Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials


CRD summary
This review concluded that androgen deprivation therapy was not associated with an increased risk of cardiovascular death and was associated with a lower risk of prostate cancer-specific and all-cause mortality. Given the potential limitations of the review and included studies, the results should be treated with some caution.

Authors' objectives
To investigate any association between androgen deprivation therapy (ADT) and mortality (cardiovascular, prostate cancer-specific or all-cause) in men with unfavourable-risk, non-metastatic prostate cancer.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles in English from 1966 to April 2011; search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared immediate treatment predominantly with a gonadotropin-releasing hormone (GnRH) agonist with no immediate ADT in patients with non-metastatic and non-hormone-refractory disease were eligible for inclusion. Studies had to have a median follow-up of at least one year and report on either cardiovascular deaths or prostate cancer-specific and all-cause mortality.

The trials included patients with non-metastatic disease at various stages. Median age of participants ranged from 61 to 73 years. Most studies evaluated goserelin with or without flutamide. Duration of ADT varied from three months to lifelong. Local therapy, where conducted, was either external beam radiation or surgery. Some trials included a substantial proportion of patients with lymph node involvement.

The authors did not report how many reviewers selected studies for the review.

Assessment of study quality
Trial quality was assessed using the Jadad scale of randomisation, blinding and reporting of withdrawals.

The authors did not report how many reviewers performed the quality assessment.

Data extraction
Data on mortality rates were extracted by two independent reviewers. Discrepancies between reviewers were resolved by consensus. Risk ratios (RR) and 95% confidence intervals (CIs) were calculated. A 0.5 continuity correction was applied for cells with zero events.

Methods of synthesis
Where no substantial heterogeneity was observed, summary risk ratios and 95% CIs were calculated using a fixed-effect model using the inverse variance method. A DerSimonian and Laird random-effects model was used where substantial heterogeneity was observed. Heterogeneity was investigated using the Cochran Q and I² statistics. Where studies evaluated more than one duration of ADT, these arms were combined. Subgroup analyses were performed to investigate the duration of ADT treatment (short course ≤6 months, long course ≥3 years), age (<70 or ≥70 years) and use of radiation. Meta-regression was undertaken. Publication bias was evaluated through funnel plots and Begg and Egger tests.

Results of the review
Eight multicentre RCTs met the inclusion criteria (4,141 participants, range 98 to 985). None of the trials included a double-blinded placebo. Seven RCTs scored 3 out of 5 and four scored 2 out of 5 on the quality assessment. Where reported, median follow-up ranged from 6.8 to 13.2 years. There was no evidence of publication bias for any outcome.

**Cardiovascular mortality (eight RCTs)**: There were 255 cardiovascular deaths across 2,200 patients in the ADT groups and 252 across 1,941 patients in the control groups; there was no statistically significant difference between groups (RR 0.93, 95% CI 0.79 to 1.10) and no significant heterogeneity. Results were similar when studies that used short course or long course ADT and trials with median participant ages under and over 70 were analysed separately.

**Prostate cancer-specific mortality (11 RCTs)**: There were 443 prostate cancer-specific deaths across 2,527 patients in the ADT groups and 552 across 2,278 patients in the control groups. There were statistically significantly fewer deaths in those who received ADT (RR 0.69, 95% CI 0.56 to 0.84), but heterogeneity was observed ($I^2=59.3\%$).

**All-cause mortality (11 RCTs)**: There were 1,140 deaths across 2,527 patients in the ADT groups and 1,213 across 2,278 patients in the control groups. There were statistically significantly fewer deaths in those who received ADT (RR 0.86, 95% CI 0.80 to 0.93), but heterogeneity was observed ($I^2=40.7\%$).

**Authors’ conclusions**
ADT use was not associated with an increased risk of cardiovascular death. It was associated with a lower risk of prostate cancer-specific and all-cause mortality.

**CRD commentary**
The authors addressed a clear review question supported by appropriate inclusion criteria. Relevant sources were searched. The review was restricted to studies in English, so language bias could not be ruled out. There was no specific search for unpublished studies. There was an investigation into publication bias and none was observed. Data extraction was conducted in duplicate; it was unclear whether similar methods were used to reduce error and bias during study selection and quality assessment. Study quality was assessed with a published scale, but results were not given individually for each study and this made it unclear which was prone to which bias. Allocation concealment was not assessed.

Methods of synthesis seemed generally appropriate and potential sources of heterogeneity investigated for one outcome, although the overall pooled results were based upon clinically heterogeneous studies.

Given the potential limitations of the review and included studies, the results should be treated with some caution.

**Implications of the review for practice and research**
**Practice**: The authors did not state any implications for practice.

**Research**: The authors recommended that future RCTs that test the value of ADT should stratify by cardiovascular morbidity.

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