# Cardiovascular status and events in patients with prostate cancer treated with a luteinising hormone-releasing hormone agonist or degarelix: A comparison of USA/Canada vs Europe

MP-12.11

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## INTRODUCTION

Data from observational studies, recently evaluated in two meta-analyses, suggest that men with prostate cancer (PCa) receiving androgen deprivation therapy (ADT) have an increased risk of cardiovascular (CV) morbidity and mortality.[1,2]

There may be a difference in the risk of CV events between luteinizing hormone-releasing hormone (LHRH) agonists and the antagonist, degarelix.

- Pooled data from six phase III trials comparing LHRH agonists and degarelix reported a lower risk of CV events or death with degarelix.[3]

The risk of CV events and mortality with ADT in PCa is greatest in those with a history of CV disease (CVD).[3-6]

We now report the impact of baseline CV risk status and regional differences on the incidence of CV events in men treated with either degarelix or LHRH agonist.

## METHODS

A pooled analysis of phase III clinical trials was performed with the following pre-defined criteria:

- Randomised, comparative trials of degarelix and LHRH agonists
- ADT exposure of at least 6 months.

Patients from three trials were eligible for inclusion: two 12-month trials (CS21 [n=555][7] and CS35 [n=779][8]) and one trial with a duration of 7–14 months (CS37, n=403).[9]

Individual patient data on baseline CVD, CV risk factors and subsequent CV events up to Day 364 were pooled.

History of CVD and CV events during the studies were defined by standard MedDRA query (SMQ) terminology (version 15).

- A CV event was defined as an arterial embolic or thrombotic event, a haemorrhagic or ischaemic cerebrovascular condition, myocardial infarction or other ischemic heart disease.
- High CV risk status at baseline was defined by the existence of two or more traditional CV risk factors:
  - Treated type 2 diabetes
  - Hypertension; blood pressure >90 mmHg (diastolic) or >140 mmHg (systolic)
  - Current smoker
  - Obesity; BMI >30 kg/m$^2$
  - Hypercholesterolemia; serum cholesterol >6.2 mmol/L

Subsequent CV events were analysed using cumulative incidence functions (with all-cause mortality as the competing risk) and the Gray's test. Cause-specific hazard ratios of CV events were analysed using Cox-proportional hazards regression models.

## RESULTS

Overall 1737 patients were included in the analysis, 1118 with no prior CVD and 619 with a history of CVD. Baseline characteristics are shown in Table 1.

TABLE 1

**Baseline characteristics for patients with and without CVD history at baseline**

| | No history of CVD (n=1118) | History of CVD (n=619) | Total (n=1737) |
|---|---|---|---|
| Age (years), median (range) | 71 (46–98) | 74 (51–92) | 72 (46–98) |
| Testosterone (ng/mL), median (range) | 4.11 (0.56–14.5) | 3.91 (0.37–13.2) | 4.02 (0.37–14.5) |
| High CV risk | 581 (52) | 422 (68) | 1003 (58) |
| BMI (kg/m$^2$), median (range) | 26.6 (16.1–55.8) | 27.1 (17.7–52.9) | 26.8 (16.1–55.8) |
| Obesity | 261 (23) | 167 (27) | 428 (25) |
| Elevated blood pressure | 303 (27) | 198 (32) | 501 (29) |
| Treated hypertension | 333 (30) | 171 (28) | 504 (29) |
| Treated type 2 diabetes | 118 (11) | 90 (15) | 208 (12) |
| Smoking | 539 (48) | 312 (50) | 851 (49) |
| Hypercholesterolemia | 138 (12) | 75 (12) | 213 (12) |
| Statin usage | 228 (20) | 261 (42) | 489 (28) |

Data are n (%) unless otherwise stated

### CV events in high risk vs. low risk patients

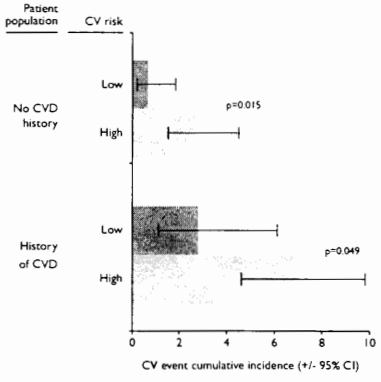
In the overall population, the cumulative incidence of CV events during up to 12 months of ADT was higher in men at high CV risk (4.5; 95% CI: 3.3–6.0) vs those at low risk (1.2; 95% CI: 0.6–2.4), p<0.001.

The cumulative incidence of CV events was higher in patients with high CV risk status both in those with and without history of CVD (Figure 1).

- In men with CVD at baseline, the cumulative incidence in those at high CV risk vs those at low CV risk was 6.9 (95% CI 4.6–9.8) vs 2.8 (95% CI 1.1–6.1); p=0.049, respectively (Figure 1).

FIGURE 1

**Cumulative incidence of AEs according to CV risk status**




### CV events in patients treated in the USA/Canada and Europe

The baseline characteristics of men diagnosed in the USA/Canada and Europe are summarised in Table 2.

- Median age, BMI, testosterone and proportion of men with a history of CVD was broadly similar between the groups.
- Patients in USA/Canada had more severe disease and a higher CV risk (p<0.05).

TABLE 2

**Baseline demographics, CVD history and CV risk factors by region and treatment**

| | USA/Canada | | Europe | |
|---|---|---|---|---|
| | Degarelix (n=479) | LHRH agonist (n=307) | Degarelix (n=639) | LHRH agonist (n=312) |
| Age (years), median (range) | 74 (50–94) | 72 (51–98) | 72 (46–94) | 72 (51–87) |
| Testosterone (ng/mL), median (range) | 3.52 (0.7–10.8) | 3.67 (0.62–9.3) | 4.53 (0.56–14.5) | 4.33 (0.37–13.2) |
| BMI (kg/m2), median (range) | 27.4 (16.3–55.8) | 28.5 (17–52.9) | 25.9 (16.1–43.8) | 26 (17.8–38.4) |
| History of CVD | 166 (35) | 97 (32) | 238 (37) | 118 (38) |
| High CV risk | 335 (70) | 234 (76) | 301 (47) | 133 (43) |
| Obesity | 152 (32) | 117 (38) | 110 (17) | 49 (16) |
| Elevated blood pressure | 151 (32) | 89 (29) | 183 (29) | 78 (25) |
| Treated hypertension | 115 (24) | 88 (29) | 204 (32) | 97 (31) |
| Treated type 2 diabetes | 87 (18) | 54 (18) | 43 (7) | 24 (8) |
| Smoking | 276 (58) | 204 (66) | 254 (40) | 117 (38) |
| Hypercholesterolemia | 24 (5) | 18 (6) | 129 (20) | 42 (13) |
| Statin usage | 239 (50) | 140 (46) | 65 (10) | 45 (14) |

Data are n (%) unless otherwise stated.

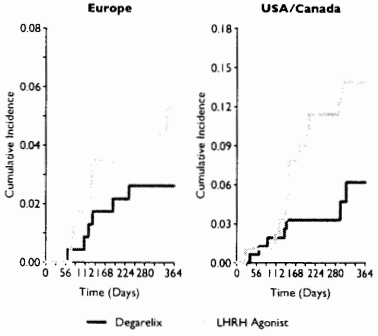
In men with CVD at baseline, the unadjusted cumulative incidence of a CV event during up to 12 months of ADT was higher in USA/Canada (9.4, 95% CI 5.8–14.0) than Europe (3.5; 95% CI 1.9–5.9), p=0.006.

However, as suggested by the cumulative incidences in each treatment group and region (red and grey lines in Figure 2) the relative hazard for degarelix is lower in both regions when compared with LHRH agonist treatment.

- In a Cox-regression analysis with a treatment-by-region interaction term, the effect of region is non-significant (p>0.05).
- In this model the pooled estimate of the treatment HR across both regions is 0.42 (95% CI 0.20–0.88; p=0.021).

FIGURE 2

**Cumulative incidence of CV events in EU and USA/Canada**




## CONCLUSIONS

Men in the USA/Canada with PCa and CVD and who were treated with ADT were more likely to experience a CV event than their counterparts in Europe.

The geographical differences in the 1-year CV event risk (greater in USA/Canada) likely reflects the greater severity of baseline CVD and higher CV risk in these patients.

Despite a lower CV event rate in Europe compared with the USA/Canada, the degree of reduction in the risk of CV events with degarelix compared with a LHRH agonist was similar in both regions.

**References**

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**Acknowledgements**

The trials reported in this analysis were sponsored by Ferring Pharmaceuticals. Additional statistical analysis support was provided by Dr Kyle Raymond of Ferring Pharmaceuticals R&D. Medical writing support (funded by Ferring) was provided by Dr Matthew deSchoolmeester of Bioscript Medical.

SIU, Melbourne, Australia, 2015