principal comparator (orchidectomy or estramustine phosphate) from the trials for which full data could reliably be extracted are shown in figures 4 and 5.

Five studies compared parenteral oestrogen+ with orchidectomy,²⁵⁻²⁹ two did not report mortality.^{25, 27} One multicentric Finnish study (n = 277) compared parenteral oestrogen+ (PEP 160mg monthly reducing to 80mg plus oral oestrogen) to orchidectomy.²⁶ All cause mortality was similar between groups at five-year follow-up (parenteral oestrogen+: 69%, orchidectomy: 66%). Cancer-specific mortality was lower under hormone treatment (parenteral oestrogen+: 31%, orchidectomy: 36%), while CVS mortality was higher (parenteral oestrogen+: 24%, orchidectomy: 18%). The second multicentric Finnish study compared PEP 160mg monthly reducing to 80mg plus oral oestrogen with orchidectomy and with megavoltage radiotherapy.²⁸ All cause mortality at four-year follow-up was highest in the orchidectomy arm (41%) and lowest in the radiotherapy arm (20%). In the parenteral oestrogen+ group mortality was 32%. The other Swedish study compared parenteral oestrogen+ (PEP 80mg/month + ethinyl estradiol 150ug/day) with orchidectomy and found very similar all cause mortality rates at 7–10 years follow-up (73% versus 71%).²⁹

Three multicentric Swedish studies compared parenteral oestrogen+ with estramustine phosphate.^{24,25,30} In two of these studies mortality was not reported.^{24,25} In the other study, patients (n = 285) with moderately or well-differentiated carcinoma (stages I to III) were randomised to PEP 80mg i.m. plus oral oestrogen, estramustine phosphate, or surveillance with delayed endocrine treatment (LHRH or orchidectomy) at progression.³⁰ All cause mortality was not significantly different between groups for the 228 patients who remained in the trial (53% versus 54% versus 60%). CVS mortality (parenteral oestrogen+: 21%, estramustine: 15%, surveillance: 16%), and CVS morbidity leading to withdrawal (parenteral oestrogen+: 56%, estramustine: 41%, surveillance: 13%), was higher for parenteral oestrogen+ patients although not significantly so.

One study in patients with evidence of progressive metastatic disease (n = 188) compared DES plus doxorubicin, to doxorubicin.³¹ Median overall-survival times did not differ between the groups (8.5 versus 7.7 months in an intention to treat analysis).

4.4.3 Adverse effects

The primary adverse effects occurring in these studies were cardiovascular morbidity and mortality. Some studies concentrated on such morbidity to the exclusion of all other outcomes, but almost all studies reported these events. There is some debate as to the length of time required to determine the cardiovascular toxicity of a treatment regime. It has been argued that the great majority of treatment-related CVS events will occur within 12 months, with a majority of these within 6 months of treatment inception. A number of studies report follow-up times which accord with these guidelines. Other studies, concerned with effectiveness as well as adverse effects, report follow-up times in excess of 5 years. Other adverse events reported were gynaecomastia and hot flushes.

Table 3: Summary of studies using parenteral oestrogen+ and reporting survival data.

Study	Follow-up period	Comparator	All cause mortality		Prostate cancer mortality		Tumour response	
			PEP	Comparator	PEP	Comparator	PEP	Comparator
PEP 80mg + oral oestrogen								
Lundgren, 1995 ³⁰	> 10 yrs	Estramustine phosphate Surveillance	35 in 66	Estramustine phosphate: 40 in 74 Surveillance: 53 in 88	8 in 66	Estramustine phosphate: 13 in 74 Surveillance: 25 in 88	Developed Metastases: 11 in 66	Developed Metastases: Estramustine phosphate: 15 in 74 Surveillance: 25 in 88
Haapiainen, 1986 ²⁶	5 yrs	Orchidectomy	101 in 146	86 in 131	45 in 146	47 in 131	Disease progression: 25 in 146	Disease progression: 49 in 131
Aro, 1988, ²⁸	Mean: 96 mon (range: 84 - 120)	Orchidectomy Radiotherapy	16 in 50	23 in 56 9 in 45	Not reported	Not reported	Cumulative non progression rate: 0.72	Cumulative non progression rate: Orchidectomy: 0.64 Radiotherapy: 0.69
Johansson, 1991 ²⁹	Mean: 96 mon (range: 84 - 120)	Orchidectomy	54 in 74	54 in 76	27 in 74	36 in 76	Disease progression: 27 in 74	Disease progression: 39 in 76
DES + Doxorubicin								
Leaf, 2003 ³¹	> 5 years	Doxorubicin 50mg/m2/3 wks	N = 74 Median overall survival: 8.5 months	N = 76 Median overall survival: 7.7 months	N = 74 Not reported, median failure free survival: 3.2 months	N = 76 Not reported, median failure free survival: 2.6 months	Clinical improvement: 18 in 74	Clinical improvement: 16 in 76

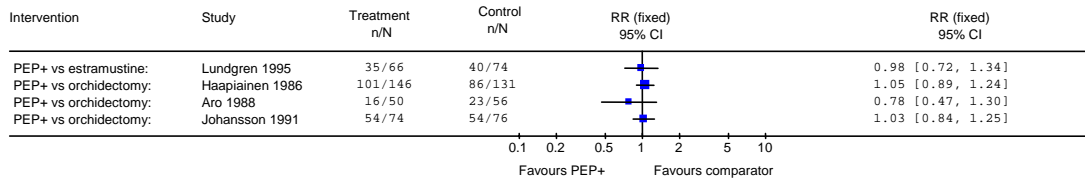


Figure 4: Overall survival in trials using parenteral oestrogens in combination with oral oestrogens for which data were fully reported

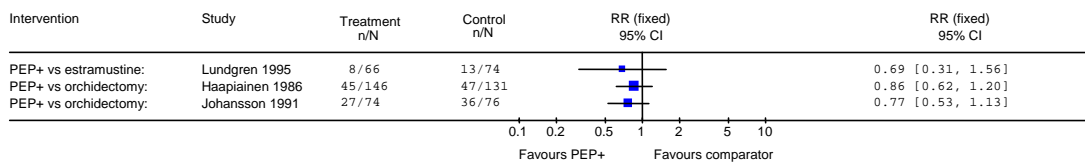


Figure 5: Prostate cancer mortality in trials using parenteral oestrogens in combination with oral oestrogens for which data were fully reported

Trials involving parenteral oestrogen alone

A summary of the reported CVS events and deaths in studies using PEP alone is provided in Table 4. The trials in which mortality or morbidity were fully reported are shown in figures 6 and 7.

One multicentric Scandinavian study (n = 917) randomised patients to PEP 240mg every two weeks for two months, and every month thereafter or to either combined androgen ablation (CAD) including LHRH agonist triptorelin and flutamide (n = 298) or, optionally, orchidectomy (n = 159).²³ No significant differences in CVS mortality were found (5% versus 5%), but CVS morbidity was higher in the PEP arm (13% versus 8%), significantly so for ischemic heart disease (p < 0.01) and heart decompensation (p = 0.035).

Four studies compared parenteral oestrogen with orchidectomy.^{17, 18, 21, 22} In the British study, patients (n = 117) with advanced prostatic carcinoma were randomised to PEP 160mg every month or orchidectomy.¹⁷ Similar levels of CVS mortality (5% in PEP arm versus 7% in orchidectomy arm) were observed, although nonfatal CVS events were observed only in the PEP arm (in 8% of patients). In the study linked to Finnprostate II (n = 200) which compared PEP 160mg with orchidectomy for newly diagnosed prostate cancer, patients in the PEP arm were randomised to daily low dose aspirin or placebo during the first six months of drug treatment in order to evaluate the effect on possible CVS complications, although the results were subsequently combined. CVS mortality was comparable in the two arms (1% versus 2%).¹⁸ Non-fatal CVS events were not reported. The study (n = 444) linked to Finnprostate VI compared an initial dose of PEP 320mg followed by 240mg monthly on locally advanced or metastasized disease with orchidectomy.²¹ CVS deaths (6% versus 2%) and complications (4% versus 2%) were significantly more common in the PEP arm (p < 0.05 for all CVS adverse incidents at 2 year follow-up). In the Swedish study, patients (n = 33) with advanced disease were randomised to orchidectomy or PEP 240mg every two weeks for two months, and every month thereafter.²² CVS events were markedly fewer in the PEP arm (6% versus 24%), and all except two CVS events occurred in patients with a CVS history.

Two studies compared a parenteral oestrogen with an LHRH.^{19,20} One of the two multicentric Finnish studies (n = 147) compared PEP 160mg with the LHRH agonist buserelin.¹⁹ Both CVS mortality (6% versus 5%) and non-fatal CVS events (1% versus 3%) were comparable in the two arms. The other study (n = 236) compared PEP 160mg with goserelin acetate (Zoladex).²⁰ CVS events favoured LHRH (PEP: 16 in 107 patients; LHRH: 4 in 129 patients). CVS mortality was comparable in the two arms (PEP: 7 in 107 patients; LHRH: 8 in 129 patients).

One German study (n = 42) compared parenteral oestrogen (intramuscular estradiol undecylate 100mg/month) with the anti-androgen cyproterone acetate. CVS mortality and CVS morbidity were both lower in the cyproterone arm (parenteral oestrogen: 2 deaths, 14 adverse CVS events, cyproterone: 0 for both).¹⁵

The French study compared parenteral oestrogen with oral oestrogen, and patients (n = 56) were randomised to receive 17-beta-diethyl-estradiol 5mg applied twice daily as a topical ointment or DES. CVS adverse events were significantly less frequent in the parenteral oestrogen arm (0% versus 19%, p < 0.05).¹⁶

Table 4: Cardiovascular events and deaths reported in studies employing PEP alone.

Study	Comparator	Follow-up period	CVS complications: PEP	CVS complications: comparator	CVS deaths: PEP	CVS deaths: comparator
PEP 240mg						
Hedlund, 2002 ²³	LHRH or Orchidectomy	PEP mean: 27.1 mon LHRH mean: 27.4 mon	57 in 455	36 in 455	23 in 455	23 in 455
Mikkola, 1998 ²¹	Orchidectomy	2 yrs	10 in 227	5 in 217	14 in 227	5 in 217
Henriksson, 1999 ²²	Orchidectomy	2 yrs	1 in 17	4 in 16	Not reported	Not reported
PEP 160mg						
Lukkarinen, 1994 ²⁰	LHRH	PEP mean: 23 mon LHRH mean: 26 mon	16 in 107	5 in 129	7 in 107	8 in 129
Haapiainen, 1990 ¹⁸	Orchidectomy	2 yrs	N/A	N/A	2 in 125	1 in 75
Aro, 1993 ¹⁹	LHRH	Not reported	1 in 70	2 in 77	4 in 70	4 in 77
Oestradiol undecylate 100mg						
Jacobi, 1980 ¹⁷	Cyproterone acetate	Not reported	14 in 21*	0 in 21	2 in 21	0 in 21
Beta-diethyl –estradiol 5mg (b.i.d.cream)						
Steg 1983 ¹⁶	Oral DES	Not reported	0 in 29	3 in 27	0 in 29	2 in 27

*One patient experienced two events.

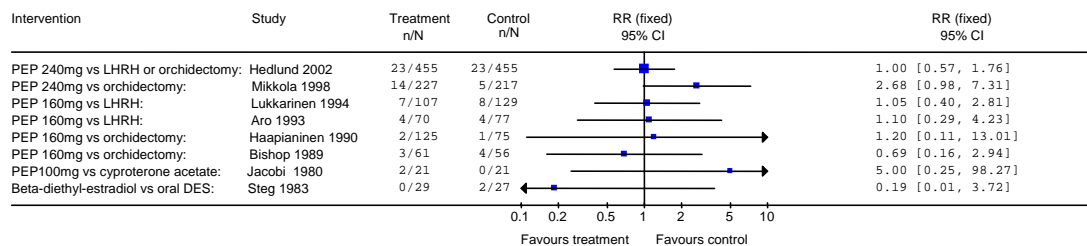


Figure 6: Cardiovascular mortality in trials involving parenteral oestrogen alone for which data were fully reported

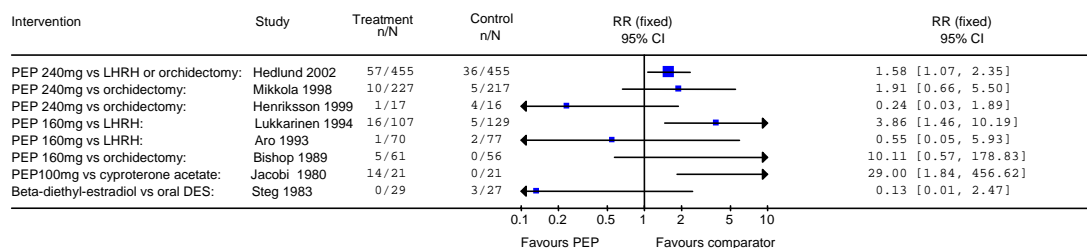


Figure 7: Cardiovascular morbidity in trials involving parenteral oestrogen alone for which data were fully reported

Trials involving parenteral oestrogen in combination (parenteral oestrogen+)

A summary of the reported CVS events and deaths in studies using parenteral oestrogen+ is provided in Table 5. The CVS mortality and morbidity for the parenteral oestrogen+ and principal comparator (orchidectomy or estramustine phosphate) from the trials for which full data could reliably be extracted are shown in figures 8 and 9.

Five studies compared parenteral oestrogen+ with orchidectomy.²⁵⁻²⁹ A multicentric Finnish study assigned patients (n = 277) to parenteral oestrogen+ (PEP 160mg monthly reducing to 80mg plus oral oestrogen) or orchidectomy.²⁶ CVS mortality was higher in the parenteral oestrogen+ group (24% versus 18%). One Swedish single-site study assigned patients (n = 30) with newly diagnosed disease to PEP 80mg i.m. combined with oral ethinyl estradiol, bilateral orchidectomy, or estramustine.²⁵ At six months follow-up there had been one CVS-related death in the estramustine arm, and one DVT in each of the parenteral oestrogen+ and estramustine arms. The second single-site Swedish study assigned patients (n = 100) to parenteral oestrogen+ (PEP 160mg monthly reducing to 80mg plus oral oestrogen) or orchidectomy.²⁷ CVS mortality was not reported but morbidity including fatal events was higher in the parenteral oestrogen+ arm (parenteral oestrogen+: 25%, orchidectomy 0%). The third Swedish single-site study assigned patients (n = 150) with locally advanced disease or metastases to either PEP 80mg i.m. combined with oral ethinyl estradiol or bilateral total orchidectomy.²⁹ At five years, CVS mortality and morbidity were higher in the parenteral oestrogen+ arm (mortality: 18% versus 12%; morbidity: 31% versus 5%). Patients with locally advanced disease and no acute thromboembolic episodes in the previous six months (n = 151) were assigned to PEP 160mg monthly reducing to 80mg plus oral oestrogen, or orchidectomy, or megavoltage radiotherapy in a multicentric Finnish study.²⁸ There were no significant differences in CVS mortality rates between groups at four years. Non-fatal CVS events occurred most often in the oestrogen arm (parenteral oestrogen+: 26%, orchidectomy: 13%, radiotherapy: 7%).

Three multicentric Swedish studies compared parenteral oestrogen+ with estramustine phosphate.^{24,25,30} One of these studies, also had an orchidectomy arm and is discussed in the paragraph above.²⁵ In one study adverse events were not reported except for the statement that there was no marked difference between the arms.²⁴ In the third study, patients (n = 285) with moderately or well-differentiated carcinoma (stages I to III) were randomised to PEP 80mg i.m. plus oral oestrogen, estramustine, or surveillance with delayed endocrine treatment (LHRH or orchidectomy) at progression.³⁰ A large number of patients (n = 44) were withdrawn before the study began, due to incorrect randomisation and protocol violations, and it appears that a per protocol analysis was conducted, in which these patients and those (n= 13) recruited subsequent to a protocol amendment were not included. CVS mortality was higher for parenteral oestrogen+ patients, although not significantly so (parenteral oestrogen+: 21%, estramustine: 15%, surveillance: 16%). CVS morbidity in the parenteral oestrogen+ arm occurred at such a high rate (parenteral oestrogen+: 56%, estramustine: 40%, surveillance: 13%) that recruitment to this arm was terminated early. Patients recruited during the final year of the recruitment phase were randomised to a new arm receiving PEP alone, although parenteral oestrogen+ treatment was continued for those already enrolled. Data for these patients was not reported.

Following bilateral orchidectomy and/or oestrogen therapy for confirmed prostatic cancer, patients with evidence of progressive metastatic disease (n = 188) were randomised to DES plus doxorubicin, or doxorubicin alone.³¹ A large number of patients were withdrawn (n = 38), having not received therapy or been deemed ineligible, and it was not reported to which arm these individuals had been assigned. These patients were not included in the reported analysis. Serious cardiac events (including death) were significantly more common in the parenteral oestrogen+ arm (13.5% versus 1.3%, p = 0.0041), while superficial and deep vein thrombosis, and pulmonary embolism were seen only in the parenteral oestrogen+ arm (8.2% versus 0%).

Table 5: Cardiovascular events and deaths reported in studies employing parenteral oestrogen in combination

Study	Comparator	Follow-up period	CVS complications*: parenteral oestrogen+	CVS complications*: comparator	CVS deaths: parenteral oestrogen+	CVS deaths: comparator
PEP 80mg + oral oestrogen						
Lundgren, 1995 ³⁰	Estramustine phosphate Surveillance	> 10 yrs	37 in 66* (81 randomised, data for 15 withdrawals not reported).	Estramustine phosphate: 30 in 74* (93 randomised, data for 19 withdrawals not reported). Surveillance: 11 in 88* (98 randomised, data for 10 withdrawals not reported).	14 in 66 (4 on treatment) (81 randomised, data for 15 withdrawals not reported).	Estramustine phosphate: 11 in 74 (5 on treatment) (93 randomised, data for 19 withdrawals not reported). Surveillance: 14 in 88 (11 on treatment) (98 randomised, data for 10
Haapiainen, 1986 ²⁶	Orchidectomy	Complications: 1 yr Deaths: 2 & 5 yrs	24 in 146	4 in 131	2 yrs: 17 in 146 5 years: 35 in 146	2 yrs: 8 in 131 5 yrs: 24 in 131
Andersson, 1980 ²⁴	Estramustine phosphate	≥ 2yrs	No sig diff between groups (values not reported)			
Aro, 1988 ²⁸	Orchidectomy Radiotherapy	4 yrs	13 in 50 (19 events)	Orchidectomy: 7 in 56 (8 events) Radiotherapy: 3 in 45	5 in 50	Orchidectomy: 6 in 56 Radiotherapy: 3 in 45
Johansson, 1991 ²⁹	Orchidectomy	Mean: 96 mon (range: 84 – 120)	23 in 74	4 in 76	13 in 74	9 in 76
Henriksson, 1986 ²⁷	Orchidectomy	1 yr	13 in 53	0 in 47	Not reported	Not reported
Daehlin, 1986 ²⁵	Orchidectomy Estramustine phosphate	6 mon	1 in 10	Orchidectomy: 0 in 10 Estramustine phosphate: 1 in 10	0 in 10	Orchidectomy: 0 in 10 Estramustine phosphate: 1 in 10
DES + doxorubicin						
Leaf, 2003 ³¹	Doxorubicin 50mg/m ² /3 wks	> 5 yrs	N = 74 Cardiac: total: 13.5% (6.8% severe; 5.4% life threatening; 1.4% lethal). Non-cardiac: total: 8.2% (6.8% severe, 1.4% life-threatening)	N = 76: Cardiac: total: 1.3%, all severe. Non-cardiac: total: 0%	N = 74: 1.4%	N = 76: 0%

* events leading to withdrawal

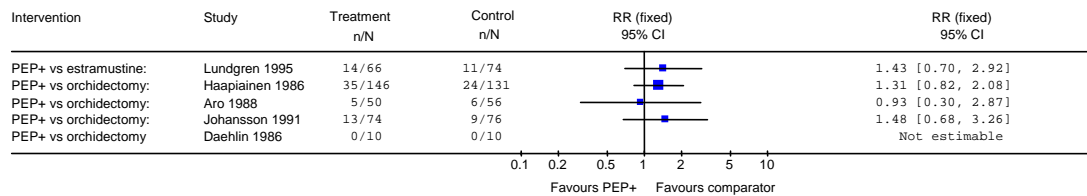


Figure 8: Cardiovascular mortality in trials using parenteral oestrogens in combination with oral oestrogens in which data were fully reported

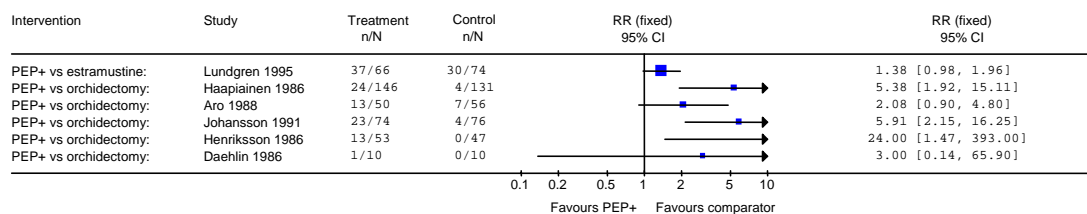


Figure 9: Cardiovascular morbidity in trials using parenteral oestrogens in combination with oral oestrogens in which data were fully reported

Table 6: Summary of studies using parenteral oestrogen and reporting testosterone levels.

Study	Parenteral oestrogen	Comparator	Interval between measurements		Parenteral oestrogen		Comparator	
					Baseline	Post-treatment	Baseline	Post-treatment
Henriksson, 1999 ²²	PEP 240mg	Orchidectomy	4 weeks	Units reported (nmol/l)	15	1.3	15.7	17 x 10.5 (limit of determination)
				ng/ml	4.33	0.38	4.53	4.90 x 10 ⁻³
Lukkarinen, 1994 ²⁰	PEP 160mg	LHRH	24 weeks	Units reported (ng/ml)	16.3	2.8	17.6	1.2
				ng/ml	16.3	2.8	17.6	1.2
Jacobi, 1980 ¹⁵	Estradiol undecylate 100mg	Cyproterone acetate	24 weeks	Units reported (ng/100ml)	416	29.6	434	102
				ng/ml	4.16	0.30	4.34	1.02
Steg, 1983 ¹⁶	17- beta estradiol 10mg/d	DES	12 weeks	Units reported (ng/ml)	4.5	1.8	4.2	0.51
				ng/ml	4.5	1.8	4.2	0.51

4.4.4. Biochemical markers

The main biochemical markers used to assess effectiveness were testosterone levels, oestrogen levels and PSA levels. Of these testosterone was the most frequently reported. However, many studies did not assess these surrogate markers of clinical effectiveness.

Trials involving parenteral oestrogen alone

A summary of the studies using parenteral oestrogen and reporting testosterone data is given in Table 6.

One Scandinavian study which compared PEP to LHRH or orchidectomy did not report hormone levels.²³

Four studies compared parenteral oestrogen with orchidectomy.^{17,18,21,22} Two of these studies did not report hormonal data.^{18,21} In a British study, patients (n = 117) with advanced prostatic carcinoma were randomised to PEP 160mg every month or orchidectomy.¹⁷ After at least three months in the PEP arm, unresponsive or relapsing patients were given orchidectomy. Plasma testosterone, LH and estradiol levels were reported for individual patients, but without appropriate summary measures. In a Swedish study, patients (n = 33) with advanced disease were randomized to orchidectomy or PEP 240mg every two weeks for two months, and every month thereafter.²² Serum testosterone levels decreased more rapidly in the orchidectomy arm, but mean levels below or close to the level of determination (17 pmol/l) were maintained after up to six weeks in the PEP arm, compared to a mean level below the limit of determination in the orchidectomy group.

Two studies compared a parenteral oestrogen with an LHRH.^{19,20} Only one of these, the multicentric Finnish study (n = 236), which compared PEP 160mg with goserelin acetate (Zoladex), reported hormone levels.²⁰ Serum concentrations of testosterone fell slightly more rapidly in the LHRH group (Table 6), but were comparable after two years' treatment, attaining castrate levels in both arms.

Patients with prostatic adenocarcinoma (n = 42) were randomized to intramuscular estradiol undecylate 100mg monthly or cyproterone acetate in a German study.¹⁵ Testosterone levels were three times higher in parenteral oestrogen patients at 24 weeks (parenteral oestrogen: 2.9 ng/ml, cyproterone: 1 ng/ml).

Uniquely, parenteral oestrogen was applied transdermally in a French study.¹⁶ Patients (n = 56) were randomized to receive 17-beta-diethyl-estradiol 5mg applied twice daily as a topical ointment, or DES 1mg daily orally. Plasma levels of testosterone, estradiol, follicle stimulating hormone (FSH) and luteinising hormone (LH) were reported. Testosterone levels showed a significant fall in both arms, from 4.5 to 1.8ng/ml in the transdermal arm and from 4.2 to 0.51ng/ml in the oral oestrogen arm (P < 0.001 in both cases). The transdermal oestrogen arm showed a significant rise from 30 to 107 pg/ml (p < 0.01) while the DES arm showed a non-significant fall from 26 to 19 pg/ml in estradiol levels. Both FSH and LH levels showed significant falls in both arms (FSH: p < 0.001 in both arms; LH: p < 0.01 in both arms). FSH fell from 4.7 to 1.7µg/ml in the transdermal arm and from 5.8 to 1.7µg/ml in the oral oestrogen arm, while LH fell from 3.2 to 2µg/ml in the transdermal arm and from 4 to 1.7µg in the oral oestrogen arm.

Trials involving parenteral oestrogen in combination (parenteral oestrogen+)

Five studies compared parenteral oestrogen+ with orchidectomy.²⁵⁻²⁹ Only one of these assessed changes in biochemical markers (Table 7).²⁵ Patients (n = 30) with newly diagnosed disease were assigned either to PEP 80mg i.m. combined with oral ethinyl estradiol, bilateral orchidectomy, or estramustine in a Swedish single-site study. Concentrations of pregnancy zone protein (PZP), sex hormone binding globulin (SHBG), FSH, LH, prolactin, estradiol-17beta, and cortisol were reported in addition to testosterone. Testosterone levels declined significantly in the drug arms (p < 0.05 in both arms), and most steeply after orchidectomy (p < 0.01). Levels of PZP and SHBG increased similarly in the two drug arms and remained unchanged in the orchidectomy arm. FSH concentrations increased significantly in all three arms (p < 0.05 in 2 drug arms; p < 0.01 in orchidectomy arm). LH concentrations fell significantly in the drug arms (parenteral oestrogen+: p < 0.05; estramustine: p < 0.01) and increased significantly in the orchidectomy arm (p < 0.01). Oestradiol-17beta increased

significantly in all three arms (parenteral oestrogen+: $p < 0.05$; estramustine: $p < 0.01$; orchidectomy: $p < 0.05$). Cortisol concentrations changed significantly only in the estramustine arm ($p < 0.05$).

Table 7: Summary of study using parenteral oestrogen+ and reporting testosterone data

Parenteral oestrogen +	Comparator	Interval between measurements		Parenteral oestrogen		Orchidectomy		Estramustine phosphate	
				Base-line	Post-treatment	Base-line	Post-treatment	Base-line	Post-treatment
PEP 80mg + ethinyl estradiol ²⁵	Orchidectomy Estramustine phosphate	6 months	Units reported (nmol/)	19.4	3.2	18.7	2.6	22.1	5.6
			ng/ml	5.60	0.92	5.39	0.75	6.38	1.62

Three multicentric Swedish studies compared parenteral oestrogen+ with estramustine phosphate.^{24,25,30} One of these studies, also had an orchidectomy arm and is discussed in the paragraph above,²⁵ and one did not report any hormonal outcomes.³⁰ The multicentric Swedish study, in which patients ($n = 263$) with moderately to well differentiated carcinoma (stages II to IV) were randomised to PEP 80mg i.m. plus oral oestrogen or estramustine phosphate, reported acid phosphatase levels.²⁴ 50% of patients in the parenteral oestrogen+ arm and 60% in the estramustine arm showed normalised levels after 2 months. This difference was not statistically significant.

One study compared DES plus doxorubicin, with doxorubicin. No hormonal outcomes were assessed.³¹

4.5 Dose response

In two Swedish studies patients were assigned to monthly injections of 320mg, 240mg, or 160mg PEP.^{37, 38} A small RCT ($n = 27$) reported disease progression, stratified as response, stable disease and no response, and a pattern of better response to high and medium doses is apparent as well as an absence of observed CVS events.³⁸ Gynecomastia was experienced by 78% of patients (not stratified by dose). The trial also investigated testosterone suppression, and times to castrate levels were dose dependent (six months to the upper level in the low dose group). In an unrandomised study the majority of patients ($n = 38$) responded to treatment, without any clear correlation with different dosages, and no CVS events were observed.³⁷

Patients in a third Swedish study ($n = 17$) received six monthly injections of 320mg PEP, before being randomly assigned to either 80mg or 160mg every month, for a further 6 months.³⁹ Disease progression was again stratified as response, stable disease and no response, with a slight benefit from the higher dose apparent. No CVS events were observed. Testosterone suppression to castrate levels was achieved in both groups before dose reduction and was dose dependent thereafter, not being maintained in low dose patients.

None of the three studies included statistical tests for between-group differences, probably because of the small populations included.

Historical overview of development of oestrogen therapy

Oral oestrogen was employed as a treatment for prostate cancer until the high levels of cardiovascular complications (30-35% at higher doses) and the development of alternative treatment in the form of LHRH analogues and orchidectomy made it unacceptable as routine therapy. These alternative hormonal treatments, while avoiding the elevated levels of cardiovascular morbidity and mortality associated with oral oestrogens, do cause other side effects such as osteoporosis, osteoporotic fractures and hot flushes. Consequently, research on the use of parenteral oestrogens has focused on the possibility that, by avoiding first-pass hepatic metabolism, the increased rate of cardiovascular events could also be avoided. Attempts to achieve this reduction in cardiovascular risk led to the investigation of a combination of a lower dose of oral oestrogens with a low dose of intramuscular PEP, and to research on the use of different doses of parenteral oestrogens alone.

Quality and quantity of evidence found

Of the seventeen trials found, the majority were of low methodological quality, or the reporting of the trial did not allow methodological quality to be judged fully. In a number of trials only selected outcomes were reported, and some reports gave little detail of reported outcomes. There was very considerable heterogeneity between trials, in terms of comparator, outcomes reported and the follow-up times for which they were reported, and the profile of the patients included, particularly in terms of cardiovascular risk. Consequently, statistical pooling of data was not possible.

Eight of the trials were concerned with parenteral estrogens combined with another treatment, in seven of these the therapy consisted of PEP at 80mg/month and oral oestrogen at 150µg/day, and in one of intravenous DES combined with doxorubicin. None of these trials was of high methodological quality.

No trials which examined the use of oestrogen patches were found, and only one trial was found which examined the use of transdermal oestrogen.¹⁶ This was a small study which used a comparator of oral oestrogen. Cream was used as the mode of administration.

The remainder of the trials using parenteral estrogens alone employed intramuscular PEP at 100mg, 160mg or 240mg/month. Of the eight trials which administered PEP alone, one used 100mg/month with a comparator of cyproterone acetate and four used 160mg/month with two using orchidectomy and two using LHRH as the comparator. These doses were insufficient to induce to castrate levels of testosterone. The question of whether it is necessary to obtain castrate levels of testosterone in order to obtain clinical efficacy is one of the issues considered. Of the three studies which used a dose of 240mg/month,²¹⁻²³ one was extremely small,²² while two were large studies,^{21,23} one of which had high methodological quality.²³ Two of these trials compared PEP with orchidectomy,^{21,22} while one compared PEP with either orchidectomy or combined androgen deprivation.²³ There were no trials which compared parenteral oestrogens administered alone with parenteral oestrogens given in combination. One trial did terminate recruitment to a combined parenteral and oral oestrogen arm, randomising patients to parenteral oestrogen alone instead. However, only 13 patients were randomised to the parenteral oestrogen alone treatment and outcomes were not reported for these patients.³⁰ Consequently, no direct comparisons between the regimes are possible.

Effectiveness

The trials using PEP alone showed that it was as effective as comparators when prostate cancer mortality was considered. In particular the most recent, largest and highest quality study, which used a dose of 240mg, considered sufficient to obtain castrate levels of testosterone, showed treatment effectiveness equivalent to that of combined androgen deprivation or orchidectomy on a number of measures including time to clinical progression, prostate cancer mortality and overall survival.²³ The other large study which used PEP at 240mg/month reported similar all cause mortality, and also

equivalent rates of both prostate cancer mortality and disease progression in the PEP and orchidectomy groups.²¹ Of the studies using PEP at 160mg/month, the two relatively large studies that reported prostate-cancer deaths showed equivalent mortality rates as well as equivalent all cause mortality.^{18,20} However, levels of tumour response and progression-free survival were lower in the parenteral oestrogen groups, in these and the other studies using 160mg/month, indicating that PEP at this dose was less effective than orchidectomy¹⁸ and LHRH.²⁰

The results of the one study which employed a transdermal oestrogen showed lower efficacy than the oral oestrogen comparator.¹⁶ However, this study was small (n = 56) and was published over 20 years ago. In addition, the mode of administration (cutaneous application of cream) meant that the effective concentration of oestrogen was difficult to determine.

Trials using parenteral oestrogen in combination with oral oestrogen showed equivalence of cancer mortality with LHRH and orchidectomy and equivalence or slightly better performance on measures of tumour response and non-progression. Three of the studies did not report overall survival, but those that did showed similar levels of mortality.^{24,25,27} The single trial involving parenteral oestrogen in combination with doxorubicin involved patients with very advanced disease but also showed equivalence of clinical response and overall survival.³¹

Adverse effects

No trials were found which examined adverse events in conjunction with efficacy in parenteral oestrogens given for conditions other than prostate cancer (Q3). However, there were data on adverse events in the trials included in Q1. Despite the importance of side effects, and cardiovascular risk in particular, some trials did not report data on this outcome, did not distinguish between cardiovascular morbidity and mortality, or gave no information on the nature or severity of the cardiovascular events which occurred.

The trials varied considerably in the profile of the patient population with respect to previous cardiovascular history, and thus the underlying risk of future cardiovascular events. However, in none of the trials which reported the data was the mortality associated with cardiovascular events in patients given parenteral oestrogen alone significantly greater than that in comparison groups treated with orchidectomy, LHRH or combined androgen deprivation. In particular, the two large trials which compared PEP 240mg/month with either orchidectomy²¹ or combined androgen deprivation or orchidectomy²³ found no significant differences, while the largest and best conducted study²³ showed almost identical CVS mortality rates in the two groups. This is particularly striking as this study included a considerable number of patients with a history of cardiovascular incidents.

However, the incidence of non-fatal CVS events does not give PEP such a favourable profile. The extent of CVS morbidity was difficult to assess in some trials, as details of events, and thus their severity were not reported. The incidence of CVS morbidity was lower than was found to be the case with oral oestrogens, but was higher than in the comparison groups. In the case of the two largest studies^{21,23} (including the largest and highest quality study in the review²³) which both employed PEP at a dose of 240mg/month, the incidence of CVS morbidity was significantly higher in the PEP groups, although this was not the case for CVS mortality. However, morbidity was not higher in trials using PEP at 240mg/month than in those using 160mg/month. There are some indications that careful screening of patients may reduce the incidence of CVS events further, as it was clear that studies with stricter exclusion criteria for cardiovascular history reported lower rates of CVS events.

The single trial employing transdermal oestrogens showed no CVS events in this group, compared to significant toxicity for DES in the small numbers randomised to the treatments.¹⁶

The majority of trials using parenteral oestrogen in combination with oral oestrogen (parenteral oestrogen+) found that both cardiovascular morbidity and mortality were significantly higher in the parenteral oestrogen+ group than in the comparison groups of orchidectomy, estramustine phosphate or surveillance, although there were exceptions to this, in particular a reasonably large trial by Lundgren reported similar numbers of events leading to withdrawal in the parenteral oestrogen+ and estramustine groups.³⁰

Q2: Dose response

The few studies available for Q2 were insufficient to answer the question of the optimum dose, although they indicate a potential dose-response relationship for efficacy.

Summary

Parenteral oestrogen alone

Nine of the 17 trials included in the review examined the effectiveness of a parenteral oestrogen given alone.

Transdermal oestrogen

There is very little evidence on the efficacy of transdermal oestrogens. No RCTs using oestrogen patches were found. The single trial found was small, published over 20 years ago, not of high methodological quality, and the use of cream rather than patches meant that it was difficult to ascertain the effective dose of oestrogen.¹⁶ The trial also had a follow-up period of only six months. However, the trial results do indicate that, while efficacy was lower than that of oral oestrogens, and plasma testosterone did not reach castrate levels, cardiovascular events were absent from the parenteral arm, in contrast to the oral oestrogen arm.

Intramuscular parenteral oestrogen alone

There is considerably more evidence relating to the use of intramuscular oestrogen in the form of PEP. Of the eight trials examining PEP alone, many were small trials or trials in which the dose of PEP was insufficient to achieve castrate levels of testosterone, and which suffered a corresponding loss of efficacy on measures other than cancer mortality. However, there were two large trials which examined the use of PEP at 240mg/month.^{21,23} Both of these, and in particular the largest most recent study²³ showed treatment effectiveness equivalent to that of CAD or orchidectomy, but with some increased cardiovascular morbidity. No direct comparisons with oral oestrogen therapy were found. However, the levels of cardiovascular morbidity appear considerable lower than had been previously documented with the use of oral oestrogens.⁸

Parenteral oestrogen in combination

Eight of the 17 trials examined parenteral oestrogen given in combination with another agent, in seven of these the regimen was PEP 80mg/month combined with oral DES at 150µg/day. In contrast with the results of studies examining PEP alone, the combination of PEP and oral oestrogen caused high levels of both cardiovascular morbidity and mortality, although efficacy was equivalent to that of orchidectomy or LHRH.

The use of parenteral oestrogen at a dose of 80mg/month in combination with oral estrogens at doses of 150µg/day does not alleviate the cardiovascular toxicity of oral estrogens. Both mortality and morbidity from this cause were significantly higher in the majority of trials in which this combination was used and for which data were reported, although the trials that reported overall survival did not show a corresponding increase in overall mortality rates. Additionally, the trial in which intravenous DES was combined with doxorubicin also showed a greater incidence of cardiovascular events than the group given doxorubicin alone.³¹

6. Conclusions

The studies included in this review do not provide sufficient evidence to allow a clear conclusion to be reached on the effectiveness and safety of parenteral oestrogens. The great majority of the evidence is provided by studies using intramuscular administration of PEP. The evidence is that, although the treatment is effective, cardiovascular mortality and morbidity are unacceptably high when parenteral oestrogens are given in combination with oral oestrogens. By contrast, when parenteral oestrogens are given alone, cardiovascular mortality occurs at equivalent levels to comparison groups given LHRH or orchidectomy. This is the case even at the highest doses of PEP used, and therefore does not result from a corresponding loss of efficacy. Both all cause mortality and cancer specific mortality occur at levels comparable to control groups. However, the equivalent levels of CVS mortality found with parenteral oestrogen are not matched by correspondingly low levels of CVS morbidity.

Whilst the review question assessing dosage found little evidence, the results of the question addressing effectiveness and safety suggest that, while 160mg/month is effective at controlling cancer mortality, it is insufficient to prevent tumour progression occurring at higher levels than in control groups, while this is not the case with a dose of 240mg/month. There does not appear to be a dose-response relationship between the dose of PEP employed and the elevated levels of CVS morbidity, though not mortality, found in the parenteral oestrogen groups.

Research recommendations

There was very little evidence on the effectiveness and safety of transdermal oestrogen. However, there was a body of evidence concerned with intramuscular oestrogen, which was largely of poor quality or was poorly reported. Results of both the majority of these studies and the single large, recent, high quality trial suggest that parenteral oestrogens are effective. Although there was an excess of cardiovascular morbidity associated with the use of parenteral oestrogen, there was equivalent cardiovascular, cancer-specific and overall mortality. At levels sufficient to induce castrate levels of testosterone parenteral oestrogen is effective at controlling tumour progression. In the light of these results, and of the limited quality and quantity of the evidence available, further high quality and fully reported trials on the use of parenteral oestrogens are required to fully address the issues of their efficacy and safety.

The balance of the available evidence, on parenteral oestrogens in combination with oral oestrogens, which was again limited and of low or unreported quality, suggests that, although they are effective, cardiovascular mortality and morbidity is considerably elevated by their use, as was found to be the case when oral oestrogens were employed alone. It is therefore more difficult to justify further research into this combined therapy.

None of the trials in the review reported in any detail on serious adverse events associated with the comparator therapies, such as osteoporosis, and the largest and highest quality trials included in the review do not provide long-term follow-up. As much of the concern over the use of LHRH analogues stems from their use over a number of years, and orchidectomised patients may also survive for a considerable period, this is a question which would benefit from further research. The issue of side effects, and cardiovascular risk in particular, is of equal importance to the question of efficacy in the consideration of whether parenteral oestrogens constitute an appropriate therapy for prostate cancer. If further trials were undertaken, they should fully address the importance of measures of overall survival, and assess the profiles of both parenteral oestrogen and comparator with respect to both cancer-specific and cardiovascular mortality. The impact of non-fatal adverse events on patients' quality of life, the nature of these events, and the mechanism responsible for them should also be investigated fully.

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5. Cancer Research UK. *CancerStats incidence - UK [web page on the Internet]*. Cancer Research; 2004. [cited 2005 Jan]. Available from: http://www.cancerresearchuk.org/aboutcancer/statistics/statsmisc/pdfs/cancerstats_incidence.pdf.
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Appendix 1. Search Strategies

Q.1, Q.2: Efficacy, dose response

Reference sources consulted:

- British National Formulary No 46 www.bnf.org/index.htm
- Martindale : the complete drug reference, 33rd ed, Pharmaceutical Press, 2002
- Federal Drug Agency - National Drug Code Directory Database www.fda.gov/cder/ndc/database

The following databases were searched:

MEDLINE, PreMEDLINE, EMBASE, CINAHL, HMIC, Science Citation Index, ISI Proceedings, System for Information on Grey Literature (SIGLE), Cochrane Central Register of controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHS EED), National Research Register (NRR), International Cancer Research Portfolio (ICRP), Current Controlled Trials, Clinical Trials.gov, National Cancer Institute Clinical Trials PDQ and Index to Theses.

MEDLINE 1966-2004 Feb week 4

Searched via OVIDweb <http://gateway1.uk.ovid.com/ovidweb.cgi>

Search date: 6.3.04

1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinoma\$ or tumour\$ or tumor\$)).ti,ab.
3. 1 or 2
4. exp estrogens/
5. exp estradiol congeners/
6. estradiol/
7. exp diethylstilbestrol/
8. (estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).ti,ab.
9. (diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol or des).ti,ab.
10. (estracombi or estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menoest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan).ti,ab.
11. (alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb).ti,ab.
12. or/4-11
13. 3 and 12
14. exp Infusions, parenteral/
15. exp injections/
16. Administration, Topical/
17. administration cutaneous/
18. drug implants/
19. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per cutaneous\$ or transderm\$ or trans

derm\$ or intraderm\$ or intra derm\$ or topical\$ or intravenous\$ or intra venous\$ or intramuscular\$ or intra muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$).ti,ab.

20. or/14-19

21. 13 and 20

22. animal/

23. human/

24. 22 not (22 and 23)

25. 21 not 24

PREMEDLINE March 4 2004

Searched via OVIDweb <http://gateway1.uk.ovid.com/ovidweb.cgi>

Search date: 6.3.04

1. ((prostate or prostatic) adj2 (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinoma\$ or tumour\$ or tumor\$)).ti,ab
2. (estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).ti,ab.
3. (diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol or des).ti,ab.
4. (estracombi or estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menoest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan).ti,ab
5. alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb).ti,ab
6. or/2-5
7. 1 and 6
8. parenteral\$ or patch or patches or injection\$ or nonoral\$ or non oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per cutaneous\$ or transderm\$ or trans derm\$ or intraderm\$ or intra derm\$ or topical\$ or intravenous\$ or intra venous\$ or intramuscular\$ or intra muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$).ti,ab
9. 7 and 8

EMBASE 1980-2004 week 9

Searched via OVIDweb <http://gateway1.uk.ovid.com/ovidweb.cgi>

Search date: 6.3.04

1. exp prostate tumor/
2. exp prostate cancer/
3. ((prostate or prostatic) adj2 (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinoma\$ or tumour\$ or tumor\$)).ti,ab.
4. or/1-3
5. exp estrogen/
6. exp diethylstilbestrol/
7. hexestrol/
8. (estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).ti,ab.
9. (diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol or des).ti,ab.
10. (estracombi or estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menoest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan).ti,ab.

11. (alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb).ti,ab.
12. or/5-11
13. 4 and 12
14. parenteral drug administration/
15. Topical Drug Administration/
16. transdermal drug administration/
17. Intradermal Drug Administration/
18. Intramuscular Drug Administration/
19. subcutaneous drug administration/
20. intravenous drug administration/
21. intradermal drug administration/
22. intranasal drug administration/
23. drug implant/
24. transdermal patch/
25. exp gel/
26. nose spray/
27. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per cutaneous\$ or transderm\$ or trans derm\$ or intraderm\$ or intra derm\$ or topical\$ or intravenous\$ or intra venous\$ or intramuscular\$ or intra muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$).ti,ab.
28. or/14-27
29. 13 and 28
30. exp animal/
31. exp nonhuman/
32. 30 or 31
33. exp human/
34. 32 not (32 and 33)
35. 29 not 34

CINAHL 1982-2004 Feb week 4

Searched via OVIDweb <http://gateway1.uk.ovid.com/ovidweb.cgi>

Search date: 6.3.04

1. prostatic neoplasms/
2. ((prostate or prostatic) adj2 (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinoma\$ or tumour\$ or tumor\$)).ti,ab.
3. 1 or 2
4. estrogens/
5. estriol/
6. estradiol/
7. diethylstilbestrol/
8. (estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).ti,ab.
9. (diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol or des).ti,ab.
10. (estracombi or estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menorest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan).ti,ab.
11. (alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb).ti,ab.
12. or/4-11
13. 3 and 12

14. Infusions, parenteral/
15. exp injections/
16. Administration, Topical/
17. administration, transcutaneous/
18. exp administration, intravenous/
19. administration, intranasal/
20. infusions, intravenous/
21. infusions, subcutaneous/
22. transdermal patches, drugs/
23. gels/
24. drug implants/
25. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per cutaneous\$ or transderm\$ or trans derm\$ or intraderm\$ or intra derm\$ or topical\$ or intravenous\$ or intra venous\$ or intramuscular\$ or intra muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$).ti,ab.
26. or/14-25
27. 13 and 26

HMIC 1979-2004 Jan

Searched via OVIDweb <http://gateway1.uk.ovid.com/ovidweb.cgi>

Search date: 6.3.04

1. exp PROSTATE CANCER/
2. ((prostate or prostatic) adj2 (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinoma\$ or tumour\$ or tumor\$)).ti,ab.
3. 1 or 2
4. exp oestrogens/
5. diethylstilboestrol/
6. (estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).ti,ab.
7. (diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stiboestrol or hexestrol or des).ti,ab.
8. (estracombi or estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menorest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan).ti,ab.
9. (alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb).ti,ab.
10. or/4-9
11. 3 and 10

ISI Science Citation Index 1981-2004 7th March

Accessed via Web of Knowledge <http://wok.mimas.ac.uk/>

Search date: 9.3.04

- 1.TS=((prostate or prostatic) same (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*))
- 2.TS=(estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)
- 3.TS=(diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol or des)

- 4.TS=(estracombi or Estraderm tts or Estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menoest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan)
- 5.TS=(alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or Estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
- 6.#2 or #3 or #4 or #5
- 7.#6 and #1
- 8.TS=(parenteral* or patch or patches)
- 9.TS=(injection* or nonoral* or non oral* or depot)
- 10.TS=(cutaneous* or subcutaneous* or percutaneous* or per cutaneous*)
- 11.TS=(transderm* or trans derm* or intraderm* or intra derm* or topical*)
- 12.TS=(intravenous* or intra venous* or intramuscular* or intra muscular*)
- 13.TS=(gel or gels or implant or implants or spray or sprays or cream or creams or emulsion*)
14. #8 or #9 or #10 or #11 or #12 or #13
15. 7 and 14

ISI Proceedings 1990-2004 5th March

Accessed via Web of Knowledge <http://wok.mimas.ac.uk/>

Search date: 9.3.04

- 1.TS=((prostate or prostatic) same (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*))
- 2.TS=(estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)
- 3.TS=(diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
- 4.TS=(estracombi or Estraderm tts or Estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menoest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan)
- 5.TS=(alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
6. #2 or #3 or #4 or #5
7. #1 and #6
- 8.TS=(parenteral* or patch or patches or injection* or nonoral* or non oral* or depot or cutaneous* or subcutaneous* or percutaneous* or per cutaneous* or transderm* or trans derm* or intraderm* or intra derm* or topical* or intravenous* or intra venous* or intramuscular* or intra muscular* or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion*)
9. #7 and #8

SIGLE (System for Information on Grey Literature) 1980-2003/12

Searched via OVID WebSPIRS

<http://arc.uk.ovid.com/webSPIRS/start.ws?customer=yku>

Search date: 9.3.04

- #1 (prostate or prostatic) near2 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumor* or tumour*)
- #2 (estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)
- #3 (diethylstilbestrol or diethyl-stilbestrol or diethylstilboestrol or diethyl-stilboestrol or stilbestrol or stilboestrol or hexestrol or des)

- #4 (estracombi or estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menorest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan)
 #5. (alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
 #6. #2 or #3 or #4 or #5
 #7. #1 and #6

Cochrane Library (CENTRAL & CDSR) Issue 1 2004

Accessed via <http://www.nelh.nhs.uk/cochrane.asp>

Search date: 9.3.04

- #1 (PROSTATIC NEOPLASMS single term MeSH)
 #2 (prostate near neoplasm*) or (prostate near cancer*) or (prostate near carcinoma*) or (prostate near adenocarcinoma*) or (prostate near tumour*) or (prostate near tumor*)
 #3 ((prostatic near neoplasm*) or (prostatic near cancer*) or (prostatic near carcinoma*) or (prostatic near adenocarcinoma*) or (prostatic near tumour*) or (prostatic near tumor*))
 #4 #1 or #2 or #3
 #5 ESTROGENS explode all trees (MeSH)
 #6 ESTROGENS SYNTHETIC explode all trees (MeSH)
 #7 ESTRADIOL single term (MeSH)
 #8 DIETHYLSTILBESTROL explode all trees (MeSH)
 #9 (estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)
 #10 (diethylstilbestrol or (diethyl next stilbestrol) or diethylstilboestrol or (diethyl next stilboestrol) or stilbestrol or stilboestrol or hexestrol or des)
 #11 (estracombi or (estraderm next tts) or (estraderm next mx) or estrapak or evorel or fempak or dermestril or (elleste next solo next mx) or fematrix or femseven or menorest or (progynova next ts) or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or (ortho next gynest) or etivex or honvan)
 #12 (alora or climara or (clinagen next la) or delestrogen or combipatch or depestrate or depgynogen or esclim or (estra next val) or estraderm or (estragyn next la) or (estrate next la) or fempatch or (gynogen next la) or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
 #13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
 #14 INFUSIONS PARENTERAL explode tree 1 (MeSH)
 #15 INJECTIONS explode tree 1 (MeSH)
 #16 ADMINISTRATION TOPICAL single term (MeSH)
 #17 ADMINISTRATION CUTANEOUS single term (MeSH)
 #18 DRUG IMPLANTS single term (MeSH)
 #19 (parenteral* or patch or patches or injection* or nonoral* or (non next oral*) or depot or cutaneous* or subcutaneous* or percutaneous* or (per next cutaneous*) or transderm* or (trans next derm*) or intraderm* or (intra next derm*) or topical* or intravenous* or (intra next venous*) or intramuscular* or (intra next muscular*) or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion*)
 #20 #14 or #15 or #16 or #17 or #18 or #19
 #21 #4 and #13 and #20

NRR (National Research Register) Issue 1 2004

Accessed via CDROM

Search date: 16.3.04

- #1 Prostatic neoplasms*:ME
 #2 (prostate near neoplasm* or prostate near cancer* or prostate near carcinoma* or prostate near adenocarcinoma* or prostate near tumor* or prostate near tumour*)

#3 (prostatic near neoplasm* or prostatic near cancer* or prostatic near carcinoma* or prostatic near adenocarcinoma* or prostatic near tumor* or prostatic near tumour*)
 #4 #1 or #2 or #3
 #5 estrogens*:ME
 #6 estrogens-synthetic*:ME
 #7 estradiol:ME
 #8 diethylstilbestrol*:ME
 #9 (estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)
 #10 (diethylstilbestrol or diethyl next stilbestrol or diethylstilboestrol or diethyl next stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
 #11 (estracombi or estraderm next tts or estraderm next mx or estrapak or evorel or fempak or dermestril or elleste next solo next mx or fematrix or femseven or menorest or progynova next ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho next gynest or etivex or honvan)
 #12 (alora or climara or clinagen next la or delestrogen or combipatch or depestrate or depgynogen or esclim or estra next val or estraderm or estragyn next la or estrate next la or fempatch or gynogen next la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
 #13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
 #14 Infusions-parenteral*:ME
 #15 injections*:ME
 #16 administration-topical*:ME
 #17 drug implants:ME
 #18 (parenteral* or patch or patches or injection* or nonoral* or non next oral* or depot or cutaneous* or subcutaneous* or percutaneous* or per next cutaneous* or transderm* or trans next derm* or intraderm* or intra next derm* or topical* or intravenous* or intra next venous* or intramuscular* or intra next muscular* or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion*).
 #19 #14 or #15 or #16 or #17 or #18
 #20 #4 and #13 and #19

DARE (Database of Abstracts of Reviews of Effects) 1995-2004

Accessed via Internal CAIRS T system

Search date: 9.3.04

1. ((prostate or prostatic) (w2) (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinoma\$ or tumour\$ or tumor\$))
- 2.(estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).
3. (diethylstilbestrol or diethyl (w) stilbestrol or diethylstilboestrol or diethyl (w) stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
4. (estracombi or Estraderm (w) tts or estraderm (w) mx or estrapak or evorel or fempak or dermestril or elleste (w) solo (w) mx or fematrix or femseven or menorest or progynova (w) ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho (w) gynest or etivex or honvan)
5. (alora or climara or clinagen (w) la or delestrogen or combipatch or depestrate or depgynogen or esclim or estra (w) val or estraderm or estragyn (w) la or estrate (w) la or fempatch or gynogen (w) la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
6. #2 or #3 or #4 or #5
7. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non (w) oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per (w) cutaneous\$ or transderm\$ or trans (w) derm\$ or intraderm\$ or intra (w) derm\$ or topical\$ or intravenous\$ or intra (w) venous\$ or intramuscular\$ or intra (w) muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$)
8. #1 and #6 and #7

HTA (Health Technology Assessment Database) 1995-2004

Accessed via Internal CAIRS T system

Search date: 9.3.04

1. ((prostate or prostatic) (w2) (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinoma\$ or tumour\$ or tumor\$))
- 2.(estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).
3. (diethylstilbestrol or diethyl (w) stilbestrol or diethylstilboestrol or diethyl (w) stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
4. (estracombi or estraderm (w) tts or estraderm (w) mx or estrapak or evorel or fempak or dermestril or elleste (w) solo (w) mx or fematrix or femseven or menoest or progynova (w) ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho (w) gynest or etivex or honvan)
5. (alora or climara or clinagen (w) la or delestrogen or combipatch or depestrate or depgynogen or esclim or estra (w) val or estraderm or estragyn (w) la or estrate (w) la or fempatch or gynogen (w) la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
6. #2 or #3 or #4 or #5
7. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non (w) oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per (w) cutaneous\$ or transderm\$ or trans (w) derm\$ or intraderm\$ or intra (w) derm\$ or topical\$ or intravenous\$ or intra (w) venous\$ or intramuscular\$ or intra (w) muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$)
8. #1 and #6 and #7

NHS EED (NHS Economic Evaluations Database) 1995-2004

Accessed via Internal CAIRS T system

Search date: 9.3.04

1. ((prostate or prostatic) (w2) (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinoma\$ or tumour\$ or tumor\$))
- 2.(estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).
3. (diethylstilbestrol or diethyl (w) stilbestrol or diethylstilboestrol or diethyl (w) stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
4. (estracombi or Estraderm (w) tts or estraderm (w) mx or estrapak or evorel or fempak or dermestril or elleste (w) solo (w) mx or fematrix or femseven or menoest or progynova (w) ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho (w) gynest or etivex or honvan)
5. (alora or climara or clinagen (w) la or delestrogen or combipatch or depestrate or depgynogen or esclim or estra (w) val or estraderm or estragyn (w) la or estrate (w) la or fempatch or gynogen (w) la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
6. #2 or #3 or #4 or #5
7. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non (w) oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per (w) cutaneous\$ or transderm\$ or trans (w) derm\$ or intraderm\$ or intra (w) derm\$ or topical\$ or intravenous\$ or intra (w) venous\$ or intramuscular\$ or intra (w) muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$)
8. #1 and #6 and #7

International Cancer Research Portfolio 2000-2004

<http://www.cancerportfolio.org>

Search date: 17.3.04

Type of Cancer: Prostate Cancer

The following terms were searched individually with prostate cancer selected.

estrogen\$ oestrogen\$ estradiol oestradiol estriol oestriol estrone oestrone estradurin
polyestradiol polyoestradiol diethylstilbestrol diethylboestrol stilbestrol stilboestrol hexestrol

parenteral patch\$ injection\$ nonoral\$ 'non oral\$' depot cutaneous subcutaneous percutaneous
transderm\$ intraderm\$ topical intravenous\$ intramuscular\$ gel implant spray cream emulsion

Current Controlled Trials

<http://controlled-trials.com/mrct/search.asp>

Searched 17.3.04

((prostate or prostatic) and (estrogen! or estradiol! or estriol! or estrone! or estradurin or
polyestradiol or diethylstilbestrol or diethylstilboestrol or stilbestrol or stilboestrol or hexestrol)
and (parenteral% or patch% or injection% or nonoral% or "non oral%" or depot or cutaneous!
or transderm% or intraderm% or topical or intravenous% or intramuscular% or gel or implant or
cream or emulsion%)))

Clinical Trials.gov

<http://www.clinicaltrials.gov/>

Searched 17.3.04

"Prostatic neoplasms" [condition] and Any of these words: parenteral\$ patch\$ injection\$
nonoral\$ 'non oral\$' depot cutaneous\$ subcutaneous\$ percutaneous\$ transderm\$ intraderm\$
topical\$ intravenous\$ intramuscular\$ gel implant spray cream emulsion\$

National Cancer Institute Clinical Trials PDQ

www.cancer.gov/clinicaltrials

Search date: 26.3.04

Type of cancer: Prostate cancer

Type of trial: all

Drug: estrogen\$; oestrogen\$; estradiol; oestradiol; estriol; oestriol; estrone; oestrone; estradurin

Type of cancer: prostate cancer

Type of trial: all

Drug: polyestradiol; polyoestradiol; diethylstilbestrol; diethylboestrol; stilbestrol; stilboestrol; hexestrol

Type of cancer: prostate cancer

Type of trial: all

Drug: estracombi; Estraderm; estrapak; evorel; fempak; dermestril; elleste; fematrix; femseven;
menorest; progynova; oestrogel; sanrena; organon; aeriodol; estradot; ovestin; ortho gynest; etivex;
honvan

Type of cancer: all

Type of trial: all

Drug: alora; climara; clinagen; delestrogen; combipatch; depestrate; depgynogen; esclim; estra val; Estraderm; estragyn; estrate; fempatch; gynogen; lunelle; vivelle; premarin; kestrone; vagifem; estrace; estrasorb

Index to theses 1970-2003

Accessed via <http://www.theses.com/idx>

Searched 17.3.04

(((((prostate or prostatic) near (neoplasm* or carcinoma* or adenocarcinoma* or tumour* or tumor*))AND (estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep or diethylstilbestrol or diethylstilboestrol or stilbestrol or stilboestrol or hexestrol or des) AND (parenteral* or patch or patches or injection* or nonoral* or "non oral*" or depot* or cutaneous* or subcutaneous* or percutaneous* or transderm* or intraderm* or topical* or intravenous* or intramuscular* or gel or implant or spray or cream or emulsion*)))

Q.3 strategies

The following databases were searched:

MEDLINE, EMBASE, CINAHL, HMIC, Science Citation Index, ISI Proceedings, System for Information on Grey Literature (SIGLE), Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHS EED), National Research Register (NRR), International Cancer Research Portfolio (ICRP), Current Controlled Trials, Clinical Trials.gov, National Cancer Institute Clinical Trials PDQ and Index to Theses.

MEDLINE 1966- 2004 March Week 2

Searched via OVIDweb <http://gateway1.uk.ovid.com/ovidweb.cgi>

Search date: 24.3.04

- 1 exp estrogens/
- 2 exp estradiol congeners/
- 3 estradiol/
- 4 exp diethylstilbestrol/
- 5 (estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).ti,ab.
- 6 (diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol or des).ti,ab.
- 7 (estracombi or estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menorest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan).ti,ab.
- 8 (alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or estrace or vagifem or estrasorb).ti,ab.
- 9 or/1-8
- 10 exp Infusions, parenteral/
- 11 exp injections/
- 12 Administration, Topical/

13 administration cutaneous/
 14 drug implants/
 15 (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non oral\$ or depot or
 cutaneous\$ or subcutaneous\$ or percutaneous\$ or per cutaneous\$ or transderm\$ or trans derm\$
 or intraderm\$ or intra derm\$ or topical\$ or intravenous\$ or intra venous\$ or intramuscular\$ or
 intra muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or
 emulsion\$).ti,ab.
 16 or/10-15
 17 9 and 16
 18 transsexualism/
 19 (transsexual\$ or trans sexual\$ or cross sex\$).ti,ab.
 20 male/
 21 or/18-20
 22 17 and 21
 23 animal/
 24 human/
 25 23 not (23 and 24)
 26 22 not 25
 27 randomized controlled trial.pt
 28 controlled clinical trial.pt.
 29 Randomized Controlled Trials/
 30 random allocation/
 31 double blind method/
 32 Single-Blind Method/
 33 clinical trial.pt.
 34 exp Clinical Trials/
 35 controlled clinical trials/
 36 multicenter studies/
 37 clin\$ trial\$.ti,ab.
 38 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (mask\$ or blind\$)).tw.
 39 placebos/
 40 placebo\$.ti,ab.
 41 random\$.ti,ab.
 42 (control\$ adj (trial\$ or stud\$)).ti,ab,sh.
 43 crossover.ti,ab,sh.
 44 Comparative Study/
 45 or/27-44
 46 26 and 45

EMBASE 1980-2004 week 12

Searched via OVIDweb <http://gateway1.uk.ovid.com/ovidweb.cgi>

Search date: 24.3.04

1. exp estrogen/
2. exp diethylstilbestrol/
3. hexestrol/
4. (estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone
or estradurin or polyestradiol or polyoestradiol or pep).ti,ab.
5. (diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or
stilboestrol or hexestrol or des).ti,ab.
6. (estracombi or estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or
elleste solo mx or fematrix or femseven or menoest or progynova ts or oestrogel or sanrena or
organon or aeriodol or estradot or ovestin or ortho gynec or etivex or honvan).ti,ab.
7. (alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen

or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb).ti,ab.

8. or/1-7

9. parenteral drug administration/

10. Topical Drug Administration/

11. transdermal drug administration/

12. Intradermal Drug Administration/

13. Intramuscular Drug Administration/

14. subcutaneous drug administration/

15. intravenous drug administration/

16. intradermal drug administration/

17. intranasal drug administration/

18. drug implant/

19. transdermal patch/

20. exp gel/

21. nose spray/

22. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per cutaneous\$ or transderm\$ or trans derm\$ or intraderm\$ or intra derm\$ or topical\$ or intravenous\$ or intra venous\$ or intramuscular\$ or intra muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$).ti,ab.

23. or/9-22

24. 8 and 23

25. male/

26. transsexualism/

27. (transsexual\$ or trans-sexual\$ or crossex\$ or cross-sex\$).ti,ab.

28. or/25-27

29. 24 and 28

30. exp animal/

31. exp nonhuman/

32. 30 or 31

33. exp human/

34. 32 not (32 and 33)

35. 29 not 34

36. randomized controlled trial/

37. randomization/

38. double blind procedure/

39. single blind procedure/

40. exp clinical trial/

41. controlled study/

42. clin\$ trial\$.ti,ab.

43. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab.

44. placebo\$.ti,ab.

45. placebo/

46. random\$.ti,ab.

47. evaluation/

48. followup/

49. exp methodology/

50. prospective study/

51. (control\$ or prospectiv\$ or volunteer\$).ti,ab.

52. or/36-51

53. 35 and 52

CINAHL 1982-2004 week 3

Searched via OVIDweb <http://gateway1.uk.ovid.com/ovidweb.cgi>

Search date: 24.3.04

1. estrogens/
2. estriol/
3. estradiol/
4. diethylstilbestrol/
5. (estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).ti,ab.
6. (diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol or des).ti,ab.
7. (estracombi or estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menoest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan).ti,ab.
8. (alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb).ti,ab.
9. or/1-8
10. Infusions, parenteral/
11. exp injections/
12. Administration, Topical/
13. administration, transcutaneous/
14. exp administration, intravenous/
15. administration, intranasal/
16. infusions, intravenous/
17. infusions, subcutaneous/
18. transdermal patches, drugs/
19. gels/
20. drug implants/
21. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per cutaneous\$ or transderm\$ or trans derm\$ or intraderm\$ or intra derm\$ or topical\$ or intravenous\$ or intra venous\$ or intramuscular\$ or intra muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$).ti,ab.
22. or/10-21
23. 9 and 22
24. Transsexualism/
25. (transsexual\$ or trans-sexual\$ or crossex\$ or cross-sex\$).ti,ab.
26. Male/
27. or/24-26
28. 23 and 27

HMIC 1979- 2004/Jan

Searched via OVIDweb <http://gateway1.uk.ovid.com/ovidweb.cgi>

Search date: 24.3.04

1. exp oestrogens/
2. diethylstilboestrol/
3. (estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).ti,ab.
4. (diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stiboestrol or hexestrol or des).ti,ab.
5. (estracombi or estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menoest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or orthogynest or etivex or honvan).ti,ab.
6. (alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen

or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb).ti,ab.

7. or/1-6

8. parenteral infusion pumps/

9. exp injections/

10. transdermal drug administration/

11. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per cutaneous\$ or transderm\$ or trans derm\$ or intraderm\$ or intra derm\$ or topical\$ or intravenous\$ or intra venous\$ or intramuscular\$ or intra muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$).ti,ab.

12. or/8-11

13. 7 and 12

ISI Science Citation Index 1981- 21.3.2004

Accessed via Web of Knowledge <http://wok.mimas.ac.uk/>

Search date: 24.3.04

1. TS=(estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)
2. TS=(diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
3. TS=(estracombi or estraderm tts or Estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menorest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan)
4. TS=(alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
5. TS=(parenteral*or patch or patches)
6. TS=(injection* or nonoral* or non oral* or depot)
7. TS=(transderm* or trans derm* or intraderm* or intra derm* or topical*)
8. TS=(cutaneous* or subcutaneous* or sub cutaneous* or percutaneous* or per cutaneous*)
9. TS=(intravenous* or intra venous* or intramuscular* or intra muscular*)
10. TS=(gel or gels or implant or implants or spray or sprays)
11. TS=(cream or creams or emulsion*)
12. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13. TS=(male or males or men or mens or man or mans or transsexual* or trans-sexual* or trans sexual* or cross-sex* or cross sex)
14. #11 and #12

ISI Proceedings 1990-19.3.04

Accessed via Web of Knowledge <http://wok.mimas.ac.uk/>

Search date 24.3.04

1. TS=(estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)
2. TS=(diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
3. TS=(estracombi or Estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menorest or progynova ts or

- oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan)
4. TS=(alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or estrace or vagifem or estrasorb)
 5. #1 or #2 or #3 or #4
 6. TS=(parenteral* or patch or patches or injection* or nonoral* or non oral* or depot or cutaneous* or subcutaneous* or sub cutaneous* or percutaneous* or per cutaneous* or transderm* or trans derm* or intraderm* or intra derm* or topical* or intravenous* or intra venous* or intramuscular* or intra muscular* or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion*)
 7. #5 and #6
 8. TS=(male or males or men or mens or man or mans or transsexual* or trans-sexual* or trans sexual* or crossex* or cross-sex* or cross sex*)
 9. #8 and #7

SIGLE (System for Information on grey literature) 1980-2003/12

Searched via OVID WebSPIRS

<http://arc.uk.ovid.com/webspirs/start.ws?customer=yku>

Search date: 24.3.04

- #1 (estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)
- #2 (diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
- #3 (estracombi or estraderm tts or estraderm mx or estrapak or evorel or fempak or dermestril or elleste solo mx or fematrix or femseven or menorest or progynova ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho gynest or etivex or honvan)
- #4 (alora or climara or clinagen la 40 or delestrogen or combipatch or depestrate or depgynogen or esclim or estra val 20 or estraderm or estragyn la or estrate la or fempatch or gynogen la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
- #5 #1 or #2 or #3 or #4
- #6 (parenteral* or patch or patches or injection* or nonoral* or non oral* or depot or cutaneous* or subcutaneous* or percutaneous* or per cutaneous* or transderm* or trans derm* or intraderm* or intra derm* or topical* or intravenous* or intra venous* or intramuscular* or intra muscular* or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion*)
- #7 #5 and #6
- #8 (male or males or men or mens or man or mans or transsexual* or trans sexual* or crossex* or cross sex*)
- #9 #7 and #8

Cochrane Central Register of Controlled Trials (CENTRAL) & Cochrane Database of Systematic Reviews (CDSR) The Cochrane Library Issue 1 2004

Accessed via <http://www.nelh.nhs.uk/cochrane.asp>

Search Date: 24.3.04

- #1 estrogens explode all trees (MeSH)
- #2 estrogens synthetic explode all trees (MeSH)
- #3 estradiol single term (MeSH)
- #4 dithystilbestrol explode all trees (MeSH)
- #5 (estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)

#6 (diethylstilbestrol or diethyl next stilbestrol or diethylstilboestrol or diethyl next stilboestrol or stilbestrol or stilboestrol or hexestrol or des)

#7 (estracombi or Estraderm next tts or Estraderm next mx or estrapak or evorel or fempak or dermestril or elleste next solo next mx or fematrix or femseven or menoest or progynova next ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho next gynest or etivex or honvan)

#8 (alora or climara or clinagen next la or delestrogen or combipatch or depestrate or depgynogen or esclim or estra next val or Estraderm or estragyn next la or estrate next la or fempatch or gynogen next la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

#10 infusions parenteral explode all trees term (MeSH)

#11 Injections explode all trees (MeSH)

#12 administration topical single term (MeSH)

#13 administration cutaneous single term (MeSH)

#14 drug implants single term (MeSH)

#15 (parenteral* or patch or patches or injection* or nonoral* or non next oral* or depot or cutaneous* or subcutaneous* or percutaneous* or per next cutaneous* or transderm* or trans next derm* or intraderm* or intra next derm* or topical* or intravenous* or intra next venous* or intramuscular* or intra next muscular* or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion*)

#16 #10 or #11 or #12 or #13 or #14 or #15

#17 #9 and #16

#18 male check tag (MeSH)

#19 transsexualism single term (MeSH)

#20 (transsexual* or trans next sexual* or crossex* or cross next sex*)

#21 #18 or #19 or #20

#22 #17 and #21

Database of Abstracts of Reviews of Effects (DARE) 1995-2004

Accessed via Internal CAIRS T system

Search date 24.3.04

- 1.(estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep).
2. (diethylstilbestrol or diethyl (w) stilbestrol or diethylstilboestrol or diethyl (w) stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
3. (estracombi or Estraderm (w) tts or estraderm (w) mx or estrapak or evorel or fempak or dermestril or elleste (w) solo (w) mx or fematrix or femseven or menoest or progynova (w) ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho (w) gynest or etivex or honvan)
4. (alora or climara or clinagen (w) la or delestrogen or combipatch or depestrate or depgynogen or esclim or estra (w) val or estraderm or estragyn (w) la or estrate (w) la or fempatch or gynogen (w) la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
5. #1 or #2 or #3 or #4
6. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non (w) oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per (w) cutaneous\$ or transderm\$ or trans (w) derm\$ or intraderm\$ or intra (w) derm\$ or topical\$ or intravenous\$ or intra (w) venous\$ or intramuscular\$ or intra (w) muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$)
7. #5 and #6
8. (male or males or men or mens or man or mans or transsexual\$ or trans(w)sexual\$ or crossex\$ or cross(w)sex\$)
9. #7 and #8

HTA (Health Technology Assessment Database) 1995-2004

Accessed via Internal CAIRS T system

Search date; 24.3.04

- 1.(estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)
2. (diethylstilbestrol or diethyl (w) stilbestrol or diethylstilboestrol or diethyl (w) stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
3. (estracombi or estraderm (w) tts or estraderm (w) mx or estrapak or evorel or fempak or dermestril or elleste (w) solo (w) mx or fematrix or femseven or menocest or progynova (w) ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho (w) gynest or etivex or honvan)
4. (alora or climara or clinagen (w) la or delestrogen or combipatch or depestrate or depgynogen or esclim or estra (w) val or estraderm or estragyn (w) la or estrate (w) la or fempatch or gynogen (w) la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
5. #1 or #2 or #3 or #4
6. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non (w) oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per (w) cutaneous\$ or transderm\$ or trans (w) derm\$ or intraderm\$ or intra (w) derm\$ or topical\$ or intravenous\$ or intra (w) venous\$ or intramuscular\$ or intra (w) muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$)
7. #5 and #6
8. (male or males or men or mens or man or mans or transsexual\$ or trans(w)sexual\$ or crossex\$ or cross(w)sex\$)
9. #7 and #8

NHS Economic Evaluations Database (NHS EED) 1995-2004

Accessed via Internal CAIRS T system

Search date: 24.3.04

- 1.(estrogen\$ or oestrogen\$ or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)
2. (diethylstilbestrol or diethyl (w) stilbestrol or diethylstilboestrol or diethyl (w) stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
3. (estracombi or Estraderm (w) tts or estraderm (w) mx or estrapak or evorel or fempak or dermestril or elleste (w) solo (w) mx or fematrix or femseven or menocest or progynova (w) ts or oestrogel or sanrena or organon or aeriodol or estradot or ovestin or ortho (w) gynest or etivex or honvan)
4. (alora or climara or clinagen (w) la or delestrogen or combipatch or depestrate or depgynogen or esclim or estra (w) val or estraderm or estragyn (w) la or estrate (w) la or fempatch or gynogen (w) la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
5. #1 or #2 or #3 or #4
6. (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non (w) oral\$ or depot or cutaneous\$ or subcutaneous\$ or percutaneous\$ or per (w) cutaneous\$ or transderm\$ or trans (w) derm\$ or intraderm\$ or intra (w) derm\$ or topical\$ or intravenous\$ or intra (w) venous\$ or intramuscular\$ or intra (w) muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$)
7. #5 and #6

8. (male or males or men or mens or man or mans or transsexual\$ or trans(w)sexual\$ or crossex\$ or cross(w)sex\$)
 9. #7 and #8

National Research Register (NRR) Issue 1 2004

Accessed via CDROM

Search date: 26.3.04

- #1 Estrogens*:ME
- #2 Estrogens-synthetic*:ME
- #3 Estradiol:ME
- #4 Diethylstilbestrol*:ME
- #5 (Estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol)
- #6 (estrone or oestrone or estradurin or polyestradiol or polyoestradiol or pep)
- #7 (Diethylstilbestrol or diethyl next stilbestrol or diethylstilboestrol or diethyl next stilboestrol or stilbestrol or stilboestrol or hexestrol or des)
- #8 (estracombi or Estraderm next tts or estraderm next mx or estrapak or evorel)
- #9 (fempak or dermestril or elleste next solo next mx or fematrix or femseven)
- #10 (menorest or progynova next ts or oestrogel or sanrena or organon or aeriadol)
- #11 (estratot or ovestin or ortho next gynest or etivex or honvan)
- #12 (alora or climara or clinagen next la or delestrogen or combipatch or depestrate or depgynogen or esclim or estra next val or estraderm or estragyn next la or estrate next la)
- #13 (fempatch or gynogen next la or lunelle or vivelle or premarin or kestrone or vagifem or estrace or estrasorb)
- #14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
- #15 Infusions-parenteral*:ME
- #16 Injections*:ME
- #17 Administration-topical:ME
- #18 Administration-cutaneous:ME
- #19 Drug implants:ME
- #20 (parenteral\$ or patch or patches or injection\$ or nonoral\$ or non next oral\$ or depot)
- #21 (cutaneous\$ or subcutaneous\$ or percutaneous\$ or per next cutaneous\$)
- #22 (transderm\$ or trans next derm\$ or intraderm\$ or intra next derm\$ or topical\$ or intravenous\$ or intra next venous\$)
- #23 (intramuscular\$ or intra next muscular\$ or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion\$)
- #24 #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
- #25 Transsexualism*:ME
- #26 (transsexual* or trans next sexual* or crossex* or cross next sex*)
- #27 Male*:ME
- #28 (male or males or men or mens or man or mans)
- #29 #25 or #26 or #27 or #28
- #30 #14 and #24 and #29

International Cancer Research Portfolio 2000-2004

<http://www.cancerportfolio.org>

Search date 26.3.04

The terms: estrogen\$ oestrogen\$ estradiol oestradiol estriol oestriol estrone oestrone estradurin polyestradiol polyoestradiol diethylstilbestrol diethylboestrol stilbestrol stilboestrol hexestrol

were searched individually with the terms:

Parenteral\$ patch\$ injection\$ nonoral\$ 'non oral\$' depot cutaneous\$ subcutaneous\$
percutaneous\$ transderm\$ intraderm\$ topical\$ intravenous\$ intramuscular\$ gel implant spray
cream emulsion\$

Current Controlled Trials

<http://controlled-trials.com/mrct/search.asp>

Search date 26.3.04

((estrogen! or estradiol! or estriol! or estrone! or estradurin or polyestradiol or polyoestradiol or diethylstilbestrol or diethylstilboestrol or stilbestrol or stilboestrol or hexestrol) and (parenteral% or patch% or injection% or nonoral% or "non oral%" or depot or cutaneous! or transderm% or intraderm% or topical or intravenous% or intramuscular% or gel or implant or cream or emulsion%))

Clinical Trials.gov

<http://www.clinicaltrials.gov/>

Search date: 26.3.04

The following terms were searched individually:

estrogen\$ oestrogen\$ estradiol oestradiol estriol oestriol estrone oestrone estradurin
polyestradiol polyoestradiol diethylstilbestrol diethylboestrol stilbestrol stilboestrol hexestrol

Within each set of results the following terms were searched:

parenteral or patch\$ or injection\$ or nonoral\$ or 'non oral\$' or depot or cutaneous or
subcutaneous or percutaneous or transderm\$ intraderm\$ or topical or intravenous\$ or
intramuscular\$ or gel or implant or spray or cream or emulsion

National Cancer Institute Clinical Trials PDQ

www.cancer.gov/clinicaltrials

Searched 6.4.04

Type of cancer: all

Type of trial: all

Drug: estrogen\$; oestrogen\$; estradiol; oestradiol; estriol; oestriol; estrone; oestrone; estradurin

Type of cancer: all

Type of trial: all

Drug: polyestradiol; polyoestradiol; diethylstilbestrol; diethylboestrol; stilbestrol; stilboestrol; hexestrol

Type of cancer: all

Type of trial: all

Drug: estracombi; estraderm; estrapak; evorel; fempak; dermestril; elleste; fematrix; femseven;
menorest; progynova; oestrogel; sanrena; organon; aeriodol; estradot; ovestin; ortho gynest; etivex;
honvan

Type of cancer: all

Type of trial: all

Drug: alora; climara; clinagen; delestrogen; combipatch; depestrate; depgynogen; esclim; estra val; Estraderm; estragyn; estrate; fempatch; gynogen; lunelle; vivelle; premarin; kestrone; vagifem; estrace; estrasorb

Index to Thesis 1970-2003

Accessed via <http://www.theses.com/idx>

Searched 29.3.04

((estrogen* or oestrogen* or estradiol or oestradiol or estriol or oestriol or estrone or oestrone or estradurin or polyestradiol or polyoestradiol or diethylstilbestrol or diethyl stilbestrol or diethylstilboestrol or diethyl stilboestrol or stilbestrol or stilboestrol or hexestrol) AND (parenteral* or patch or patches or injection* or nonoral* or depot or cutaneous* or subcutaneous* or percutaneous* or transderm* or intraderm* or topical* or intravenous* or intramuscular* or gel or gels or implant or implants or spray or sprays or cream or creams or emulsion*) AND (transsexual* or trans-sexual* or cross-sex* or male or males or men or mens or man or mans)))

Appendix 2. Data Extraction Form

Study Details	Participants	Intervention(s)	Outcomes: description	Outcomes: results	Comments
Author, Year	Diagnostic model used	(including number of participants in intervention and control groups, treatment type/drug and dose)	1.	Results	Additional outcomes reported
Endnote reference			2.		
Country/ies	Co-morbid disorders		3.	Adverse events	
Language of publication			4.		
Study objective	Number of participants		5.	Author's conclusions	Reviewer Comment
Study design	Number of withdrawals				
	Age (range)				
Funding source	Gender (Q.2 - side effects)				

Appendix 3. Quality Assessment Proforma

Each question may be answered as 'yes', 'no', 'not described', 'not relevant', or with free text to allow for assessment of studies where criteria are met in part, or there is reasonable room for doubt.

1. Was the study described as randomised?
2. Was the method of randomisation truly random?
3. Was the method of randomisation adequately concealed?
4. Was the study described as double blind?
5. Was the method of blinding appropriate?
6. Was the study description of withdrawals and drop-outs?

A comments field is also provided.

Appendix 4. List of Abbreviations

AS	Androgen suppression
b.i.d.	bis in die (twice daily)
CAD	Combined androgen ablation
CI	Confidence interval
CVS	Cardiovascular
DES	Diethylstilbestrol
DVT	Deep venous (vein) thrombosis
ECOG	Eastern Cooperative Oncology Group
FSH	Follicle stimulating hormone
LH	Luteinising hormone
LHRH	Luteinising hormone-releasing hormone
HR	Hazard ratio
i.m.	intramuscular
ITT	Intention to treat
i.v.	intravenous
MI	Myocardial Infarction
mon	month/s
NS	Not significant
OR	Odds ratio
Parenteral oestrogen+	Parenteral oestrogen combined with another treatment
PC	Prostate cancer
PEP	Polyestradiol phosphate
p.o.	per os (by mouth, orally)
RCT	Randomised clinical trial
SEM	Standard error of mean
SHBG	Sex hormone binding globulin
SPCG	Scandinavian Prostatic Cancer Group
t.i.d	ter in die (three times daily)
TNM	Tumour-node-metastasis
QoL	Quality of life
Wk(s)	week/s
WHO	World Health Organisation
yr(s)	year/s

Appendix 5. Stages and Grades

Staging classifies cancer according to its spread, with the most commonly used scheme assessing the tumour (T), lymph nodes (N) and secondary cancer or metastases (M) separately.

Tx	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
T1a	Clinically unapparent tumour not palpable or visible by imaging: incidental histological finding in 5% or less of tissue resected.
T1b	Clinically unapparent tumour not palpable or visible by imaging: incidental histological finding in more than 5% of tissue resected.
T1c	Clinically unapparent tumour not palpable or visible by imaging: tumour identified by needle biopsy (e.g. because of elevated PSA).
T2a	Tumour confined within the prostate gland: tumour involves one lobe.
T2b	Tumour confined within the prostate gland: tumour involves both lobes.
T3a	Tumour extends through the prostatic capsule: extracapsular extension.
T3b	Tumour extends through the prostatic capsule: tumour invades seminal vesicle(s).
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall.

Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastases.
N1	Regional lymph node metastases.

Mx	Distant metastases cannot be assessed.
M0	No distant metastases.
M1a	Metastases in non-regional lymph nodes.
M1b	Metastases in bone(s).
M1c	Metastases in other site(s).

Where Stages 1 through 4 are indicated, these broadly correlate with T1 through T4 above. In cases where metastases have occurred but the prostate tumour is still very small, the cancer is regarded as Stage 4. The Dukes' Jewett Staging System refers to these four stages as A through D.

Histopathological *grading* involves the qualitative assessment of the differentiation of a tumour expressed as the extent to which it resembles the normal tissue at that site.

Gx	Grade cannot be assessed.
G1	Well differentiated (slight anaplasia).
G2	Moderately differentiated (moderate anaplasia).
G3	Poorly differentiated/undifferentiated (marked anaplasia).

The Gleason system grades cancer according to its ability to form glandular structures. Two grades, taken from the two most common cell patterns of a sample, are added to give a reading of between 2 and 10.

1	Closely packed, well-defined glands within the prostate.
2	Less uniformly shaped glands.
3	Irregular gland of variable size.
4	A mass of fused glands.
5	Few, or no, visible glands; very little difference between them.

Appendix 6: List of Excluded Studies

Review question on efficacy and safety and review question on dose

1. Ockrim JL, Lalani EN, Laniado ME, Carter SS, Abel PD. Transdermal oestrogen therapy for advanced prostate cancer. *Br J Surg* 2002;89:634.
2. Herbert Irving Comprehensive Cancer Center. *Zoledronate and estradiol in preventing bone loss in patients with prostate cancer*⁴¹. National Cancer Institute (NCI), 2002. Available from: <http://controlled-trials.com/mrct/trial/ZOLEDRONATE/1059/63335.html>. [cited 2004 Jan 20]
3. Ockrim JL, Lalani EN, Laniado ME, Carter SS, Abel PD. Transdermal estrogen therapy for advanced prostate cancer - forward to the past? *J Urol* 2002;167:175.
4. Ahmed M, Choksy S, Chilton CP, Munson KW, Williams JH. High dose intravenous oestrogen (fosfestrol) in the treatment of symptomatic, metastatic, hormone-refractory carcinoma of the prostate. *Int Urol Nephrol* 1998;30:159-64.
5. Birke G, Wadstrom LB. Progynon, a depot preparation with oestrogenic action, in the treatment of prostatic carcinoma. *Acta Chir Scand* 1965;130:388-92.
6. Heap G. Proceedings: treatment of carcinoma of the prostate by continuous infusion of stilboestrol diphosphate (Honvan). *Br J Urol* 1976;48:152-3.
7. Takezawa Y, Nakata S, Kobayashi M, Kosaku N, Fukabori Y, Yamanaka H. Moderate dose diethylstilbestrol diphosphate therapy in hormone refractory prostate cancer. *Scand J Urol Nephrol* 2001;35:283-7.
8. Gerber GS, Zagaja GP, Ray PS, Rukstalis DB. Transdermal estrogen in the treatment of hot flushes in men with prostate cancer. *Urology*. 2000;55:97-101.
9. Aro J, Rannikko S, Haapiainen R, Alfthan O. Parenteral estrogen decreases cardiovascular mortality in prostatic cancer patients. *Eur J Surg Oncol* 1992;18 Suppl 1:70.
10. Collins G. Stillboestrol vs bicalcutamide in advanced prostate cancer. In: *National Research Register Issue 1 2004*. Oxford: Update Software.
11. Murphy GP. Follow-up evaluation of National Prostatic Cancer Project protocols and other studies. *Urology* 1994;44(6 suppl):61-6.
12. Protheroe A. A randomised phase II trial of dexamethasone and aspirin (DA) versus dexamethasone, diethylstilbestrol and aspirin (DAS) in locally advanced or metastatic cancer of the prostate. In: *National Research Register Issue 1 2004*. Oxford: Update Software.
13. Shipley WU. Phase III trial of androgen suppression before and during radiation therapy for locally advanced prostatic cancer: abstract report of RTOG 8610. *Prostate* 1994;24 Suppl 5:2-3.
14. Steg A, Benoit G. Prostatic carcinoma. Bilateral orchiectomy versus percutaneous administration of large doses of 17 beta estradiol. A comparative study. *Ann Urol* 1983;17:286-8.
15. Steg A, Benoit G, Limouzin-Lamothe MA. Percutaneous 17 beta-estradiol in treatment of cancer of the prostate. *Revue Francaise D'Endocrinologie Clinique Nutrition et Metabolisme* 1979;20:284-5.
16. Bulow H. Experience with polyestradiol phosphate (Estradurin) in treatment of advanced prostatic carcinoma. *Med Welt* 1980;31:1215-7.
17. Burke D. Bicalutamide and stiboestrol in advanced prostate cancer. In: *National Research Register Issue 1 2004*. Oxford: Update Software.
18. Cervellino JC, Araujo CE, Pirisi C, Podskubka O, Morera E. Combined hormonal therapy with high-dose diethylstilbestrol diphosphate (DES-DP) intravenous infusion plus vindesine (VND) for the treatment of advanced prostatic carcinoma: a controlled study. *J Surg Oncol* 1990;43:250-3.

19. Chamberlain J, Melia J, Moss S, Brown J. Report prepared for the health technology assessment panel of the NHS executive on the diagnosis, management, treatment and costs of prostate cancer in England and Wales. *Br J Urol* 1997;79:1-32.
20. Cox RL, Crawford ED. Estrogens in the treatment of prostate cancer. *J Urol* 1995;154:1991-8.
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Review question on adverse events

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Appendix 7: Data Extraction Tables

Q1: Review of effectiveness and safety

**Table 1: Parenteral oestrogens given alone
PEP i.m. at 240mg/month**

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Hedlund, 2002²³ Country: Multinational</p> <p>Language of Publication: English</p> <p>Setting: Multicentre: 61 Hospitals in Denmark, Finland, Iceland, Norway, Sweden</p> <p>Study Objective: 1. To compare overall survival between PEP and CAD (combined androgen ablation), assuming equivalence. 2. To compare time to clinical progression, cancer-specific survival, CVS toxicity, other adverse events, QoL.</p> <p>Funding Source: Ferring AB Sweden; Ferring Laegemidler A/S, Denmark; Pharmacia AB, Sweden; Schering-Plough AB, Sweden</p> <p>Duration: Trial period: Dec 1992 - Jun 1997; Follow-up period (median): Arm 1 - 27.1 mon, Arm 2 - 27.4 mon</p> <p>Analysis: Cox regression; Kaplan-Meier curves; Log-rank tests.</p>	<p>No. participants: 917</p> <p>No. withdrawn: 7</p> <p>Inclusion criteria: 1. Advanced prostatic carcinoma: Stage T0-4, Nx, M1, grade 1-3 TNM classification. 2. WHO performance status: 0-2. [Staging was based on histologic or cytologic findings, and existence of bone disease (M1) by scans.] 3. No previous systemic prostate cancer treatment. 4. No previous diagnosis with malignant disease (except basal cell carcinoma of the skin). 5. No myocardial or cerebral infarction = 1 mon before start of study. 6. No previous or present liver disease. 7. No belief that patient will be unable to comply with study protocol.</p> <p>Additional info: Patients stratified by country, ECOG performance status 0-1 vs 2, alkaline phosphatase < or > 1.25 x normal upper limit, previous CVS history. No significant differences in demographics, performance, CVS history and alkaline phosphatase level found at entry. Patients examined at 1 mon, 3 mon, and every 6 mon thereafter. Blood tests at 9 mon, and every 6 mon thereafter. The extent of bone disease calculated by a modified Soloway score.</p> <p>Tumour stages/grades: Arm 1: T0 [n=1]; T1 [n=14]; T2 [n=68]; T3 [n=244]; T4 [n=110] Soloway: 1 [n=152]; 2 [n=250]; 3 [n=49]</p>	<p>Parenteral oestrogen: Alone</p> <p>Arm 1: Polyoestradiol phosphate (PEP) (Estradurin) 240 mg i.m. every 2 w for 2 mon, every mon subsequently. No. patients: 455 No. withdrawn:</p> <p>Arm 2: Flutamide & Triptorelin or Orchiectomy 250 mg Flutamide p.o. t.i.d; 3.75 mg Triptorelin i.m. every mon (n = 298), or optionally bilateral orchidectomy (n = 159). No. patients: 455 No. withdrawn:</p>	<p>Disease Progression: Median time to clinical progression Arm 1: 13.7 mon (95% CI: 12.5, 14.9) Arm 2: 13.5 mon (95% CI: 12.4, 14.6) Stats: NS difference (p = 0.87, log rank) Subgroups:</p> <p>Survival: Cancer-specific mortality Arm 1: 239/455 Arm 2: 252/455 Stats: HR = 0.91 (95% CI: 0.77, 1.08), NS Equally effective in terms of survival (p = 0.001 Kaplan-Meier) Subgroups:</p> <p>Survival: All-cause mortality Arm 1: 277/455 Arm 2: 279/455 Stats: HR = 0.96 (95% CI: 0.82, 1.12), NS Equally effective in terms of survival (p = 0.001 Kaplan-Meier) Subgroups: Arm 1 vs Arm 2: prostate cancer: 223 vs 223 other disease with prostate cancer contributing: 16 vs 29 (NS) other disease without prostate cancer contributing: 29 vs 21 (NS) unknown: 9 vs 6</p> <p>Survival: CVS mortality [CVS disease predefined as MI, angina pectoris, cerebrovascular infarction/transitory ischemic attacks, intermittent claudication, cardiac decompensation, or thromboembolism.] Arm 1: 23/455 Arm 2: 23/455 Stats: Not reported Subgroups: Prostate cancer contribution: 8 vs 10</p>	<p>Authors' conclusions: Treatments are equally efficacious in terms of disease progression, and cancer-specific and overall survival. No significant increase in CVS mortality was seen with PEP, but there was a significant increase in non-fatal ischaemic heart disease and heart decompensation.</p> <p>Additional outcomes: Dose reduction/termination due to adverse events: Arm 1: CVS: n=1/10; gynaecomastia: n=0/1; misunderstanding: n=2/1 Arm 2: flushes: n=0/2</p> <p>Reviewer comment: This report supersedes Hedlund and Henriksson, 2000⁴¹. Cause of death and assessment of CVS events was determined by a cardiologist blind to treatment.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Yes 3. Randomization adequately concealed? Not described 4. Described as double-blind? No* 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Yes</p>

	<p>Grade: 1 [n=67]; 2[n =211]; 3 [n=163]</p> <p>Arm 2: T0 [n=4]; T1 [n=19]; T2 [n=78]; T3 [n=249]; T4 [n=98] Solway: 1 [n=167]; 2 [n=233]; 3 [n=49] Grade: G1 [n=69]; G2 [n=203]; G3 [n=177]</p> <p>Diagnosis: Prostatic carcinoma</p> <p>Co-morbidity:</p> <p>Age (range): Arm 1: 71.9 y; Arm 2: 72.2 y (Arm 1: 71.2 - 72.6 y; Arm 2: 71.5 - 72.9 y)</p>		<p>Adverse Events: CVS morbidity</p> <p>Arm 1: 57/455 Arm 2: 36/455</p> <p>Stats: Ischemic heart disease p = 0.009 Heart decompensation p = 0.035</p> <p>Subgroups: Arm 1 vs Arm 2: ischemic heart disease: 17 vs 5 heart decompensation: 20 vs 9 ischemic cerebral disease: 9 vs 10 venous thromboembolism: 9 vs 10 intermittent claudication: 2 vs 3</p>	
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STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Mikkola, 1998²¹ Country: Finland</p> <p>Language of Publication: English</p> <p>Setting: Multicentre: No further detail</p> <p>Study Objective: To evaluate the clinical efficacy and CVS complications of orchidectomy or Polyoestradiol phosphate (PEP) in the treatment of advanced prostatic cancer.</p> <p>Funding Source: Not reported (Study based on Finnprostate 6)</p> <p>Duration: Diagnosis period: Jan 1990 - Mar 1994; Follow-up period: 2 y</p> <p>Analysis: Life-table techniques; Log-rank tests.</p>	<p>No. participants: 444</p> <p>No. withdrawn: Not reported.</p> <p>Inclusion criteria: 1. Locally advanced (T3-4 M0) or metastasized (T1-4 M1) prostatic cancer. 2. Patient consent. 3. Compliance. 4. No other malignancy except skin cancer (not melanoma). 5. No previous hormonal therapy. 6. No symptomatic coronary heart disease. 7. No contraindications to oestrogen therapy (untreated heart failure, previous pulmonary embolism or deep vein thrombosis, permanent antithrombotic therapy, liver insufficiency).</p> <p>Additional info: Tumour stages/grades: Grade I, T3-4M0 [Arm 1: n=28 (24%); Arm 2: n=36 (29%)] Grade I, T1-4M1 [Arm 1: n=20 (20%); Arm 2: n=27 (26%)] Grade 2, T3-4M0 [Arm 1: n=73 (61%); Arm 2: n=71 (57%)] Grade 2, T1-4M1 [Arm 1: n=60 (61%); Arm 2: n=57 (56%)] Grade 3, T3-4M0 [Arm 1: n=18 (15%); Arm 2: n=18 (14%)] Grade 3, T1-4M1 [Arm 1: n=18 (18%); Arm 2: n=18 (18%)]</p> <p>Diagnosis: Prostatic carcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): 73 y (45 - 91 y)</p>	<p>Parenteral oestrogen: Alone</p> <p>Arm 1: Orchidectomy Bilateral total or subcapsular. No. patients: 217 No. withdrawn: Not reported.</p> <p>Arm 2: Polyoestradiol phosphate (PEP) (Estradurin) 320 mg i.m. initially, 240 mg every mon subsequently. Single pretreatment dose of irradiation to breast area. No. patients: 227 No. withdrawn: Not reported.</p>	<p>Disease Progression: Evidence of progression [Evaluated with SPCG criteria] Arm 1: 32/217 (15%) patients at 1 y follow-up; 33/176 (19%) additional patients at 2 y follow-up Arm 2: 33/227 (15%) patients at 1 y follow-up; 31/176 (18%) additional patients at 2 y follow-up Stats: No significant difference. Subgroups: M0 subgroup: Arm 1: 4/119 (3%) patients during 1st y, 10/112 (9%) patients during 2nd y Arm 2: 7/125 (6%) patients during 1st y, 10/112 (9%) patients during 2nd y</p> <p>M1 subgroup: Arm 1: 28/98 (29%) patients during 1st y, 23/64 (36%) patients during 2nd y Arm 2: 26/102 (26%) during 1st y, 21/64 (33%) patients during 2nd y</p> <p>Survival: Death from prostate cancer Arm 1: 4/217 (2%) deaths at 1 y follow-up; 3/176 (2%) deaths at 2 y follow-up Arm 2: 6/227 (3%) deaths at 1 y follow-up; 2/176 (1%) deaths at 2 y follow-up Stats: No significant difference. Subgroups: M0 subgroup: Arm 1: 0 deaths Arm 2: 0 deaths</p> <p>M1 subgroup: Arm 1: 4/98 (4%) deaths during 1st y; 3/64 (5%) deaths during 2nd y Arm 2: 6/102 (6%) deaths during 1st y; 2/64 (3%) deaths during 2nd y</p> <p>Survival: CVS mortality Arm 1: 5 MI deaths/217 patients Arm 2: 8 MI deaths/227 patients, 2 deaths from cerebral infarction/227 patients, 4 deaths from pulmonary embolism/227 patients Stats: At 24 mon follow-up, OR=2.45 (95% CI: 1.26, 5.15) $\chi^2=5.58$, $p<0.05$ for all CVS complications Subgroups: M0 subgroup: Arm 1: 0/119 deaths during 1st y; 1/112 (1%) deaths during 2nd y</p>	<p>Authors' conclusions: PEP (240 mg/mon) was as efficient as orchidectomy in inhibiting cancer progression, but there were more CVS complications in patients treated with PEP.</p> <p>Additional outcomes: Additional adverse events were reported.</p> <p>Reviewer comment: Any losses to follow-up were not explicitly reported. There were, however, 6 cases (Arm 1: 2, Arm 2: 4) of therapy change due to non-CVS side effects.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? No</p>

			<p>Arm 2: 3/125 (2%) deaths during 1st y, 5/112 (6%) deaths during 2nd y</p> <p>M1 subgroup: Arm 1: 1/98 (1%) deaths during 1st y, 3/64 (5%) deaths during 2nd y Arm 2: 3/102 (3%) deaths during 1st y, 3/64 (5%) deaths during 2nd y</p> <p>Survival: Deaths from other cause Arm 1: 4 deaths from pneumonia/217 patients, 2 accidental deaths/217 patients, 1 death from ruptured thoracic aneurysm/217 patients, 1 death from septicaemia/217 patients, 1 death from ventricular cancer/217 patients, 1 death from volvulus and strangulation of the small bowel/217 patients, 1 death from pulmonary cancer/217 patients Arm 2: 3 deaths from pneumonia/227 patients, 1 death from gastrointestinal haemorrhage/227 patients, 1 death from ventricular cancer/227 patients Stats: Not reported. Subgroups: Not reported.</p> <p>Adverse Events: CVS morbidity Arm 1: 2 MI/217 patients, 1 cerebral infarction/217 patients, 2 DVT/217 patients Arm 2: 4 MI/227 patients, 5 cerebral infarctions/227 patients, 1 pulmonary embolism/227 patients Stats: At 24 mon follow-up, OR=2.45 (95% CI: 1.26, 5.15); $\chi^2= 5.58$, $p<0.05$ for all CVS complications</p> <p>Subgroups: M0 subgroup: Arm 1: 1/119 (1%) patient during 1st y, 2/112 (2%) patients during 2nd y Arm 2: 2/125 (2%) patients during 1st y, 2/112 (2%) additional patients during 2nd y</p> <p>M1 subgroup: Arm 1: 1/98 (1%) patients during 1st y, 1/64 (2%) patients during 2nd y Arm 2: 6/102 (6%) patients during 1st y, 0 during 2nd y</p>	
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STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Henriksson, 1999²² Country: Sweden</p> <p>Language of Publication: English</p> <p>Setting: 1 Hospital in Sweden</p> <p>Study Objective: To pilot a pharmacokinetically guided PEP dosage regime in patients with advanced prostate cancer, intended to accelerate endocrine effects and to avoid CVS side effects.</p> <p>Funding Source: Swedish Medical Research Council; LEO Research Foundation</p> <p>Duration: Trial period: Not stated; Follow-up period: 2 y</p> <p>Analysis: Descriptive analysis only.</p>	<p>No. participants: 33</p> <p>No. withdrawn: 0</p> <p>Inclusion criteria: 1. Histo- and/or cytologically verified newly detected untreated advanced prostatic carcinoma.</p> <p>Additional info: Both groups were similar for demographics, CVS history and blood pressure at baseline. There were twice as many smokers (n=8 vs n=4) in Arm 2. Digital rectal examinations were performed before treatment and every 3rd mon. Blood samples were taken from Arm 1 every 2 w for 6 mon, then every 3 mon, while they were taken only for 6 mon from Arm 2, then every 3 mon.</p> <p>Tumour stages/grades: Arm 1: T3 [n=12]; T4 [n=5]; Mets [n=2]; G2 [n=9]; G3 [n=8] Arm 2: T3 [n=10]; T4 [n=6]; Mets [n=2]; G2 [n=11]; G3 [n=5]</p> <p>Diagnosis: Locally advanced prostatic carcinoma</p> <p>Co-morbidity: None had endocrine, biliary, intestinal, renal or hepatic malfunction.</p> <p>Age (range): Arm 1: 72 y; Arm 2: 73 y (Arm 1: ± 7.2 y; Arm 2: ± 6 y)</p>	<p>Parenteral oestrogen: Alone</p> <p>Arm 1: Polyoestradiol phosphate (PEP) (Estradurin) 240 mg i.m. every 2 w for 2 mon, every mon subsequently. Single pretreatment dose of irradiation to breast area. No. patients: 17 No. withdrawn: 0</p> <p>Arm 2: Orchiectomy Bilateral. No. patients: 16 No. withdrawn: 0</p>	<p>Disease Progression: Response to therapy Arm 1: 14/17 Arm 2: 12/16 Stats: Not reported. Subgroups: Arm 1: 5 partial, 9 complete responses; 3 progressed 9-18 mon after therapy began. Arm 2: 7 partial, 5 complete responses; 3 progressed 7-15 mon after therapy began.</p> <p>Survival: All-cause mortality Arm 1: 0/17 Arm 2: 1/16 Stats: Not reported. Subgroups: 1 death unrelated to prostatic carcinoma or CVS disease.</p> <p>Adverse Events: CVS events Arm 1: 1/17 (6%) Arm 2: 4/16 (24%) Stats: Not reported. Subgroups: Arm 1: Acute MI x 1 Arm 2: Acute MI x 1, CVS lesion x 2, congestive heart failure x 1 All events occurred in patients with previous CVS history, except 2 CVS lesions.</p> <p>Adverse Events: Hot flushes Arm 1: 0/17 Arm 2: 7/16 Stats: Not reported. Subgroups:</p> <p>Adverse Events: Gynaecomastia/nipple tenderness Arm 1: 11/17 Arm 2: 0/16 Stats: Not reported. Subgroups:</p>	<p>Authors' conclusions: PEP is an efficient timesaving oestrogen treatment with a favourable side-effect profile.</p> <p>Additional outcomes: Serum estradiol: Arm 1: increased from 87 ±33 pmol/l to 1974 ±484 pmol/l after 8 w. Observed concentrations ranged from 1,400 - 4,500 pmol during remainder of 2 y period. Arm 2: reduced from 82 ±21 pmol/l to a level below the limit of determination within 4 w.</p> <p>Serum testosterone: Arm 1: decreased from pretreatment value of 15.0 ±3.3 nmol/l to 1.3 ±0.4 nmol/l after 4 w of treatment and within 6 w, and thereafter was below or close to the limit of determination. Arm 2: reduced from a pretreatment value of 15,7 ±4.0 nmol/l to a mean level below the limit of determination within 4 w.</p> <p>Coagulation factor VII</p> <p>Reviewer comment: This is a pilot study requiring confirmation in a larger RCT, with increased follow-up to evaluate disease-free survival.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Yes</p>

PEP i.m at 160mg/month

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Lukkarinen, 1994²⁰ Country: Finland</p> <p>Language of Publication: English</p> <p>Setting: 13 Hospitals</p> <p>Study Objective: To compare the efficacy of, and tolerance to an LHRH agonist with Polyoestradiol phosphate, with special attention given to CVS side effects.</p> <p>Funding Source: Not reported</p> <p>Duration: Trial period: 1986 - 1989; Follow-up period (mean): Arm 1 - 26 mon, Arm 2 - 23 mon</p> <p>Analysis: Kaplan-Meier curves, χ^2 tests; Wilcoxon's tests.</p>	<p>No. participants: 236</p> <p>No. withdrawn: Not reported.</p> <p>Inclusion criteria: 1. Histologic diagnosis of prostatic carcinoma. 2. Advanced prostatic carcinoma: T0-T4, N0-1, M1; T3-T4, N0, M0. 3. Life expectancy > 3 mon. 4. Fit for oestrogen treatment. 5. No previous hormone therapy, chemotherapy, radiotherapy or orchidectomy. 6. No severe ureteric obstruction and/or incipient spinal cord compression. 7. No severe CVS or cerebrovascular disease, atherosclerosis or >2 myocardial infarctions. 8. No concurrent malignancy.</p> <p>Additional info: Clinical stages: T2 NX M1[n=1]; T3 NX M0[n=94]; T3 NX M1[n=45]; T4 NX M0[n=36]; T4 NX M1[n=60]. Histologic grades: 1 [n=64]; 2 [n=143]; 3 [n=27]; Unknown [n=2]</p> <p>Diagnosis: Advanced prostatic carcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): 73 y (Arm 1: 49 - 100 y; Arm 2: 55 - 90 y)</p>	<p>Parenteral oestrogen: Alone</p> <p>Arm 1: Goserelin acetate (Zoladex) 3.6 mg subcutaneous depot injection every 28 day. No. patients: 129 No. withdrawn: 0</p> <p>Arm 2: Polyoestradiol phosphate (PEP) (Estradurin) 160 mg i.v. every mon. No. patients: 107 No. withdrawn: 0</p>	<p>Disease Progression: Time to progression of prostatic carcinoma [Progression defined as increase of prostatic dimensions by 50% or volume by 30%, appearance of new bone metastasis, appearance of new extraskelatal metastasis or increase by 25% of existing measurable extraskelatal metastasis.] Arm 1: Graphical presentation of data Arm 2: Graphical presentation of data Stats: $p=0.0009$ favouring Arm 1 Subgroups: Graphical presentation of data for all subgroups. Histologic differentiation grade: better response to Arm 1 treatment in highly ($p=0.01$) and moderately ($p=0.02$) differentiated prostatic carcinoma M0/M1 tumours: Arm 1 treatment showed higher effectiveness in M0 tumours ($p=0.002$)</p> <p>Disease Progression: Objective response [Objectively complete regression defined as no evidence of residual tumour. Objectively partial response defined as reduction of prostatic dimensions by 50% or volume by 35%, serum acid phosphatase normalized or reduced by 80%, decrease of bone metastases, healing of possibly osteolytic bone metastases, measurable extraskelatal metastases reduced by 50%. Objective progression defined as no objective progression and insufficient evidence for partial objective regression.] Arm 1: 84 cases/129 patients Arm 2: 50 cases/107 patients Stats: Clear difference for M0 cases but not M1. Subgroups: Arm 1: M0 subgroup: 48 cases [denominator not stated] M1 subgroup: 36 cases [denominator not stated]</p> <p>Arm 2: M0 subgroup: 25 cases [denominator not stated] M1 subgroup: 25 cases [denominator not stated]</p> <p>Survival: Mortality Arm 1: 14 deaths/129 patients (11%) Arm 2: 13 deaths/107 patients (12%)</p>	<p>Authors' conclusions: The LHRH agonist was more effective than Polyoestradiol phosphate, particularly in locally advanced and highly or moderately differentiated prostatic carcinomas. Both regimens were well tolerated with CVS related deaths equally represented.</p> <p>Additional outcomes: Subjective response to therapy [Defined as 1. No increase in tumour activity, bone pain or analgesic use. 2. Either a clear decrease in subjective symptoms or a decrease in possible tumour activity, bone pain or analgesic use.] Time to objective response Changes in prostate volume Further adverse events: affected libido, affected erection, hemiplegia, allergic dermatitis, hyperbilirubinaemia, headache, diarrhoea, increased SGOT, itching, skin rash.</p> <p>Serum concentrations of: Prostate-specific acid phosphatase (ng/ml): Arm 1: Baseline: 76.0; 24 wks: 8.3; 48 wks: 6.5; 72 wks: 2.0; 96 wks: 1.6; 120 wks:1.8; 144 wks: 2.3 Arm 2: Baseline: 33.2; 24 wks: 25.7; 48 wks: 5.2; 72 wks: 3.6; 96 wks: 2.2; 120 wks: 2.8; 144 wks: 7.4</p> <p>Testosterone (ng/ml): Arm 1: Baseline: 17.6; 24 wks: 1.2; 48 wks: 1.2; 72 wks: 1.1; 96 wks: 1.1; 120 wks:1.0; 144 wks: 0.9 Arm 2: Baseline: 16.3; 24 wks: 2.8; 48 wks: 1.9; 72 wks: 1.6; 96 wks: 2.0; 120 wks: 1.7; 144 wks: 1.0</p>

			<p>Stats: Not reported. Subgroups: Arm 1: Causes of death: MI (7), Prostatic cancer (3), Other cancer (1), Pneumonia (1), Septicaemia (1) & Cerebral embolism (1). Arm 2: Causes of death: MI (6), Prostatic cancer (3), Other cancer (1), Senility (2), Congestive cardiac failure (1).</p> <p>Adverse Events: Hot flushes Arm 1: 106/129 (85%) Arm 2: 29/107 (28%) Stats: Not reported. Subgroups: Not reported.</p> <p>Adverse Events:Gynaecomastia Arm 1: 8/129 (6%) Arm 2: 67/107 (63%) Stats: Not reported. Subgroups: Not reported.</p> <p>Adverse Events: Congestive cardiac failure Arm 1: 0/129 patients Arm 2: 4/107 patients Stats: Not reported. Subgroups: Not reported.</p> <p>Adverse Events: Myocardial Infarction Arm 1: 4/129 patients Arm 2: 8/107 patients Stats: Not reported. Subgroups: Not reported.</p> <p>Adverse Events: Tachycardia Arm 1: 0/129 patients Arm 2: 2/107 patients Stats: Not reported. Subgroups: Not reported.</p>	<p>Reviewer comment: It is not clear from the paper whether there were any losses to follow-up.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? No</p>
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STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Haapiainen, 1990¹⁸ {See also Aro, 1989³³ and Aro, 1990³⁵}</p> <p>Country: Finland</p> <p>Language of Publication: English</p> <p>Setting: 9 Hospitals</p> <p>Study Objective: 1. To compare the clinical efficacy of orchidectomy and Polyoestradiol phosphate (PEP) in patients with advanced prostatic cancer. 2. To evaluate effect of daily low dose ASA on possible CVS complications during the 1st 6 mon of oestrogen therapy.</p> <p>Funding Source: Not reported (Study based on Finnprostate II)</p> <p>Duration: Diagnosis period: Jan 1985 - Mar 1987; Follow-up period (minimum): 2 y</p> <p>Analysis: χ^2 tests; Product limit survival analysis; Cox's proportional hazards model.</p>	<p>No. participants: 200</p> <p>No. withdrawn: 17*</p> <p>Inclusion criteria: 1. No previously treated prostatic cancer. 2. No history of acute thromboembolic episode. 3. No non-respondent decompensated cardiac insufficiency. 4. No severe liver disease. 5. No daily use of acetosalicylic acid (ASA). 6. No allergy to ASA. 7. No anticoagulant therapy.</p> <p>Additional info: * denotes withdrawals documented at 6 mon.</p> <p>No significant differences re. local extent of tumour, presence of distant metastases or histological differentiation grade were detected.</p> <p>Tumour stages/grades: T0-2 [Arm 1: n=7; Arm 2: n=10] T3-4 [Arm 1: n=68; Arm 2: n=115] M0 [Arm 1: n=47; Arm 2: n=66] M1 [Arm 1: n=28; Arm 2: n=59] G1 [Arm 1: n=15; Arm 2: n=30] G2 [Arm 1: n=45; Arm 2: n=82] G3 [Arm 1: n=15; Arm 2: n=13]</p> <p>Diagnosis: Prostatic carcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): Arm 1: 72.6 y; Arm 2: 70.7 y (Arm 1: 56 - 84 y; Arm 2: 52 - 84 y, Arm 3: 55 - 82 y)</p>	<p>Parenteral oestrogen: Alone</p> <p>Arm 1: Orchidectomy Bilateral total or subcapsular. No. patients: 75 No. withdrawn: 3*</p> <p>Arm 2: Polyoestradiol phosphate (PEP) (Estradurin) & Acetosalicylic acid (ASA) 160 mg i.m. every mon & 75 mg ASA p.o. daily for first 6 mon. No. patients: 71 No. withdrawn: 6*</p> <p>Arm 3: Polyoestradiol phosphate (PEP) (Estradurin) & placebo 160 mg PEP i.m. every mon i.m.; placebo p.o. daily for 1st 6 mon. No. patients: 54 No. withdrawn: 8*</p>	<p>Disease Progression: Evidence of progression [Evaluated with SPCG Criteria] Arm 1: 16/75 (21%) patients at 2 y follow-up Arm 2: 51/125 (41%) patients at 2 y follow-up Stats: $p=0.004$ for outcomes 1 & 2 together Subgroups: M0 subgroup: Arm 1: 3/47 patients Arm 2: 22/66 patients $p=0.009$ for outcomes 1 & 2 together</p> <p>M1 subgroup: Arm 1: 13/28 patients Arm 2: 29/59 patients $p=0.3$ for outcomes 1 & 2 together</p> <p>Survival: Death from prostate cancer Arm 1: 5/75 (7%) deaths at 2 y follow-up Arm 2: 6/125 (5%) deaths at 2 y follow-up Stats: $p=0.004$ for outcomes 1 and 2 together</p> <p>Subgroups: M0 subgroup: Arm 1: 3/47 deaths Arm 2: 0/66 deaths $p=0.009$ for outcomes and 2 together</p> <p>M1 subgroup: Arm 1: 2/28 deaths Arm 2: 6/59 deaths $p=0.3$ for outcomes 1 and 2 together</p> <p>Survival: CVS mortality Arm 1: 1 death/75 patients Arm 2: 2 deaths/125 patients</p> <p>Survival: Other mortality Arm 1: 0 deaths/75 patients Arm 2: 4 deaths/125 patients</p> <p>Subgroups: 1 suicide, 2 pneumonias, 1 uraemia not related to basic disease</p> <p>Adverse Events: ASA allergic reactions/haemorrhagic complications Arm 1: 0 Arm 2: 0 Arm 3: 0</p>	<p>Authors' conclusions: PEP 160mg/mon is clinically insufficient in the treatment of advanced prostatic cancer. Orchidectomy is still an important method for treating patients with locally advanced or metastatic prostatic carcinoma.</p> <p>Additional outcomes: Aro, 1990³⁵ measured urinary flow in the same patient group. Aro, 1989³³ measured same outcomes at 6 mon follow-up.</p> <p>Reviewer comment: Note that ASA + placebo were initially randomised in the oestrogen group, but treatment was identical after the first 6 mon - arms 2 + 3 are combined in the results. A box of envelopes was delivered to each hospital with one-third of the envelopes coded for each treatment arm. The randomisation of oral ASA or placebo to the oestrogen-treated patients was described as double blind. A description of withdrawals is given only at 6 mon. Apparently well conducted although results for arms 2 and 3 were undifferentiated. Exclusion of patients with previous incidence of CVS disease associated with low incidence of CVS events.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Partly</p>

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Aro, 1993¹⁹ Country: Finland</p> <p>Language of Publication: English</p> <p>Setting: Multicentre: (Finnprostate IV)</p> <p>Study Objective: 1. To compare the clinical efficacy of PEP and Buserelin in prostate cancer; 2. To evaluate the CVS complications and mortality of the two treatments.</p> <p>Funding Source: Finnish Cancer Foundation; Hoechst AG</p> <p>Duration: Follow-up period: 36 mon</p> <p>Analysis: χ^2 tests; Product limit survival analysis.</p>	<p>No. participants: 147</p> <p>No. withdrawn: 0</p> <p>Inclusion criteria: 1. Locally advanced (T3 or more) or metastasised (M1) prostatic adenocarcinoma, confirmed cyto- and/or histologically. 2. No previous diagnosis or treatment of prostate cancer. 3. No history of other malignancy. 4. No history of acute thromboembolic episode. 5. No myocardial infarction in past y. 6. No treatment-resistant decompensated cardiac insufficiency. 7. No known severe liver disease. 8. No known senility or mental disturbance.</p> <p>Additional info: Patients examined at 2 or 3, 6, and 12 mon, and every 6 mon thereafter. Also examined whenever symptoms suggested progression. Progression defined as tumour or metastases growth > 25%, or new metastases.</p> <p>Tumour stages/grades: T0-2 [Arm 1: n=6; Arm 2: n=7] T3-4 [Arm 1: n=64; Arm 2: n=70] G1 [Arm 1: n=16; Arm 2: n=16] G2 [Arm 1: n=37; Arm 2: n=55] G3 [Arm 1: n=17; Arm 2: n=6] M0 [Arm 1: n=41; Arm 2: n=47] M1 [Arm 1: n=29; Arm 2: n=30]</p> <p>Diagnosis: Advanced prostatic carcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): 72 y (55 - 86 y)</p>	<p>Parenteral oestrogen: Alone</p> <p>Arm 1: Polyoestradiol phosphate (PEP) (Estradurin) 160 mg i.m every mon. Single pretreatment dose of irradiation to breast area =< 2 w before treatment. No. patients: 70 No. withdrawn: 0</p> <p>Arm 2: Buserelin & Cypreterone acetate 6.6 mg Buserelin subcutaneous implant every 8 w. 100 mg Cypreterone acetate p.o. daily, from 1 w before until 2 w after starting Buserelin. No. patients: 77 No. withdrawn: 0</p>	<p>Disease Progression: Non-progression rate at 3 y Arm 1: 0.53 Arm 2: 0.70 Stats: $p < 0.001$ Subgroups:</p> <p>Survival: CVS Mortality Arm 1: 4/70 Arm 2: 4/77</p> <p>Adverse Events: CVS complications Arm 1: 1/70 Arm 2: 2/77</p>	<p>Authors' conclusions: PEP 160 mg/mon was not associated with increased risk of CVS complications, but was too low a dose to be effective.</p> <p>Additional outcomes:</p> <p>Reviewer comment:</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Yes 3. Randomization adequately concealed? Yes 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Not relevant</p>

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Bishop, 1989¹⁷ Country: United Kingdom</p> <p>Language of Publication: English</p> <p>Setting: Not stated</p> <p>Study Objective: To review the use of oestrogens as a means of treating prostatic cancer.</p> <p>Funding Source: Financial assistance from individual</p> <p>Duration: Not reported</p> <p>Analysis:</p>	<p>No. participants: 117</p> <p>No. withdrawn: Not reported.</p> <p>Inclusion criteria: 1. Advanced prostatic carcinoma. 2. Advanced symptomatic disease.</p> <p>Additional info: 32 patients randomised to oestrogen treatment were subsequently given orchidectomy after non-response or early relapse following 3 mon oestrogen treatment. 11 patients had no evidence of bone metastases. Percentages of patients with obstruction, lymphoedema or lymphadenopathy or M1 patients with skeletal pain are given with the results.</p> <p>Diagnosis: Advanced prostatic carcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): Not reported. ()</p>	<p>Parenteral oestrogen: Alone</p> <p>Arm 1: Polyoestradiol phosphate (PEP) (Estradurin) 160 mg every mon. Orchidectomy for unresponsive or relapsed patients after 3 mon PEP. No. patients: 61 No. withdrawn: 0</p> <p>Arm 2: Orchidectomy Bilateral supcapsular. No. patients: 56 No. withdrawn: 0</p>	<p>Disease Progression: Local disease response improvement Arm 1: 72% (n=25) response: of these: 84% bladder response; 8% ureteric response; 8% rectal response; 28% no response Arm 2: 89% (n=18) response: Of these 72% bladder response; 17% ureteric response; 11% rectal response; 11% no response</p> <p>Disease Progression: Reduction of skeletal pain from bone metastases Arm 1: Max response achieved within <1mon: 58%; 1-2mon: 27%; >2mon: 12%; no response: 0 (n=36) Arm 2: Max response achieved within < 1mon: 44%; 1-2 mon: 36%; >2 mon: 16%; no response: 4% (n=25)</p> <p>Disease Progression: Diminution of lymphoedema or lymphadenopathy Arm 1: 5/5 Arm 2: 15/15</p> <p>Adverse Events: CVS morbidity including death Arm 1: 8/61 (13%) (5 non-fatal events and 3 deaths) Arm 2: 4/56 (7%) (all deaths from MI)</p> <p>Adverse Events: CVS mortality Arm 1: 3/61(5%) MI Arm 2: 4/56 (7%) MI</p>	<p>Authors' conclusions: Most prostate cancer patients will respond to low dose (parenteral) oestrogen therapy. Monitoring of plasma testosterone levels is required to achieve maximal tumour suppression with minimal risk of thromboembolic side-effects. Given these improvements, oestrogen therapy can be considered as a third option which compares favourably with costly LHRH analogues and surgical orchidectomy.</p> <p>Additional outcomes: Plasma testosterone levels; plasma LH levels; plasma estradiol levels: In each case individual patient data is presented without appropriate summary measures.</p> <p>Reviewer comment: No survival data is presented so the authors' conclusions with respect to efficacy should be treated with caution. Minimal information is given regarding the comparability of the two groups at baseline. It is unclear which treatment arms the 11 M0 patients were allocated to. No statistical tests were carried out. There is not enough information to determine whether the method of randomisation was appropriate or whether there was adequate concealment of allocation. No loss to follow-up was reported.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? No</p>

Other parenteral oestrogen preparations

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Jacobi, 1980¹⁵ Country: Germany</p> <p>Language of Publication: English</p> <p>Setting: Not stated</p> <p>Study Objective: To assess Cyproterone acetate as an alternative treatment for advanced prostatic cancer in terms of tumour response.</p> <p>Funding Source: Not reported</p> <p>Duration: Recruitment period: 15 mon; Treatment period: 6 mon</p> <p>Analysis: Not reported.</p>	<p>No. participants: 42</p> <p>No. withdrawn: 0</p> <p>Inclusion criteria: 1. Histologically proven prostatic adenocarcinoma including classification of tumour grade (G0-GIII). 2. No previous treatment. 3. Either t3 or t4 N1-4 M0/1 lesions. 4. No CVS disease. 5. No hepatic disease. 6. No urinary obstruction requiring catheter drainage. 7. Life expectancy of 6 mon or longer.</p> <p>Additional info: Clinical tumour stage assessed by rectal examination, cytoscopy, intravenous urography with roentgenographic proof of residual urine, chest X-ray, bone survey, radioisotope scan, serum phosphatases determination, open skeletal diagnosis by random iliac crest puncture. All patients had had pedal lymphangiography & 5 patients had had staging pelvic lymphadenectomy.</p> <p>Tumour stages/grades: Stage T3/4 M0 [Arm 1: n=15; Arm 2: n=14] Stage T3/4 M1 [Arm 1: n=6; Arm 2: n=7]</p> <p>Grade G0-G1 [Arm 1: n=13; Arm 2: n=13] Grade GII-GIII [Arm 1: n=8; Arm 2: n=8]</p> <p>Diagnosis: Prostatic adenocarcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): Overall: 67.6 y; Arm 1: 67.3 y; Arm 2: 67.8 y (51 - 84 y)</p>	<p>Parenteral oestrogen: Alone</p> <p>Arm 1: Cyproterone acetate 300 mg i.m. every w. Treatment stopped if tumour progression required other forms of treatment or CVS or hepatic side effects occurred and required such a change. No patients required this. After 6 mon evaluation all patients entered a therapy protocol determined according to presence or absence of distant metastases. No. patients: 21 No. withdrawn: 0</p> <p>Arm 2: Oestradiol undecylate 100 mg i.v. every mon Treatment stopped if tumour progression required other forms of treatment or CVS or hepatic side effects occurred and required such a change. No patients required this. After 6 mon evaluation all patients entered a therapy protocol determined according to presence or absence of distant metastases. No. patients: 21 No. withdrawn: 0</p>	<p>Disease Progression: Performance status [Evaluated with Karnofsky Index 1953] Arm 1: 19/21 gained weight (0.5 - 3.5kg) Arm 2: 12/21 gained weight Stats: If Karnofsky Index above 60 is acceptable, no significant difference was found. Subgroups: Arm 1: Patients with bone pain responded promptly to treatment. Arm 2: Patients with bone pain responded promptly to treatment but 1 patient relapsed after 4 mon.</p> <p>Disease Progression: Tumour response Arm 1: Regressed 16/21 (11 T0) (76%); stable 2/21 (10%); progressed 3/21 (14%); histological regression, tumour still present: 10/21; no tumour on re-biopsy: 9/21 Arm 2: Regressed 11/21 (2T0) (52%); stable 8/21 (38%); progressed 2/21 (10%); histological regression, tumour still present: 11/21; no tumour on re-biopsy: 2/21</p> <p>Adverse Events: CVS mortality Arm 1: 0/21 Arm 2: 2/21</p> <p>Adverse Events: CVS morbidity Arm 1: Oedema/thrombophlebitis 0/21, lower extremity thrombosis 0/21, coronary heart disease 0/21 Arm 2: Oedema/thrombophlebitis 8/21, lower extremity thrombosis 1/21, coronary heart disease 5/21 Stats: Subgroups: Patient with severe thrombosis in Arm 2 was withdrawn after 3 mon.</p> <p>Adverse Events: Gynaecomastia Arm 1: 2/21 Arm 2: 21/21</p>	<p>Authors' conclusions: Cyproterone acetate is an acceptable and interesting medical alternative in the treatment of advanced prostatic cancer.</p> <p>Additional outcomes: Plasma testosterone levels: Cyproterone acetate: testosterone fell from 434 ±42.7 to 107 ±14.2 ng/100ml after 3 mon and remained at this level after 6 mon (102 ±16.6 ng/100ml). Oestradiol undecylate: testosterone fell from 416 ±51.1 to 38 ±4.1 after 3 mon and to 29.6 ±3.7 ng/100ml after 6 mon. The difference in suppression was significant (p< 0.05)</p> <p>Micturition Other side effects - gastrointestinal symptoms, pathological liver tests, pruritus, dermatitis, impotence.</p> <p>Reviewer comment: There is not enough information to determine if the randomisation was appropriate or if there was adequate allocation concealment. No loss to follow-up was reported.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? No</p>

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Steg, 1983¹⁶ Country: France</p> <p>Language of Publication: French</p> <p>Setting: 1 Hospital in France</p> <p>Study Objective: To compare clinical and metabolic effects of DES and 17 beta-diethyl-estradiol (17 b E2) before and after 3 mon' treatment.</p> <p>Funding Source: Not reported</p> <p>Duration: Treatment period: 3 mon</p> <p>Analysis: χ^2 tests; t-tests.</p>	<p>No. participants: 56</p> <p>No. withdrawn: 3</p> <p>Inclusion criteria: 1. Histologically confirmed untreated prostate cancer. 2. No previous CVS or thromboembolic disease.</p> <p>Additional info: Tumour stages/grades: A [Arm 1: n=5; Arm 2: n=4] B [Arm 1: n=6; Arm 2: n=12] C [Arm 1: n=18; Arm 2: n=11]</p> <p>Diagnosis: Prostatic carcinoma</p> <p>Co-morbidity:</p> <p>Age (range): Arm 1: 73.2 y; Arm 2: 73.3 y (Arm 1: \pm 8; Arm 2: \pm 8.6)</p>	<p>Parenteral oestrogen: Alone</p> <p>Arm 1: 17 Beta-diethyl-estradiol 5 mg applied twice daily as ointment to hypogastric region. No. patients: 29 No. withdrawn: 3</p> <p>Arm 2: Diethylstilboestrol (DES) 1 mg p.o. t.i.d. No. patients: 27 No. withdrawn:</p>	<p>Disease Progression: Clinical response [Defined in terms of urinary function, prostatic volume, intravenous urography.] Arm 1: 10/29 (34%) Arm 2: 17/27 (63%) Stats: $p < 0.05$ Subgroups:</p> <p>Adverse Events: Thromboembolic events Arm 1: 0/29 Arm 2: 5/27 (19%) Stats: $p < 0.05$ Subgroups: Arm 2 deaths = 2 (1 disseminated intravascular coagulation, 1 mesenteric ischaemia); phlebitis = 1, phlebitis with pulmonary embolism = 1, cerebrovascular accident = 1</p>	<p>Authors' conclusions: Biochemical markers responded more to DES, but there were significantly more thromboembolic complications than with 17 b-E2. However, the oestrogen dose in commercial ointments was too low and is also less well absorbed when applied to the hypogastric region compared with the forearm. It was difficult to communicate the need for a long course of treatment with an ointment to patients and clinicians, without better information.</p> <p>Additional outcomes: Plasma oestradiol levels: Arm 1 rose from 30 to 107 pg/ml ($p < 0.01$), Arm 2 fell from 26 to 19 pg/ml (NS).</p> <p>Plasma testosterone levels: Arm 1 fell from 4.5 to 1.8 ng/ml, Arm 2 fell from 4.2 to 0.51 ng/ml (both arms $p < 0.001$).</p> <p>Plasma FSH levels: Arm 1 fell from 4.7 to 1.7 μg/ml, Arm 2 fell from 5.8 to 1.7 μg/ml (both arms $p < 0.001$).</p> <p>Plasma LH levels: Arm 1 fell from 3.2 to 2 μg/ml, Arm 2 fell from 4 to 1.7 μg/ml (both arms $p < 0.01$).</p> <p>Other reported outcomes: testosterone binding index, lipid levels, coagulation factor VIII, antigen factor VIII.</p> <p>Reviewer comment: Insufficient details were given of the nature and measurement of clinical response.</p> <p>Quality assessment:</p> <ol style="list-style-type: none"> 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Yes

**Table 2: Parenteral oestrogen preparations
PEP i.m. at 80mg/month combined with oral ethinyl estradiol at 150µg/day**

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Lundgren, 1995³⁰ Country: Sweden</p> <p>Language of Publication: English</p> <p>Setting: 5 Urological or Surgical Clinics</p> <p>Study Objective: To determine if early endocrine treatment prolongs the interval to metastasis and/or cancer related or overall survival and to investigate the interval to treatment failure (progression of malignant disease or side effects of primary treatment) compared with therapy initiated at appearance of symptoms</p> <p>Funding Source: Not reported</p> <p>Duration: Recruitment period: 6 y, Nov 1978 - Jul 1984; Follow-up period: until Aug 1993</p> <p>Analysis: Kaplan-Meier curves; Log-rank tests; Cox's proportional hazards model.</p>	<p>No. participants: 285</p> <p>No. withdrawn: 57*</p> <p>Inclusion criteria: 1. Prostatic carcinoma. 2. No previous treatment. 3. Well or moderately well differentiated prostatic adenocarcinoma. 4. Stages I - III. 5. Stages T0a - T3NXM0. 6. No other malignancy. 7. No previous or present CVS disease.</p> <p>Additional info: *There were 44 withdrawals before the study began: 14 "incorrectly randomised" [Arm 1: n=2; Arm 2: n= 5; Arm 3: n=7] 30 "protocol violations" [Arm 1: n=13; Arm 2: n=14; Arm 3: n=3] In addition Arm 4 was not reported due to insufficient numbers: 13 Patients were randomised to this in final y instead of Arm 1 due to high frequency of CVS complications. Therefore a total of 57 patients were excluded from the analysis. 228 patients are reported with 186 documented withdrawals due to disease progression or other symptoms (see results): Evaluated patients: Arm 1: n=66; Arm 2: n=74; Arm 3: n=88</p> <p>Tumour stages/grades: Well differentiated [Arm 1: n=46; Arm 2: n=53; Arm 3: n=60] Moderately well differentiated [Arm 1: n=20; Arm 2: n=21 Arm 3: n=28]</p> <p>(VACURG) Stage I [Arm 1: n=32; Arm 2: n=31; Arm 3: n=36] Stage II [Arm 1: n=30; Arm 2: n=33; Arm 3: n=44] Stage III [Arm 1: n=4; Arm 2: n=10; Arm 3: n=8]</p> <p>(TNM) T0a [Arm 1: n=18; Arm 2: n=17; Arm 3: n=18]</p>	<p>Parenteral oestrogen: Combined</p> <p>Arm 1: Polyoestradiol phosphate (PEP) (Estradurin) & Ethinyl estradiol (EE) (Etivex) 80 mg i.m. every 4 w. 50 µg EE t.i.d. No. patients: 81 No. withdrawn: 15</p> <p>Arm 2: Estramustine phosphate (Estracyt) 280 mg twice daily. No. patients: 93 No. withdrawn: 19</p> <p>Arm 3: Surveillance/deferred endocrine treatment Endocrine treatment at progression to symptomatic or metastatic disease (orchidectomy or LHRH treatment). No. patients: 98 No. withdrawn: 10</p> <p>Arm 4: Polyoestradiol phosphate (PEP) (Estradurin) 80 mg i.m. every 4 w. No. patients: 13 No. withdrawn: 13</p>	<p>Disease Progression: Metastasis-free survival Arm 1: 11/66 (17%) developed metastases Arm 2: 15/74 (20%) developed metastases Arm 3: 25/88 (28%) developed metastases Arm 4: Stats: Arm 1 had a significantly lower risk of metastasis compared to Arm 3 (p = 0.044) No significant differences in interval to metastasis (p = 0.07). No difference between Arms 1 and 2 and Arm 3 in interval to metastasis (p = 0.4). Subgroups: Significant difference between patients with well (n=159) and moderately well differentiated (n=69) tumours in interval to metastasis (p = 0.001). Patients with stage T0a tumours (n=53) had a significantly longer interval to development of metastases (p = 0.0008) than T0b - T3 tumour patients (n=175) Patients with well differentiated tumours stages T0b to T2 and T3 in Arm 1 had lower risk of metastasis (p = 0.04) compared to Arm 3. Patients with moderately well differentiated T0b-T3 tumours in Arm 2 had nonsignificantly lower risk of metastases than Arm 3 patients (p = 0.06)</p> <p>Disease Progression: Cancer progression leading to withdrawal Arm 1: 2/66 (3%) Arm 2: 6/74 (8%) Arm 3: 38/88 (43%)</p> <p>Stats: "significantly more" in deferred</p>	<p>Authors' conclusions: In patients with nonmetastatic prostate cancer (stages T0b to T3) with an estimated survival time of >10 y, early treatment should be recommended. Curative alternatives are reasonable in patients with prostate-confined disease but in elderly or non sexually active patients immediate endocrine treatment without CVS side effects may be an alternative.</p> <p>Additional outcomes: Other reasons for withdrawal including: other diseases, other treatments, gastrointestinal disease, other oestrogenic side effects and other symptoms.</p> <p>Reviewer comment: The fact that 57 patients including 44 in main 3 arms are not included in the analysis should be noted, particularly given that the reasons for these exclusions are incorrect randomisation and protocol violation. There is not enough information to determine if the randomisation was appropriate or if there was adequate allocation concealment.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Yes</p>

	<p>T0b [Arm 1: n=12; Arm 2: n=13; Arm 3: n=16] T0x [Arm 1: n=2; Arm 2: n=1; Arm 3: n=1] T1 [Arm 1: n=12; Arm 2: n=7; Arm 3: n=14] T2 [Arm 1: n=18; Arm 2: n=26; Arm 3: n=31] T3 [Arm 1: n=4; Arm 2: n=10; Arm 3: n=8]</p> <p>Diagnosis: Prostatic adenocarcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): 70 y (52 - 90 y)</p>		<p>group experienced progression compared with Arms 1 & 2.</p> <p>Survival:All-cause mortality Arm 1: 35/66 (53%) Arm 2: 40/74 (54%) Arm 3: 53/88 (60%)</p> <p>Stats: No difference in overall survival (p = 0.48).</p> <p>Survival: Death from prostate cancer Arm 1: 8/66 (12%) Arm 2:13/74 (18%) Arm 3:25/88 (28%)</p> <p>Stats: Significantly more patients in Arm 3 died of prostatic cancer than other groups (p = 0.03). Arm 1 compared to Arm 3 (p = 0.014). Subgroups: Significant difference in prostate cancer deaths between patients with well differentiated and moderately well differentiated tumours. Patients with stage T0a tumours had a significantly lower rate of prostatic cancer death (p = 0.0001).</p> <p>In patients with well differentiated tumours (T0b-T3) risk was lower in Arm 1 compared to Arm 3 (p = 0.03), and in moderately well differentiated T0b-T3 patients risk in Arm 2 was lower compared to Arm 3 (p=0.046) (n's not reported).</p> <p>Adverse Events CVS mortality, including death after withdrawal from study Arm 1: 14/66 (21%) (4 while on treatment) Arm 2: 11/74 (15%) (5 while on treatment)</p>	
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			<p>Arm 3: 14/88 (16%) (11 while on treatment)</p> <p>Stats: No significant differences, but over-representation of patients in y 1 of Arm 1.</p> <p>Adverse Events CVS morbidity leading to withdrawal</p> <p>Arm 1: 37/66 (56%) Arm 2: 30/74 (40%) Arm 3: 11/88 (13%)</p>	
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STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Haapiainen, 1986²⁶ (Haapiainen, 1985;⁴⁰ Haapiainen, 1991³²)</p> <p>Country: Finland</p> <p>Language of Publication: English</p> <p>Setting: Helsinki University Central Hospital</p> <p>Study Objective: To compare the primary clinical efficacy of orchidectomy and i.m. Polyoestradiol phosphate (PEP) in combination with oral Ethinyl oestradiol (EE) in the treatment of locally advanced or metastatic prostatic cancer.</p> <p>Funding Source: Not reported (Study based on Finnprostate)</p> <p>Duration: Diagnosis period: Feb 1979 - Dec 1982; Follow-up period: 5 y</p> <p>Analysis: χ^2 tests; Product limit survival analysis; Cox's proportional hazards model.</p>	<p>No. participants: 277</p> <p>No. withdrawn: Not reported.</p> <p>Inclusion criteria: 1. No previous treatment for prostatic cancer. 2. No previous irradiation to the pelvic region. 3. No other malignancy or serious untreatable disease. 4. Life expectancy of 3 mon or more. 5. No acute thromboembolic disease within the previous 6 mon. 6. No liver disease. 7. No chronic mental depression.</p> <p>Additional info: There were no significant differences between groups at time of diagnosis.</p> <p>80/146 (55%) in Arm 1 and 59/131 (45%) in Arm 2 had bone metastases at time of diagnosis. 5 patients in Arm 1 and 4 patients in Arm 2 had elevated acid phosphatase but no other signs of metastasis.</p> <p>Tumour stages/grades: T0-2 [Arm 1: n=24; Arm 2: n=20] T3-4 [Arm 1: n=122; Arm 2: n=111]</p> <p>M0 [Arm 1: n=66; Arm 2: n=72] M1 [Arm 1: n=80; Arm 2: n=59] G1 [Arm 1: n=43; Arm 2: n=33] G2 [Arm 1: n=73; Arm 2: n=64] G3 [Arm 1: n=30; Arm 2: n=34]</p> <p>Diagnosis: Prostatic carcinoma</p> <p>Co-morbidity: CVS history was identical in both arms.</p> <p>Age (range): Arm 1: 72.7 y; Arm 2: 71.8 y (Not reported.)</p>	<p>Parenteral oestrogen: Combined</p> <p>Arm 1: Polyoestradiol phosphate (PEP) (Estradurin) & Ethinyl oestradiol (EE) (Etivex) 160 mg PEP i.m., 80 mg every mon subsequently; 1 mg EE for 2 w, 150 µg daily subsequently. No. patients: 146 No. withdrawn:</p> <p>Arm 2: Orchidectomy Total or subcapsular. No. patients: 131 No. withdrawn:</p>	<p>Disease Progression: Evidence of progression [Progression defined as an increase in size of primary tumour and increase in metastases.] Arm 1: 11/146 (8%) at 2 y; 25/146 (17%) at 5 y Arm 2: 30/131 (23%) at 2 y; 49/131 (37%) at 5 y Stats: p<0.01 at 2 y p<0.05 at 5 y (for outcomes 1 & 2) Subgroups: Graphical presentation of timing of progression within 2 y follow-up period: Arm 1: progression evenly distributed Arm 2: 2/3 of progressions appeared within 1 y</p> <p>Cumulative non-progression curves presented for subgroups at 5 y follow-up: Effect of therapy more pronounced in M1 patients.</p> <p>Survival: Death from prostate cancer Arm 1: 2/146 deaths in 1st y; 11/146 deaths in 2nd y; 45/146 deaths at 5 y follow-up Arm 2: 7/131 deaths in 1st y; 14/131 deaths in 2nd y; 47/131 deaths at 5 y follow-up Stats: Not reported. Subgroups: Survival curves presented for sub-groups at 2 y follow-up: Arm 2 patients with poorly differentiated tumour and bone metastases had poorer prognosis than respective Arm 1 patients (p<0.01). Arm 2 patients with M1 moderately differentiated tumours also had poorer prognosis than their Arm 1 equivalents (p>0.05). No difference in survival of M1 patients with well differentiated tumours.</p> <p>Survival: All-cause mortality Arm 1: 38/146 deaths at 2 y; 101/146</p>	<p>Authors' conclusions: Polyoestradiol phosphate in combination with a strong gonadotrophin inhibitor, Ethinyl oestradiol, delayed progression more effectively than orchidectomy.</p> <p>Additional outcomes: Reviewer comment: Patients were not appropriately randomised to intervention groups - allocation was performed according to date of birth. It would appear that there was no loss to follow-up but this is not explicitly stated in the paper.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? No 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Yes</p>

			<p>(69%) deaths at 5 y Arm 2: 35/131 deaths at 2 y; 86/131 (66%) deaths at 5 y Stats: $p > 0.05$ at 2 y $p = 0.45$ at 5 y</p> <p>CVS Disease: Arm 1: 17 deaths (45% of total deaths); 35 deaths at 5 y Arm 2: 8 deaths (23% of total deaths); 24 deaths at 5 y</p> <p>Other Causes: Arm 1: 8 deaths (21% of total deaths) at 2 y; 21 deaths at 5 y Arm 2: 6 deaths (17% of total deaths) at 2 y; 15 deaths at 5 y</p> <p>Graphical presentation of timing of CVS deaths within 2 y follow-up period: Arm 1: 10/16 CVS deaths (63%) occurred in 1st y</p> <p>Adverse Events: CVS morbidity Arm 1: 24/146 during 1st y Arm 2: 4/131 during 1st y Stats: $p < 0.001$ Subgroups: DVT: Arm 1: $n = 8$ (0-6 mon), $n = 3$ (7-12 mon); Arm 2: $n = 0$ (0-6 mon), $n = 1$ (7-12 mon) Pulmonary embolism: Arm 1 - 4 (0-6 mon), 1 (7-12 mon), Arm 2 - 0 Myocardial infarction: Arm 1 - 4 (0-6 mon), 0 (7-12 mon), Arm 2 - 1 (0-6 mon), 0 (7-12 mon) Cerebral complications: Arm 1 - 3 (0-6 mon), 1 (7-12 mon), Arm 2 - 0 (0-6 mon), 2 (7-12 mon)</p> <p>19/24 complications (79%) in Arm 1 appeared within 6 mon. 63% of these were thromboembolic.</p> <p>No significant differences between M0 and M1 patients at 2 y.</p>	
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STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Andersson, 1980²⁴ Country: Sweden</p> <p>Language of Publication: English</p> <p>Setting: 4 Urology Departments & 1 Private Practice</p> <p>Study Objective: To investigate whether tumour regression could be achieved in a higher frequency or of a longer duration by giving Estramustine as the initial form of therapy as compared with routine oestrogenic treatment.</p> <p>Funding Source: Not reported</p> <p>Duration: Follow-up period (minimum): 2 y; Interim report - trial not completed</p> <p>Analysis: Not reported.</p>	<p>No. participants: 263</p> <p>No. withdrawn: 46</p> <p>Inclusion criteria: 1. Highly or moderately differentiated prostatic carcinoma in stages II-IV. 2. Treatment considered necessary. 3. No malignant illness. 4. No severe liver damage. 5. No platelet count below 100 000 per mm³. 6. No severe urinary tract infection.</p> <p>Additional info: *Only 182 cases (observed for 2 y or longer) are described in this report.</p> <p>Tumour stages/grades: Highly differentiated [Arm 1: n=12; Arm 2: n=20] Moderately differentiated [Arm 1: n=76; Arm 2: n=74] Stage II [Arm 1: n=41; Arm 2: n=42] Stage III [Arm 1 : n=20; Arm 2: n=21] Stage IV [Arm 1: n=27; Arm 2: n=31]</p> <p>Diagnosis: Prostatic carcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): Not reported. (Not reported.)</p>	<p>Parenteral oestrogen: Combined</p> <p>Arm 1: Estramustine phosphate (Estracyt) 840 mg p.o. daily in two doses No. patients: 88 No. withdrawn: 25</p> <p>Arm 2: Polyoestradiol phosphate (PEP) (Estradurin) & 17-alpha-ethinylestradiol 80 mg PEP i.m. every mon; 2 mg 17-alpha-ethinylestradiol p.o. daily for 2 w, 150 µg daily subsequently. No. patients: 94 No. withdrawn: 21</p>	<p>Disease Progression: Reduction of primary tumour [Undefined] Arm 1: 64% patients at 2 mon follow-up Arm 2: 53% patients at 2 mon follow-up Stats: No significant difference. Subgroups: Of those in remission 70% were still in remission after 1 y and approx 50% after 2 y.</p> <p>Disease Progression: Bone tissue metastases [Undefined] Arm 1: At 6 mon: increase: 3/88, no change: 6/88, decrease: 3/88 Arm 2: At 6 mon: increase: 5/94, no change: 4/94, decrease: 5/94 Stats: Not reported. Subgroups: Not reported.</p> <p>Disease Progression: Cytologic evidence of tumour devitalization Arm 1: At 6 mon: no change: 7/88, treatment effect: 40/88 Arm 2: At 6 mon: no change: 10/94, treatment effect: 33/94 Stats: Not reported. Subgroups: Not reported.</p> <p>Adverse Events Arm 1: Not reported. Arm 2: Not reported. Stats: No marked difference. Subgroups: Not reported.</p>	<p>Authors' conclusions: In the initial treatment, Estramustine offers no advantage over our conventional type of oestrogenic therapy.</p> <p>Additional outcomes: Acid phosphatase levels: Arm 1: 60% patients normalised after 2 mon Arm 2: 50% patients normalised after 2 mon For patients with elevated levels of acid phosphatase from the beginning of the study there was no statistical difference between the groups either with respect to normalisation or to later escape from normal values.</p> <p>Reviewer comment: Only a subgroup of those randomised to the trial are reported on in this paper. It is not clear how many of these subsequently left the trial. Two of the reasons given for leaving the trial are also outcomes - progressive disease and adverse reactions.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Yes</p>

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Aro, 1988²⁸ Country: Finland</p> <p>Language of Publication: English</p> <p>Setting: Multicentre: Hospitals in Finland</p> <p>Study Objective: To compare orchidectomy, oestrogen therapy and megavoltage radiation therapy in patients with locally advanced prostatic adenocarcinoma with no evidence of distant metastases at time of diagnosis.</p> <p>Funding Source: Not reported</p> <p>Duration: Follow-up period: 4 y; Diagnosis period: Feb 1979 - Dec 1982</p> <p>Analysis: Product limit survival analysis; χ^2 tests.</p>	<p>No. participants: 151</p> <p>No. withdrawn: Unclear.*</p> <p>Inclusion criteria: 1. Patients with locally advanced prostatic adenocarcinoma. 2. No previous treatment for prostatic cancer. 3. No previous irradiation to the pelvic region. 4. No other malignancy or serious untreatable disease. 5. Life expectancy of 3 mon or greater. 6. No liver disease. 7. No chronic mental depression. 8. No acute thromboembolic disease within last 6 mon.</p> <p>Additional info: * 33 withdrawals are documented [Arm 1: 13, Arm 2: 15, Arm 3: 5] but this includes withdrawals for CVS morbidity and deaths from causes other than prostate cancer as well as losses to follow-up.</p> <p>Tumour grades/stages: G1 [Arm 1: n=20; Arm 2: n=11; Arm 3: n=14] G2 [Arm 1: n=21; Arm 2: n=31; Arm 3: n=26] G3 [Arm 1: n=9; Arm 2: n=14; Arm 3: n=5]</p> <p>Diagnosis: Prostatic carcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): Arm 1: 73.0 y; Arm 2: 71.6 y; Arm 3: 70.0 y (Arm 1: 54 - 88 y; Arm 2: 52 - 85 y; Arm 3: 53 - 83 y)</p>	<p>Parenteral oestrogen: Combined</p> <p>Arm 1: Polyoestradiol phosphate (PEP) (Estradurin) & Ethinyl estradiol (EE) (Etivex) 160 mg PEP i.m. initially, 80 mg every mon subsequently. 1 mg EE p.o. daily for 2 w, 150 µg daily subsequently. No. patients: 50 No. withdrawn:</p> <p>Arm 2: Orchidectomy Total or subcapsular. No. patients: 56 No. withdrawn:</p> <p>Arm 3: Megavoltage radiotherapy 40 Gy to pelvic region; additional 26 Gy to prostate over 9 w (inc 3 w rest). No. patients: 45 No. withdrawn:</p>	<p>Disease Progression: e.g.M0 to M1; appearance of hot spot on bone scan Arm 1: Cumulative non-progression rate 0.72 (95% CI: 0.57, 0.85) (n=50) Arm 2: Cumulative non-progression rate 0.64 (95% CI: 0.50, 0.78) (n=56) Arm 3: Cumulative non-progression rate 0.69 (95% CI: 0.55, 0.83) (n=45) Arm 4: Stats: No significant difference. Subgroups: Patients with Tumour G2 Arm 1: n=21: Cumulative non-progression rate 0.66 (95% CI: 0.44, 0.88) Arm 2: n=31: Cumulative non-progression rate 0.61 (95% CI: 0.41, 0.81) Arm 3: n=26: Cumulative non-progression rate 0.72 (95% CI: 0.54, 0.88) Patients with Tumour G3 Arm 1: n=9: approx 20% progressed Arm 2: n=14: Approx 50% progressed Arm 3: n=26: Approx 20% progressed Study did not have sufficient power to draw conclusions from this data.</p> <p>Survival: All-cause mortality Arm 1: 16/50 (32%) Arm 2: 23/56 (41%) Arm 3: 9/45 (20%) Stats: X2 between Arms 2 and 3 = 5.1, p < 0.05 Subgroups:</p> <p>Adverse Events: Cumulative CVS mortality rates Arm 1: 5/50 (10%) Arm 2: 6/56 (11%) Arm 3: 3/45 (7%)</p> <p>Stats: Not significant and did not differ from male population. Subgroups:</p> <p>Adverse Events: CVS morbidity: DVT, pulmonary embolism, MI, cerebral complications Arm 1: 19 events in 13/50 patients (26%): DVT 8; pulmonary embolism 4; MI 4; cerebral complications 3</p>	<p>Authors' conclusions: Patients with a history of CVS disease should be treated by orchidectomy or radiotherapy. For patients with normal sexual function, radiotherapy offers a good chance of retaining post-treatment potency, with oestrogens or orchidectomy available in case of progression. Radiotherapy may be curative whereas oestrogen and orchidectomy are palliative.</p> <p>Additional outcomes: Also reports chronic bowel & rectal complications in the radiotherapy group.</p> <p>Reviewer comment: Patients were randomised according to date of birth, meaning that it is not truly randomised. There is not enough information to determine whether there was adequate concealment of allocation. It is not clear how many withdrawals occurred: 33 withdrawals are documented [Arm 1: 13, Arm 2: 15, Arm 3: 5] but this includes withdrawals for CVS morbidity and deaths from causes other than prostate cancer as well as losses to follow-up.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? No 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Yes</p>

			<p>Arm 2: 8 in 7/56 patients (13%): DVT 0; pulmonary embolism 1; MI 5; cerebral complications 2</p> <p>Arm 3: 3 events in 3/45 patients (7%): DVT 0; pulmonary embolism 0; MI 2; cerebral complications 1</p> <p>Subgroups: CVS complications at 1 y follow-up: Arm 1: n=14 (74% total CVS complications); Arm 2: n=3; Arm 3: n=3.</p>	
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STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Johansson, 1991²⁹ (Johansson, 1991³⁴)</p> <p>Country: Sweden</p> <p>Language of Publication: English</p> <p>Setting: Orebro Medical Center Hospital</p> <p>Study Objective: To determine the interval to progression, corrected survival, overall survival and incidence of CVS disease and other side effects of oestrogen versus orchidectomy for advanced prostatic cancer. Information on prognostic factors was also collected and analysed.</p> <p>Funding Source: Orebro County Council Research Committee; Swedish Cancer Society</p> <p>Duration: Recruitment period: Mar 1979 - Feb 1982 ; Follow-up period: until 1 Mar 1989; Follow-up period: 7-10 y</p> <p>Analysis: Kaplan-Meier curves; Cox's proportional hazards model; Log-rank tests; χ^2 tests.</p>	<p>No. participants: 150</p> <p>No. withdrawn: 0</p> <p>Inclusion criteria: 1. Metastases or locally advanced stages (T3-4). 2. No history of CVS disease.</p> <p>Additional info: Tumour stages/grades: M0 [Arm 1: n=46 (62.2%); Arm 2: n=42 (55.3%)] M1 [Arm 1: n=28 (37.8%); Arm 2: n=34 (44.7%)] >10 skeletal metastases [Arm 1: n=17 (23%); Arm 2: n=17 (22.4%)] Without skeletal metastases [Arm 1: n=2 (2.7%); Arm 2: n=3 (3.9%)]</p> <p>T1-2 [Arm 1: n=5 (6.7%); Arm 2: n=4 (5.3%)] T3 [Arm 2: n=66 (89.5%); Arm 2: n=70 (92.1%)] T4 [Arm 1: n=3 (4.1%); Arm 2: n= 2 (2.6%)]</p> <p>I [Arm 1: n=11 (14.9%); Arm 2: n=11 (14.5%)] II [Arm 1: n=39 (52.7%); Arm 2: n=33 (43.4%)] III [Arm 1: n=24 (32.4%); Arm 2: n=32 (42.1%)]</p> <p>Performance status: Normal [Arm 1: n=54 (73%); Arm 2: n=56 (73.7%)] Symptoms [Arm 1: n=10 (13.5%); Arm 2: n=11 (14.5%)] Bedridden<50% [Arm 1: n=10 (13.5%); Arm 2: n=7 (9.2%)] Bedridden>50% [Arm 1: n=0; Arm 2: n=2 (2.6%)]</p> <p>Pain: Absent [Arm 1: n=60 (81.1%); Arm 2: n=63 (82.9%)] Present (mild) [Arm 1: n=8 (10.8%); Arm 1: n=8 (10.5%)] Present (more than mild) [Arm 1: n=6 (8.1%); Arm 2: n=5 (6.6%)]</p> <p>Acid phosphatase (IU/ml): Normal (<60) [Arm 1: n=44 (59.5%); Arm 2: n=39 (51.3%)] >4 times normal upper limit [Arm 1: n=13 (17.6%); Arm 2: n=12 (15.8%)]</p>	<p>Parenteral oestrogen: Combined</p> <p>Arm 1: Polyoestradiol phosphate (PEP) (Estradurin) & Ethinyl estradiol (EE) (Etivex) 80 mg PEP i.m. every mon; 150 µg EE p.o. daily. No. patients: 74 No. withdrawn: 0</p> <p>Arm 2: Orchidectomy Bilateral total. No. patients: 76 No. withdrawn: 0</p>	<p>Disease Progression: Progression-free survival rate [Progression defined as an increase =25% size of measurable lesions, a significant increase in extent of existing lesions or occurrence of new lesions.]</p> <p>Arm 1: 27/74 patients showed progression Arm 2: 39/76 patients showed progression</p> <p>Stats: Progression-free survival at 5 y: Arm 1 - 63.6% (95% CI: 51.6, 75.6) Arm 2 - 48.6% (95% CI: 36.4, 60.8)</p> <p>Univariate Analysis: Relative Hazards: Arm 1=1.0 (reference), Arm 2=0.63; p>0.05</p> <p>Multivariate Analysis: Relative Hazards=0.68, p=0.12 favouring Arm 1 [best model] Relative Hazards=0.47, p=0.007 favouring Arm 1 [all inclusive model]</p> <p>Subgroups: M0 subgroup: Arm 1: 5/46 patients Arm 2: 12/42 patients</p> <p>Free of progression survival by M stage: Arm 1: M0 subgroup - 84.5% (95% CI: 73.1, 95.9) Arm 1: M1 subgroup - 25.4% (95% CI: 6.8, 44.0) Arm 2: M0 subgroup - 71.3% (95% CI: 56.2, 86.4) Arm 2: M1 subgroup - 20.0% (95% CI: 5.3, 34.7)</p> <p>Survival: Death from prostate cancer Arm 1: 27 deaths/74 patients Arm 2: 36 deaths/76 patients Stats: Corrected Survival at 5 y: Arm 1: 68.8% (95% CI: 57.3, 80.2) Arm 2: 60.7% (95% CI: 49.0, 72.4)</p>	<p>Authors' conclusions: Overall survival was similar. There was a tendency towards better results for the oestrogen treated patients when the corrected survival was estimated, and survival free of progression also was significantly better in this group. CVS morbidity was significantly higher among the patients treated with oestrogens.</p> <p>There was a statistically significantly better progression-free survival rate in the group treated with oestrogen. The interval to disease-specific death, however, showed no statistically significant difference between the two treatments.</p> <p>Additional outcomes: Reviewer comment: Randomisation was not appropriately conducted in this study - allocation by date of birth was employed.</p> <p>Combined with Johansson ,1991³⁴</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? No 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? No</p>

	<p>Sedimentation rate (mm/hr): <20 [n= 68] 20-60 [n=56] >60 [n=26]</p> <p>Sedimentation rate (mm/hr quartiles): 0-10 [n=35] 11-22 [n=39] 23-47 [n=37] 48-139 [n=39]</p> <p>Hemoglobin (gm/l): <115 [n=26] =115 [n=124]</p> <p>Creatinine (µmol/l): <115 [n=120] 115-230 [n=24] >230 [n=6]</p> <p>Diagnosis: New cases of prostatic carcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): Arm 1: 72.1 y; Arm 2: 72.5 y (Arm 1: 52 - 90 y; Arm 2: 48 - 88 y)</p>		<p>p=0.30</p> <p>Univariate Analysis: Relative Hazards (of disease-specific death): Arm 1=1.0 (reference), Arm 2=0.77; p>0.05</p> <p>Multivariate Analysis: No significant differences. Subgroups: Corrected survival at 5 y in patients with metastases: Arm 1: 37.8% (95% CI: 18.0, 57.6) Arm 2: 26.0% (95% CI: 10.1, 41.8)</p> <p>Survival: All-cause mortality Arm 1: 54 deaths/74 patients Arm 2: 54 deaths/76 patients Stats: Survival at 5 y: Arm 1: 50.7% (95% CI: 39.2, 62.1) Arm 2: 47.4% (95% CI: 36.1, 58.6) p=0.87</p> <p>No significant differences. Subgroups: No significant differences between M stage groups.</p> <p>Survival CVS mortality Arm 1: 13 deaths*/74 patients Arm 2: 9 deaths/76 patients Stats: *7 of these were probably caused by the oestrogen treatment. Subgroups: Not reported.</p> <p>Adverse Events CVS events Arm 1: 23 events*/74 patients: 1 MI, 6 cerebrovascular accidents, 1 pulmonary embolism, 5 DVT, 9 cardiac decompensations Arm 2: 4 events/76 patients: 1 MI, 3 cardiac decompensations Stats: * Number of events corresponds with number of patients. $\chi^2=16.82$, p<0.01 p<0.01 when considering CVS events and deaths</p>	
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			<p>Subgroups: In Arm 1, 12 patients developed complications within first 6 mon of treatment vs none in Arm 2.</p> <p>Adverse Events Other complications Arm 1: 0/74 Arm 2: 6/76 wound infections, 6/76 hematoma, 76/76 flushes Stats: Not reported. Subgroups: Not reported.</p>	
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STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Henriksson, 1986²⁷ (Henriksson, 1987³⁶)</p> <p>Country: Sweden</p> <p>Language of Publication: English</p> <p>Setting: 1 Hospital Urology Department</p> <p>Study Objective: 1. To find out if there was a difference in CVS morbidity in patients with prostate cancer treated with today's dosages of oestrogen compared with orchidectomy. 2. To find out whether it was possible to identify any predictors of CVS morbidity by careful clinical examinations and laboratory tests before the initiation of therapy.</p> <p>Funding Source: Swedish National Association Against Heart & Chest Disease</p> <p>Duration: Recruitment period: Nov 1980 - Jul 1984; Follow-up period (minimum): 1 y</p> <p>Analysis: t-tests. Life table technique used to compare major CVS complications during 1st y of treatment. Linear discriminant analysis was used to identify predictors.</p>	<p>No. participants: 91/100 randomised</p> <p>No. withdrawn: 0</p> <p>Inclusion criteria: 1. Newly diagnosed prostatic cancer. 2. Aged up to 75. 3. Judged suitable for hormonal treatment by a senior urologist. 4. No pre-existing CVS morbidity (myocardial infarction, unstable angina pectoris, severe intermittent claudication, cerebral infarction, cardiac decompensation or thromboembolic episodes). 5. Accepted CVS assessment.</p> <p>Additional info: The authors grouped non-randomised and randomised patients together when reporting baseline characteristics.</p> <p>Tumour stages/grades: T1: n=3; T2: n=24, T3: n=40, T4: n=33. There were no significant differences between the groups.</p> <p>Diagnosis: Prostatic carcinoma</p> <p>Co-morbidity: Minor signs of arteriosclerosis were detected: Arm 1: n=10 (19%); Arm 2: n=12 (26%).</p> <p>Age (range): Arm 1: 67.7 y; Arm 2: 68.7 y (includes Arm 3) (Arm 1: SEM = 0.8; Arm 2: SEM = 0.8)</p>	<p>Parenteral oestrogen: Combined</p> <p>Arm 1: Polyoestradiol phosphate (PEP) (Estradurin) + ethinyl estradiol 160 mg PEP i.m every mon for 3 mon, 80 mg every mon subsequently. Ethinyl estradiol 1mg/day p.o for 2 w then 150ug daily. No. patients: 47 No. withdrawn: 0</p> <p>Arm 2: Orchidectomy</p> <p>No. patients: 44 No. withdrawn: 0</p> <p>Arm 3: Patient or urologist choice Patient choice: 5; urologist selection: 4. Oestrogen treatment: 6; Orchidectomy: 3. Patients analysed according to treatment arm of choice/assignment. No. patients: 9 No. withdrawn: 0</p>	<p>Adverse Events: Major CVS event Arm 1: 13/53 (25%): MI 3; Intractable Angina Pectoris 2; Cerebral Infarction 1; Severe Intermittent Claudication 1; DVT 4; Cardiac failure 2. Mean time to event from start of treatment: 5.1 mon Arm 2: 0/47 for all categories Stats: Difference between groups significant: p = 0.0008. Proportion of patients escaping major CVS event by end of 1st y: Arm 1: 75%; Arm 2: 100%; p <0.001) Excluding non-randomised patients p < 0.0019 (n=91). Subgroups: Arm 1: Minor signs of arteriosclerosis n=10 - 3 had major CVS event (30%). Arm 2: No signs of arteriosclerosis n=43 - 10 had event (23%).</p>	<p>Authors' conclusions: The incidence of CVS morbidity is increased during the 1st y of oestrogen treatment in patients with prostatic cancer, even when a low dosage regimen is used. This affects patients both with and without clinically detectable arteriosclerosis. Although too soon to comment on clinical efficacy, the high incidence of CVS side effects in patients treated with oestrogen, compared with orchidectomy, should be considered in the choice of treatment for patients with prostatic cancer.</p> <p>Additional outcomes: Henriksson, 1987³⁶ looks at prognostic factors for CVS complications with oestrogen treatment.</p> <p>Reviewer comment: Non-randomised patients (n = 9) were included in the study and were not differentiated, although the overall analysis excludes them. 1 y of follow-up is not ideal although the majority of CVS events will occur in this period. No efficacy data is reported. There is not enough information to determine if the randomisation was appropriate or if there was adequate allocation concealment.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Yes</p>

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Daehlin, 1986²⁵ Country: Sweden</p> <p>Language of Publication: English</p> <p>Setting: Not stated</p> <p>Study Objective: To compare the oestrogenic effect of Ethinyl oestradiol/Polyoestradiol phosphate with Estramustine phosphate by measuring their effects on blood levels of pregnancy zone protein (PZP), sex hormone binding globulin (SHBG), Luteinizing hormone (LH), Follicle stimulating hormone (FSH) and prolactin.</p> <p>Funding Source: Swedish Cancer Society & Lions Research Foundation; Swedish Medical Research Council; Maud & Birger Gustavsson Foundation; Swedish Society for Medical Research</p> <p>Duration: Follow-up period: 6 mon</p> <p>Analysis: Wilcoxon's tests.</p>	<p>No. participants: 30</p> <p>No. withdrawn: 2</p> <p>Inclusion criteria: 1. Newly diagnosed prostatic carcinoma. 2. Assessed as acceptable for oestrogen treatment. 3. Generalised disease or localised tumour requiring symptom relief.</p> <p>Additional info: The 2 withdrawals in Arm 1 had failed to adhere to the protocol.</p> <p>Diagnosis: Prostatic carcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): 73 y (55 - 85 y)</p>	<p>Parenteral oestrogen: Combined</p> <p>Arm 1: Polyoestradiol phosphate (PEP) (Estradurin) & Ethinyl estradiol (EE) (Etivex) 80 mg PEP i.m every mon.; 50 µg EE p.o. t.i.d. No. patients: 10 No. withdrawn: 2</p> <p>Arm 2: Estramustine phosphate (Estracyt) 9.2 mg/kg/day p.o. twice daily. No. patients: 10 No. withdrawn: 0</p> <p>Arm 3: Orchiectomy Bilateral. No. patients: 10 No. withdrawn: 0</p>	<p>Adverse Events: CVS complications Arm 1: 1/10 DVT of lower extremities Arm 2: 2/10: 1 DVT of lower extremities; 1 fatal coronary artery thrombosis Arm 3: None reported.</p> <p>Stats: Not reported Subgroups: Not reported</p>	<p>Authors' conclusions: Estramustine phosphate has an oestrogenicity comparable to that of Ethinyl estradiol/Polyoestradiol phosphate.</p> <p>Additional outcomes: Pregnancy zone protein concentrations: Mean value in age-matched controls was 8.6 ±2.1 µg/ml compared with patients' baseline of 6.5 ±1.6 µg/ml. In Arm 1, the concentration increased significantly in a step-wise fashion from one measurement to the next during the 1st 3 mon of observation. In the Arm 2, group levels increased significantly throughout the observation period. In Arm 3, levels did not change significantly during follow-up.</p> <p>Sex hormone binding globulin concentrations: Pre-treatment values were within the reference range. After start of treatment there was a significant and almost parallel increase in Arms 1 and 2 after 1 w and from 1 w to 1 mon of follow-up. Concentrations did not differ between these 2 groups. Concentrations remained unchanged in Arm 3.</p> <p>FSH concentrations (u/L): Arm 1: before treatment: 32 ±9.6; after 6 mon: 1.9 ±0.5 (p< 0.05) Arm 2: before treatment: 32 ±7.9; after 6 mon: 1.2 ± 0.3 (p< 0.05) Arm 3: before treatment: 46 ±11; after 6 mon: 133 ±16 (p< 0.01)</p> <p>LH concentrations (µ/L): Arm 1: before treatment:26 ±4.5; after 6 mon:4.9 ±1.3 (p< 0.05) Arm 2: before treatment:23 ±3.2;</p>

				<p>after 6 mon: 4.3 ±0.7 (P< 0.01) Arm 3: before treatment:31 ± 8; after 6 mon: 113 ±16 (P < 0.05)</p> <p>Prolactin concentrations (µg/L) Arm 1: before treatment:8 ±3; after 6 mon: 13 ±4 (p< 0.05) Arm 2: before treatment: 5 ±1; after 6 mon:11 ± 2 (p < 0.05) Arm 3: before treatment: 6 ±1; after 6 mon: 6 ±1</p> <p>Estradiol-17beta concentrations (nM): Arm 1: before treatment:0.08 ±10.01; after 6 mon: 0.39 ± 0.06 (p< 0.05) Arm 2: before treatment:0.08 ±0.01; after 6 mon: 27.9 ±7.9 (p< 0.01) Arm 3: before treatment: 0.084 ±0.008; after 6 mon:0.037 ±0.002 (p< 0.05)</p> <p>Plasma cortisol concentrations: Arm 1: before treatment: 400 ±37; after 6 mon: 1000 ±110 Arm 2: before treatment:510 ±39; after 6 mon: 1090 ±240 (p< 0.05) Arm 3: before treatment:510 ±50; after 6 mon: 370 ±31</p> <p>Plasma testosterone level (nM): Arm 1: before treatment: 19.4 ±3.5; after 6 mon: 3.2 ±0.5 (p< 0.05) Arm 2: before treatment: 22.1 ±2.9; after 6 mon: 5.6 ±0.7 (p< 0.05) Arm 3: before treatment: 18.7 ±3.3; after 6 mon:2.6 ±0.6 (p< 0.01)</p> <p>Reviewer comment: The short length (6 mon) and failure to assess disease progression limit the value of this study. There is not enough information to determine if the randomisation was appropriate or if there was adequate allocation concealment.</p> <p>Quality assessment:</p>
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				<p>1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Yes</p>
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Other combination of parenteral oestrogen and additional therapy

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Leaf, 2003³¹ Country: United States</p> <p>Language of Publication: English</p> <p>Setting: Multicentre: Hospitals in USA (ECOG)</p> <p>Study Objective: To determine whether a combination of Doxorubicin and an intravenous formulation of DES was superior to Doxorubicin alone in men with hormone refractory prostate cancer.</p> <p>Funding Source: National Cancer Institute; National Institutes of Health; Department of Health and Human Services</p> <p>Duration: Trial period: Apr 1983 - Jun 1986, Follow-up period: over 5 y</p> <p>Analysis: A 2-sided Fisher's exact test was used for comparisons between the groups Survival curves were estimated using Kaplan and Meier's method Comparisons of</p>	<p>No. participants: 188</p> <p>No. withdrawn: 38*</p> <p>Inclusion criteria: 1. Histologic diagnosis of adenocarcinoma of the prostate gland. 2. Evidence of progressive metastatic disease following bilateral orchidectomy and/or oestrogen therapy. 3. ECOG performance status of less than 4. 4. Adequate haematologic, renal and hepatic function (white blood cell count > 4000/mm³; platelet count > 100,000/mm³; BUN < 60, creatinine < 2mg; bilirubin < 2mg). 5. No evidence of documented myocardial infarction in 12 mon before randomisation; unstable angina; significant ischemic, hypertensive or valvular heart disease; an ejection fraction of > 55% on nuclear heart scan; congestive heart failure; significant rhythm or conduction disturbance on an electrocardiogram. 6. No major arterial or venous thrombosis unrelated to prostate cancer. 7. No prior exposure to doxorubicin or i.v. DES.</p> <p>Additional info: * Not stated which arm withdrawn patients had been assigned to: 6 withdrawals did not receive assigned therapy and 32 were subsequently deemed ineligible.</p> <p>Response was additionally determined by serum acid phosphatase level, defined as a reduction > 50% in abnormal pretreatment level or return to normal range from abnormal pretreatment level maintained for at least 3 mon. Stability of level was defined as a reduction < 50% in an initially abnormal level or increase of < 25% of abnormal level or an increase in a normal pretreatment level to an abnormal</p>	<p>Parenteral oestrogen: Combined</p> <p>Arm 1: Diethylstilboestrol (DES) & Doxorubicin 1 g DES i.v. daily for 5 day, 1 g i.v. every 2 w for 4 cycles (12 w) subsequently; 50 mg/m² Doxorubicin i.v. every 3 w. After 12 w evaluation, patients with response/stable disease continued therapy until maximum dose of 500 mg/m² reached. Dose reduced or drug temporarily omitted if grade 3 or 4 toxicity developed or if severe thromboembolic disease developed. DES still given if Doxorubicin suspended due to bone marrow suppression. Patients over 70 y old & patients with extensive prior chemotherapy/radiation received 40 mg/m² Doxorubicin as initial dose with subsequent escalation to 50 mg/m². If WBC or platelet count was 3000-4000 or 75,000-100,000 respectively, 50% dose was given; if WBC < 3000 or platelet < 75,000 Doxorubicin was withheld until counts recovered. If WBC nadir < 2000 or</p>	<p>Disease Progression: Nonosseous response [Complete response defined as disappearance of all measurable disease for at least 1 mon; partial response defined as a reduction of >50% in sum of all products of tumour diameters for at least 1 mon or in case of evaluable disease, definite improvement estimated to be in excess of 50% agreed by 2 independent investigators.] Arm 1: 8/30 (27%) complete or partial response (95% CI: 12%, 46%) Arm 2: 2/32 (6.3%) complete or partial response (95% CI: 0.7%, 20.8%) Stats: Exact test comparison: p=0.04 Subgroups: Note: 11/62 were unevaluable.</p> <p>Disease Progression: Osseous response [Response defined as reduction in size or number of lesions compared to pretreatment scan.] Arm 1: 9/71 (12.7%) showed remission (95% CI: 6.0%, 22.7%) Arm 2: 9/73 (12.3%) showed remission (95% CI: 5.8%, 22.1%) Stats: Exact test comparison: P > 0.99 Subgroups: Note: 23/144 were unevaluable.</p> <p>Disease Progression: Clinical response Arm 1: 18/74 (24.3%) showed clinical improvement (95% CI: 15.1%, 35.7%) Arm 2: 16/76 (21.1%) showed clinical improvement (95% CI: 12.5%, 31.9%) Stats: p=0.70 Subgroups: Note: 3/150 were unevaluable.</p> <p>Survival: Overall survival (Defined as time from registration to death or date last known alive.) Arm 1: 9.1 mon (median) (n=148); 8.5 mon (median) (ITT analysis: n=150) Arm 2: 7.5 mon (median) (n=148); 7.7 mon (median) (ITT analysis: n=150) Stats: p=0.40 ITT analysis p=0.37 NB: 3 patients long term survivors: 5.9 y, 8.2 y, 6.7y Subgroups: Initial performance status of 0 or 1 (n=85) had median survival of 10.2 mon; initial</p>	<p>Authors' conclusions: The addition of i.v. DES to doxorubicin appeared to add little benefit. There appeared to be a greater degree of cardiac toxicity and clinically significant thromboses on the combined therapy arm.</p> <p>Additional outcomes: Adverse events: Hematologic (neutropenia?) hepatic, emesis, other gastrointestinal, infection, bleeding, skin/mucosa/genitourinary.</p> <p>Reviewer comment: There is not enough information to determine if the randomisation was appropriate or if there was adequate allocation concealment. Study was completed more than 15 y before publication Results are only presented for the 150 patients who received assigned therapy for majority of outcomes.</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Yes</p>

<p>survival-type end-points were made using the log rank test.</p>	<p>range. Responses determined by these criteria are not separately reported.</p> <p>Patients were stratified with regard to disease measurability (e.g. measurable or evaluable nonbony disease vs bone disease only); ECOG performance status (0-1 vs 2-3) and degree of weight loss in 6 mon preceding randomisation (<5% bodyweight vs > 5% bodyweight).</p> <p>Diagnosis: Prostatic adenocarcinoma</p> <p>Co-morbidity: None reported.</p> <p>Age (range): 65 y (median) (40 - 86 y)</p>	<p>platelet nadir < 50,000 in previous cycle, dose was reduced by 50% & patient was not eligible for dose escalation in subsequent cycles. Doxorubicin dose was reduced by 50% if bilirubin > 2mg. No. patients: 74 No. withdrawn: *</p> <p>Arm 2: Doxorubicin 50 mg/m² i.v. every 3 w for 4 cycles (12 w). After 12 w evaluation, patients with response/stable disease continued therapy until maximum dose of 500 mg/m² reached. Dose reduced or drug temporarily omitted if grade 3 or 4 toxicity developed or if severe thromboembolic disease developed. DES still given if Doxorubicin suspended due to bone marrow suppression. Patients over 70 y old & patients with extensive prior chemotherapy/radiation received 40 mg/m² as initial dose with subsequent escalation to 50 mg/m². If WBC or platelet count was 3000-4000 or 75,000-100,000 respectively, 50% dose was given; if WBC < 3000 or platelet < 75,000 drug was withheld until counts recovered. If WBC nadir < 2000 or platelet nadir < 50,000 in</p>	<p>performance status of 2 or 3 (=65) had median survival of 7.0 mon (p=0.029). Patients with weight loss < 5% bodyweight in 6 mon before registration (n=96) had a median survival of 10.2, those with > 5% bodyweight (n no reported) had a median survival of 6.0 mon (p=0.0093). No significant difference between patients with osseous and non osseous disease.</p> <p>Survival: Failure-free survival [Defined as time from registration to death, progressive disease, relapse after evidence of disease response or initiation of radiation therapy.] Arm 1: 3.2 mon (median) (n=74) Arm 2: 2.6 mon (median) (n=76) Stats: p=0.012 NB: 2 patients with long term freedom from failure both in Arm 1 (5.9 y and 2.3 y) Subgroups:</p> <p>Adverse Events Toxicity [cardiac events] Arm 1: 13.5%: severe events: 6.8%, life-threatening events: 5.4%, lethal events: 1.4% (n=74) Arm 2: Total: 1.3%: severe events: 1.3% (n=76) Stats: p=0.0041 Subgroups:</p> <p>Adverse Events Superficial and deep vein thrombosis, and pulmonary embolism Arm 1: Total: 8.2%, severe: 6.8%, life-threatening: 1.4% (n=74) Arm 2: 0/76</p>	
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		previous cycle, dose was reduced by 50% & patient was not eligible for dose escalation in subsequent cycles. Dose was reduced by 50% if bilirubin > 2mg. No. patients: 76 No. withdrawn: *		
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Q2 Review of Dose

Comparison of parenteral oestrogen at different doses

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Henriksson, 1988³⁷</p> <p>Country: Sweden</p> <p>Language of Publication: English</p> <p>Setting: Huddinge University Hospital</p> <p>Study Objective: To evaluate the efficacy of strict parenteral estrogen therapy - in order to lessen the estrogenic impact on the liver- in patients with prostatic cancer.</p> <p>Funding Source: Swedish National Association Against Heart and Chest Diseases</p> <p>Duration: mean therapy:12.9 month, mean follow up:14.1 month</p>	<p>No. participants: 38</p> <p>No. withdrawn: Not reported</p> <p>Inclusion criteria: 1) prostatic cancer suitable for hormonal treatment</p> <p>Additional info: T0: 2 (5%), T1 (3%): 1, T2: 11 (29%), T3: 13 (34%), T4: 11 (29%). G2: 25 (66%), G3: 13 (34%) M0: 2 (71%), M1: 11 (29%) * 3 patients had angina pectoris, 1 had intermittant claudication</p> <p>Diagnosis: prostatic cancer</p> <p>Co-morbidity: * see additional info</p> <p>Age (range): 70.7 (S.E.M. = 1.0)</p>	<p>Arm 1: high dose PEP 320mg/month i.m. No. patients: 20 No. withdrawn: 0</p> <p>Arm 2: medium dose PEP 240mg/month i.m No. patients: 9 No. withdrawn: 0</p> <p>Arm 3: low dose PEP 160mg/month i.m. No. patients: 9 No. withdrawn: 0</p>	<p>Disease Progression: Response to therapy Arm 1: 16/20 (80%) Arm 2: 5/9 (55%) Arm 3: 8/9 (89%)</p> <p>Adverse Events: Cardiovascular events Arm 1: 0 Arm 2: 0 Arm 3: 0</p>	<p>Authors' conclusions: There are indications of a drastic reduction in cardiovascular morbidity if parenteral estrogen in the form of PEP is used instead of oral estrogen in the therapy of prostatic cancer.</p> <p>Additional outcomes:</p> <p>Reviewer comment: Paper compares results with those of patients treated with combined oral and parenteral estrogens in a previous study . There is no description of how patients were assigned to treatment and no description of blinding of assessors. No loss to follow-up was reported</p> <p>Quality assessment: 1. Described as randomised? No 2. Truly random? Not relevant 3. Randomization adequately concealed? Not relevant 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Not relevant</p>

STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Stege, 1988³⁸</p> <p>Country: Sweden</p> <p>Language of Publication: English</p> <p>Setting: University Hospital</p> <p>Study Objective: To investigate testosterone suppression during different doses of i.m. PEP treatment and to study possible side effects.</p> <p>Funding Source: Riksföreningen mot cancer, Maud & Birger Gustafssons Stiftelse</p> <p>Duration: 6 months treatment/follow-up</p>	<p>No. participants: 27</p> <p>No. withdrawn: 0</p> <p>Inclusion criteria: 1. Histologically and/or cytologically proven cancer of the prostate. 2. No previous treatment for prostate cancer</p> <p>Additional info: T2-T4, G2-G3, M0-M1, Nx. No significant difference in tumour stage/grade, age or lab values between groups. No patients had signs of endocrine, cardiovascular, intestinal or renal malfunction. No patients received other medication given that could interfere with analyses performed.</p> <p>Diagnosis: cancer of the prostate</p> <p>Co-morbidity: none reported</p> <p>Age (range): 70 (SEM 1.2)</p>	<p>Arm 1: High dose PEP (Estradurin) 320mg/4 weeks i.m. No. patients: 9 No. withdrawn: 0</p> <p>Arm 2: Medium dose PEP (Estradurin) 240mg/4 weeks i.m. No. patients: 9 No. withdrawn: 0</p> <p>Arm 3: Low dose PEP (Estradurin) 160mg/4 weeks i.m. No. patients: 9 No. withdrawn: 0</p>	<p>Disease Progression: Response (R), Stable Disease (SD), Non-response (NR) Arm 1: R = 5, SD = 3, NR = 1 (N = 9) Arm 2: R = 4, SD = 3, NR = 2 (N = 9) Arm 3: R = 0, SD = 8, NR = 1 (N = 9)</p> <p>Adverse Events: Cardiovascular morbidity Arm 1: 0 Arm 2: 0 Arm 3: 0</p> <p>Adverse Events: Gynecomastia and/or breast tenderness 21/27 - not stratified by group</p>	<p>Authors' conclusions: Intramuscular PEP may be an attractive alternative endocrine treatment of prostatic cancer providing sufficient testosterone suppression at appropriate dosages and probably causing no major cardiovascular side effects.</p> <p>Additional outcomes: Erectile dysfunction</p> <p>Testosterone levels The length of treatment required to reach castration levels of testosterone was dose-dependent. In the 160 mg group the mean value was just below the upper limit of castrate levels after 6 months of treatment.</p> <p>Estradiol 17 beta levels Levels of estrogen increased in a dose-dependent manner and an accumulation was observed in all groups.</p> <p>Sex hormone binding globulin (SHBG) levels Only minor changes in levels occurred during treatment.</p> <p>Reviewer comment: Concentrates on serum hormone levels & compares results with those of patients treated with combined oral and parenteral estrogens and some patients treated with orchiectomy none of whom were part of the randomised study. NB: highest CVS risk is usually in year 1 of treatment, 6 month data only.</p> <p>Quality assessment: 1. Described as randomised? Yes</p>

				2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Not described
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STUDY DETAILS	PARTICIPANTS	INTERVENTIONS	RESULTS	CONCLUSIONS
<p>Stege, 1989³⁹</p> <p>Country: Sweden</p> <p>Language of Publication: English</p> <p>Setting: Huddinge University Hospital</p> <p>Study Objective: To study the effects of dose reduction after 6 months of treatment with the 320mg dosage of PEP.</p> <p>Funding Source: Riksföreningen mot Cancer; Swedish Medical Research Council, Karolinska Institutet's Fonder and Maud & Birger Gustafsson's Stiftelse</p> <p>Duration: treatment period: 12 months</p>	<p>No. participants: 17</p> <p>No. withdrawn: 0</p> <p>Inclusion criteria: Cytologically confirmed prostatic carcinoma</p> <p>Additional info: All patients were treated for 6 months with 320mg/4 weeks and then randomised into 2 groups. There was no significant difference in characteristics at baseline, 3 or 6 months between the 2 groups with respect to age, TNM classification, malignancy grades & hormone levels</p> <p>Tumours were T2-T4, G2-G3 and M0-M1</p> <p>None of the patients had clinical or laboratory signs of cardiovascular, hepatic, biliary, intestinal or renal malfunction, any endocrine abnormality or any medication that could interfere with serum hormone levels under investigation.</p> <p>Diagnosis: prostatic carcinoma</p> <p>Co-morbidity: none reported</p> <p>Age (range): 72.8 (66-82)</p>	<p>Arm 1: Higher dose PEP (Estradurin) 320mg/4 weeks i.m. for 6 months then 160mg/4 weeks i.m for 6 months No. patients: 8 No. withdrawn: 0</p> <p>Arm 2: Lower dose PEP (Estradurin) 320mg/4 weeks i.m. for 6 months then 80mg/4 weeks i.m for 6 months No. patients: 9 No. withdrawn: 0</p>	<p>Disease Progression: Response (R), stable disease (SD), non-response (NR) Arm 1: R = 5, SD = 2, NR = 1 (N = 8) Arm 2: R = 3, SD = 4, NR = 2 (N = 9)</p> <p>Adverse Events: Cardiovascular events Arm 1: 0/8 Arm 2: 0/9</p>	<p>Authors' conclusions: It is not possible to decide whether a maintenance dose of PEP higher than 160mg/4 weeks is advantageous. However a clinical response involving 3 non-responders out of 17 patients with no cardiovascular side effects may be considered acceptable.</p> <p>Additional outcomes: testosterone levels (nmol/l) initial treatment with 320mg Baseline: 12.3 +/- 0.6; 3 months: 0.8 +/- 0.1; 6 months: 0.7 +/- 0.1 PEP 80mg Following dose reduction, mean levels of testosterone increased significantly (P < 0.05) and were above the upper limit for orchiectomised patients after 1 month following dose reduction. At 3 months levels had increased again (P < 0.01) to a level of 4-6nmol/l. 160mg Levels increased slightly but significantly (P < 0.05 - P < 0.01) from 1st month of dose reduction but reached upper orchidectomy level after 5 months.</p> <p>estradiol-17beta levels (pmol/l) initial treatment with 320mg baseline: 68 +/- 8; 3 months: 1805 +/- 132; 6 months: 2456 +/- 148 Following dose reduction concentrations of estradiol showed a significant (P < 0.001) decrease after 1 month in both groups and a significant further decrease (P < 0.001) to plateau levels within 4 months.</p> <p>FSH levels (units/l) initial treatment with 320mg Baseline: 6.9 +/- 1.1; 3 months: <1; 6 months: < 1 Following dose reduction, levels were significantly increased in the 80mg group from month 3 (P , 0.05 - P < 0.01), but</p>

				<p>not in the 160 mg group.</p> <p>LH levels (Units/l) initial treatment with 320mg Baseline: 6.4 +/- 0.8; 3 months: 1.9 +/- 0.3; 6 months: 1.8 +/- 0.3 Following dose reduction levels were significantly increased from month 1 in the 80 mg group ($P < 0.05$ - $P < 0.01$) but not in the 160 mg group.</p> <p>There were no significant differences in hormone levels at baseline, or after 3 or 6 months of treatment with PEP 320mg between the 2 groups.</p> <p>Reviewer comment: Paper concentrates mainly on serum hormone levels which are extensively reported. There was not enough information to determine whether the method of randomisation was appropriate or whether there was adequate concealment of allocation. No loss to follow-up was reported</p> <p>Quality assessment: 1. Described as randomised? Yes 2. Truly random? Not described 3. Randomization adequately concealed? Not described 4. Described as double-blind? No 5. Blinding appropriate? Not relevant 6. Description of withdrawals and dropouts? Not described</p> <p>Reviewer quality comment: Randomisation to arms 2 and 3 was carried out after initial treatment in arm 1.</p>
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