Cardiovascular risk with GnRH agonists and antagonists: Real world evidence from UK primary care

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Declarations

- Honoraria from Ferring
- Honoraria from Novartis
- Honoraria from Zio Patch
- Honoraria from Bayer
- Honoraria from Boehringer Ingelheim
- Travel grants from MSD, Daiichi Sankyo

- This study was initiated and funded by Ferring. Analysis of data was carried out by Open Vie

ADT therapy in prostate cancer

- Effective, for a while & improves prognosis
- However, concern over long-term side effects, including cardiovascular events
- Long-term ADT appears to increase CV event rate
- 20-30% of prostate cancer patients have pre-existing cardiovascular disease – their prognosis is worse, and they may have a greater increase in CV risk with ADT

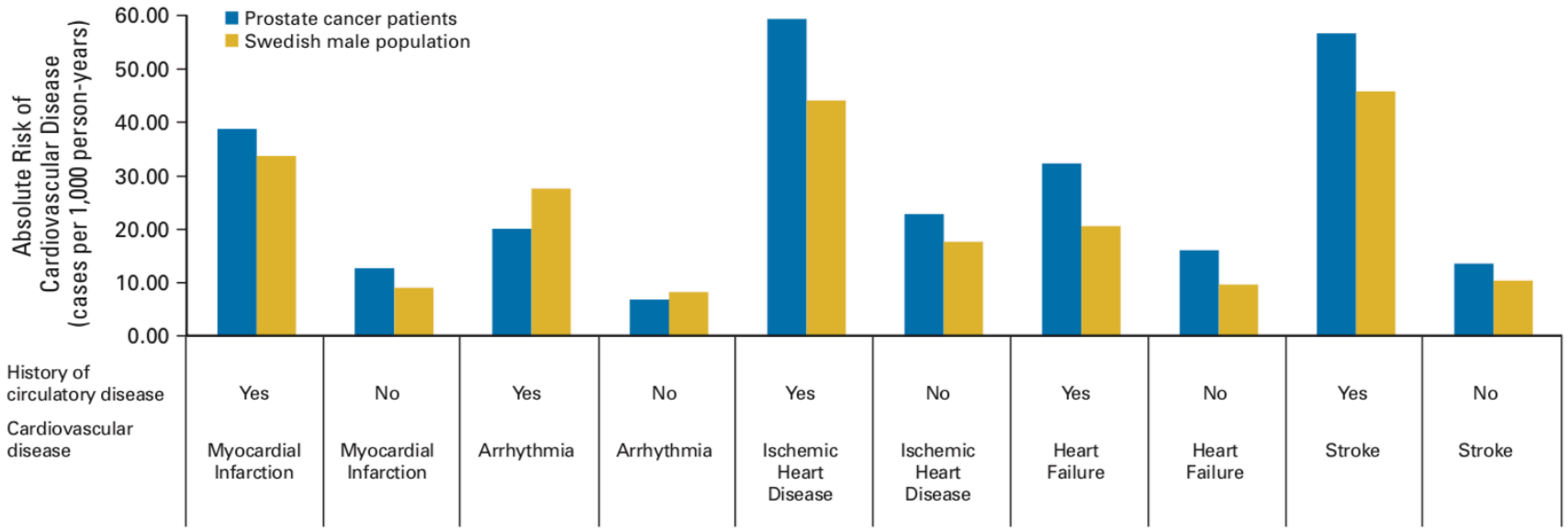
Pre-existing cardiovascular disease increases risk of death in prostate cancer

Population	n (%)	Cumulative survival (%)		Adjusted HR (95% CI)
		1-year	5-years	
Overall	30,721 (100)	84.4	41.7	—
No coronary artery disease or stroke	25,114 (82)	85.4	43.5	1.0 (ref)
Coronary artery disease	4,276 (14)	80.5	36.1	1.05 (1.00–1.10)
Stroke	1,331 (4)	77.6	26.5	1.20 (1.12–1.30)

*HR adjusted for age, stage, calendar period and comorbidity (excluding IHD and stroke)
Patients with incident prostate cancer registered in the Danish Cancer Registry from 1997 to 2008

Jespersen CG, et al. BMC Cancer 2011;11:519

Outcome with ADT related to pre-existing CV disease



Van Hemelrijck et al J Clin Oncol 28:3448-3456. DOI: 10.1200/JCO.2010.29.1567

The risk of cardiovascular events may depend on ADT modality

	Coronary artery disease		Acute myocardial infarction		Sudden cardiac death	
	10-year rates	P	10-year rates	P	10-year rates	P
No treatment	25.1	Ref	14.8	Ref	14.2	Ref
LHRH agonists	26.9	<0.001	16.6	<0.001	17.7	<0.001
Bilateral orchiectomy	23.2	0.2	14.8	0.6	16.4	0.4

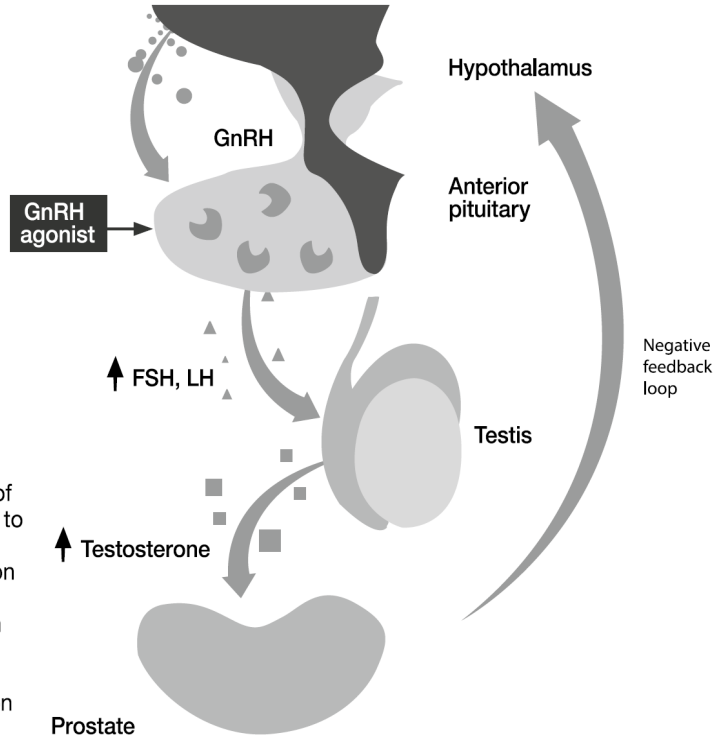
140,474 patients with histologically confirmed non-metastatic prostate cancer, aged ≥66 years and diagnosed Jan 1995 – Dec 2009: included in the Surveillance, Epidemiology and End Results (SEER) Medicare-linked database

LHRH agonists, but not orchiectomy, are associated with a significant increase in cardiac events in patients with non-metastatic prostate cancer

Gandaglia et al BJU Int. 2014 Dec;114(6b):E82-9.

Androgen deprivation therapy

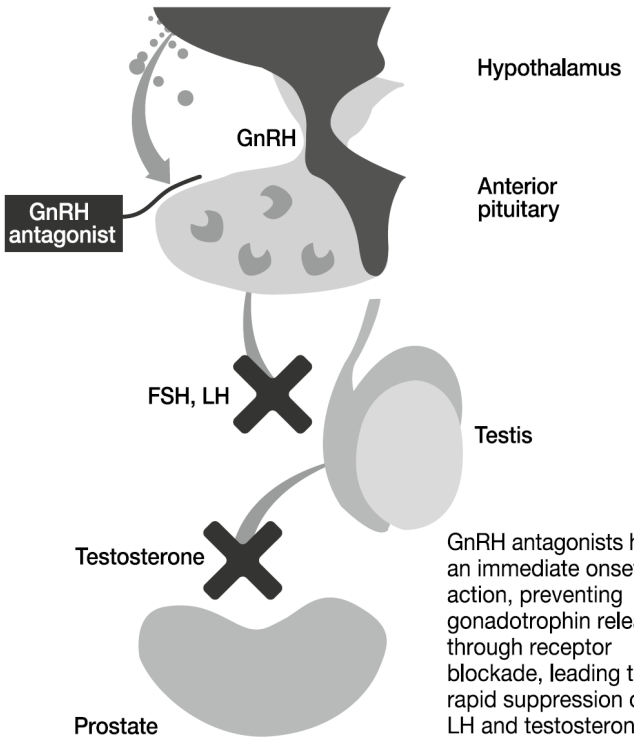
GnRH agonists



Initial overstimulation of GnRH receptors leads to an increase in LH and testosterone production

Chronic administration eventually leads to suppression of LH, resulting in suppression of testosterone

GnRH antagonists



GnRH antagonists have an immediate onset of action, preventing gonadotrophin release through receptor blockade, leading to rapid suppression of LH and testosterone

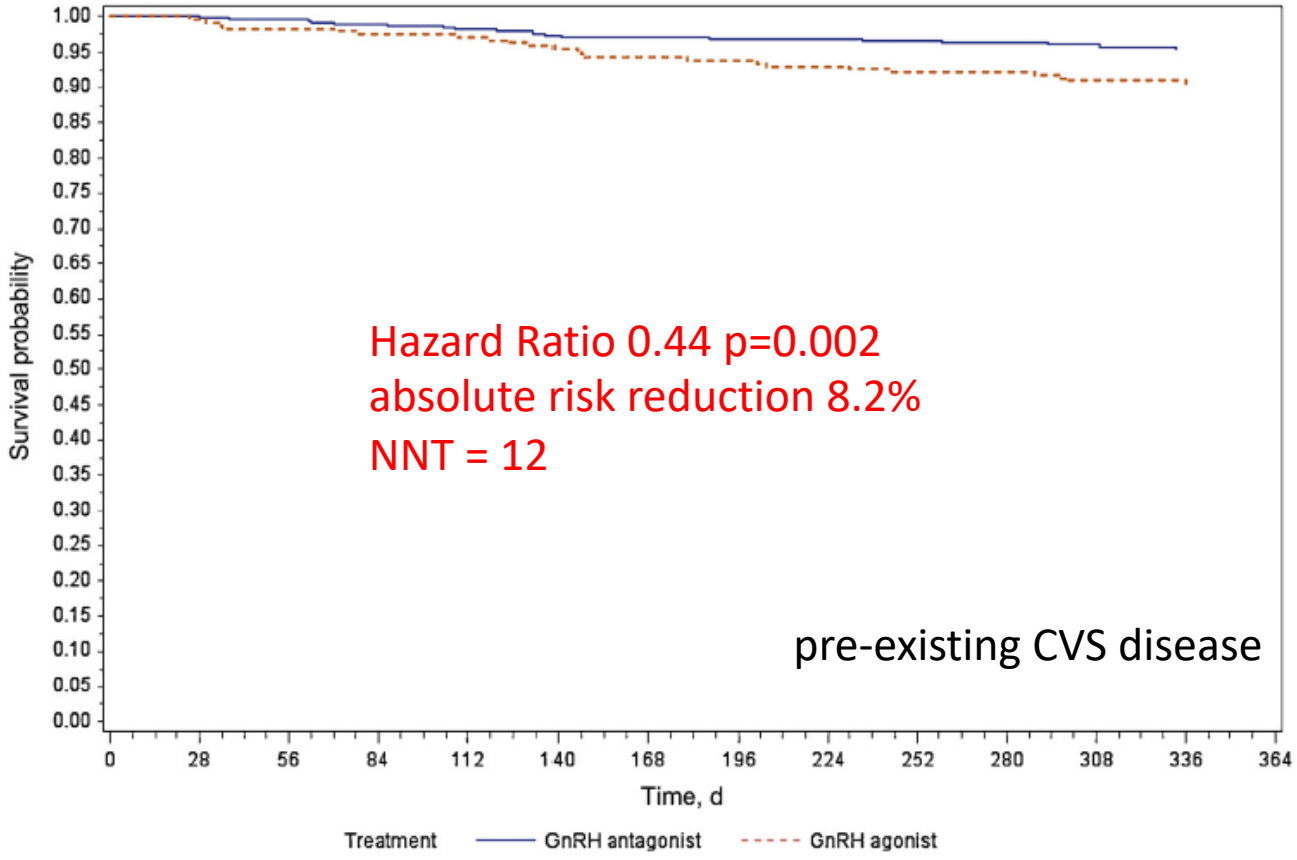
Lower CV risk with GnRH antagonists?

Baseline presence of CV disease is important

- Pooled trial data - lower CV event rate with antagonist therapy (degarelix) vs GnRH agonists
  - Patients with no CV disease at baseline:
    - no difference in CV events between treatment groups
  - with CV disease at baseline:
    - 56% relative risk reduction of a CV event with degarelix vs GnRH agonist (HR: 0.44; 95% CI, 0.26-0.74; p=0.002)
    - 8.2% ARR of a CV event or death with degarelix
    - NNT of 12 to prevent 1 CV event
- Risk reduction is associated with presence of pre-existing CVD

Albertsen et al. Eur Urol 2014;65:565-573

Lower CV risk with GnRH antagonists?



Albertsen et al. Eur Urol 2014;65:565-573

Aims/methods of the study

- To clarify using real world data whether Cardiovascular risk in prostate cancer patients is, as suggested, lower in those treated with a GnRH antagonist (degarelix) vs GnRH agonists
- Data from Optimum Patient Care Data Base ODCPR – UK primary care database, 700 GP practices, records from 8.8 million patients

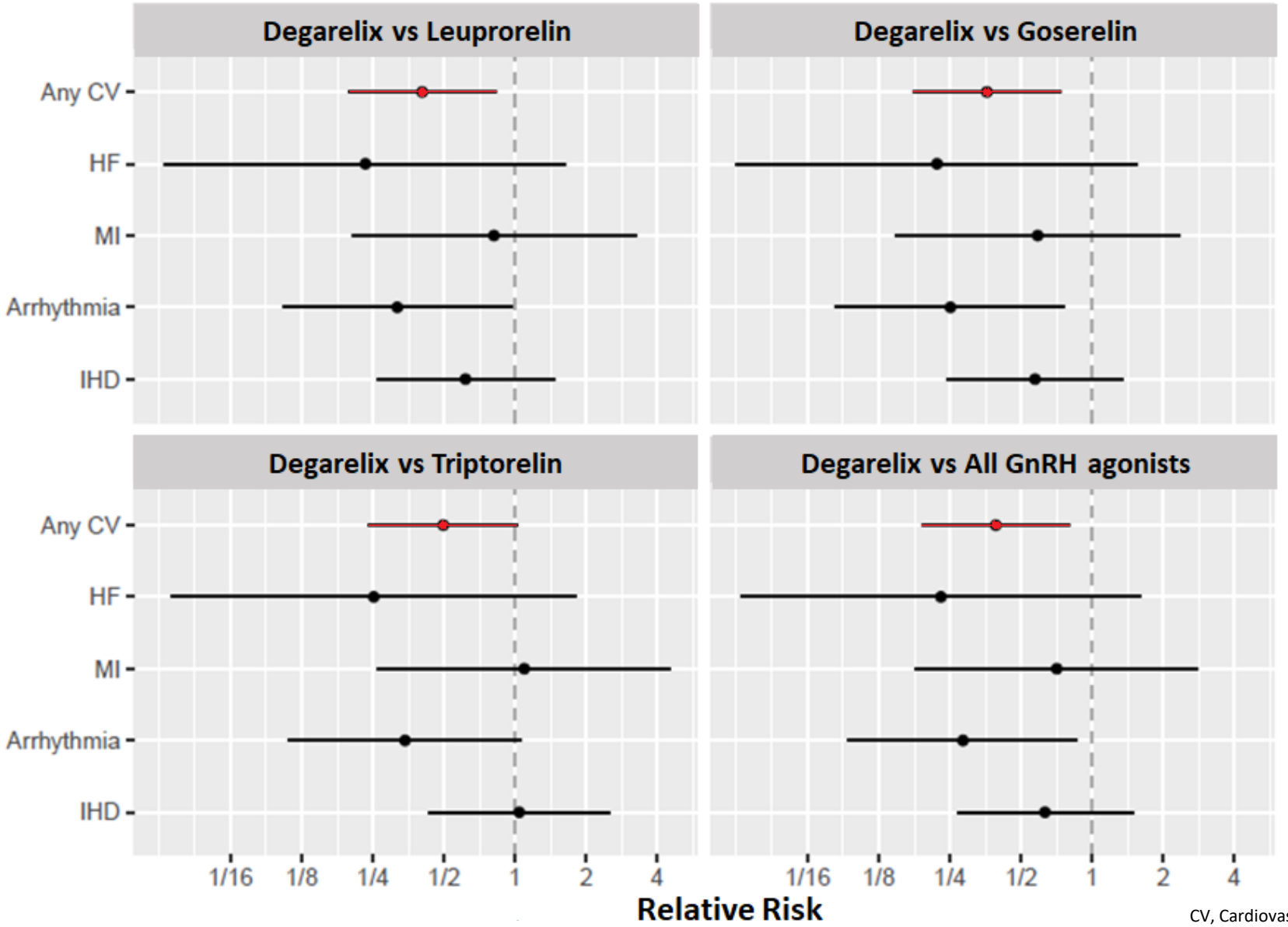
Methods

- Patients with prostate cancer who were new users of degarelix, leuprorelin, goserelin or triptorelin were identified
- The relative risk of cardiovascular events (heart failure, MI, arrhythmia and IHD) for degarelix vs GnRH agonists was determined

Results – Baseline characteristics

Baseline characteristics	Degarelix users n=146	Leuprorelin users n=3,860	Goserelin users n=5,110	Triptorelin users n=1,643
Age, Mean (SD)	74.8 (9.0)	75.9 (8.6)	74.0 (8.5)	75.3 (8.3)
PSA, ng/ml, closest to baseline, n (%)				
Median [IQR]	72.4 (3.7 – 273.0)	10.0 (1.4 – 36.7)	8.0 (0.8 – 24.9)	10.6 (1.6 – 36.4)
<20	27 (40.3)	1,727 (64.9)	2,312 (70.9)	694 (62.2)
≥20	40 (59.7)	936 (35.1)	948 (29.1)	421 (37.8)
Testosterone, ng/ml				
Mean (SD)	14.7 (4.9)	16.2 (18.4)	13.8 (13.8)	15.4 (15.1)
Cardiovascular disease baseline, n (%)	38 (37.6)	1,075 (32.7)	1,288 (29.5)	385 (29.1)
Ischaemic heart disease	22 (21.8)	639 (19.4)	822 (18.8)	213 (16.1)
Heart Failure	4 (4.0)	168 (5.1)	154 (3.5)	53 (4.0)
Myocardial Infarction	15 (14.8)	324 (9.8)	420 (9.6)	88 (6.6)
Arrhythmia	20 (19.8)	615 (18.7)	669 (15.3)	222 (16.7)
Diabetes Mellitus	19 (18.8)	532 (16.2)	704 (16.1)	213 (16.1)

Relative risk of Degarelix vs GnRH agonists



CV, Cardiovascular
HF, Heart Failure
MI, Myocardial Infarction
IHD, Ischaemic Heart Disease

Conclusions

- Real-world data of patients on a GnRH antagonist is consistent with previous studies showing lower CV risk vs agonists
- In men with pre-existing CV disease, the use of an antagonist rather than an agonist may mitigate CV risk

Assessment and mitigation of CV risk in clinical practice