Association between medical androgen deprivation therapy and long-term cardiovascular disease and all-cause mortality in non-metastatic prostate cancer

Forster RB, Engeland A, Kvåle R, Hjellvik V, Bjørge T

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Supplemental A. Outcome definitions:

The following outcomes were defined using International Classification of Diseases-Revision 10 (ICD10) and the International Classification of Primary Care-version 2 (ICPC2) codes from the Norwegian Prescription Database and the Norwegian Patient Registry.

- Myocardial infarction (ICPC2 = K75 or ICD10 = I21 or I22)
- Stroke (ICPC2 = K90 or ICD10 = I61, I63 or I64)
- Atrial fibrillation (ICPC2 = K78 or ICD10 = I48)
- Heart failure (ICPC2 = K77 or ICD10 = I11.0, I13.0, I13.2 or I50)

CVD risk factor definitions:

- Myocardial infarction, stroke, heart failure and atrial fibrillation were defined the same as the outcomes above. Diabetes was defined as ICD10 E10 or E11, ICPC2 T89 or T90 or a reimbursed ATC code within the A10 grouping
- Hypertension was defined by ICPC2 = K86 or K87 or ICD10 = I10, I11, I12, I13, I15 and/or ATC codes listed below:

| ATC Code | Description |
|---------|-------------|
| C02AC05 (moksonidin) | C08CA03 (isradipine) | C09CA03 (valsartan) |
| C02CA04 (doxazosin) | C08CA05 (nifedipine) | C09CA04 (irbesartan) |
| C02DB02 (hydralazin) | C08CA13 (lercanidipine) | C09CA06 (candesartan) |
| C03AA03 (hydroklorotiazid) | C08DB01 (diltiazem) | C09CA07 (telmisartan) |
| C03AB01 (bendroflumetiazid) | C08DA01 (verapamil) | C09CA08 (olmesartan) |
| C03DA01 (spironolakton) | C09AA01 (captopril) | C09DA01 (hydroklorotiazid and losartan) |
| C03EA01 (thiazide and amiloride) | C09AA02 (enalapril) | C09DA02 (hydroklorotiazid and eprosartan) |
| C07AA05 (propranolol) | C09AA03 (lisinopril) | C09DA03 (hydroklorotiazid and valsartan) |
| C07AB03 (atenolol) | C09AA04 (perindopril) | C09DA04 (hydroklorotiazid and irbesartan) |
| C07AB02 (metoprolol) | C09AA05 (ramipril) | C09DA06 (hydroklorotiazid and candesartan) |
| C07AB07 (bisoprolol) | C09BA02 (hydroklorotiazid and lisinopril) | C09DA07 (hydroklorotiazid and telmisartan) |
| C07AG01 (labetolol) | C09BA03 (hydroklorotiazid and enalapril) | C09DA08 (hydroklorotiazid and olmesartan) |
| C07AG02 (carvedilol) | C09BB02 (lercanidipine and enalapril) | C09DB01 (amlodipine and valsartan) |
| C08CA01 (amlodipine) | C09CA01 (Losartan) | C09DB02 (amlodipine and Olmesartan) |
| C08CA02 (felodipine) | C09CA02 (eprosartan) | |

- Hypercholesterolemia was defined as ICD10 = E78.0-E78.5 and/or ATC codes listed below:

| ATC Code | Description |
|---------|-------------|
| C10AA01 (simvastatin) | C10AX13 (evolocumab) |
| C10AA02 (lovastatin) | C10AX14 (alirocumab) |
| C10AA03 (pravastatin) | C10AC01 (colestyramine) |
| C10AA04 (fluvastatin) | C10AC04 (colesevalam) |
| C10AA05 (atorvastatin) | C10BA02 (ezetimib/simvastatin) |
| C10AA07 (rosuvastatin) | C10BA05 (ezetimib/atorvastatin) |
| C10AX09 (ezetimib) | C10BA0 (ezetimibe/rosuvastatin) |
Supplemental B. Prescription based comorbidity index

The methods of Häppölä et al. were followed as closely as possible, but we removed medications that were specific to prostate cancer, specific to female patients, or were not prescribed during the time period of the study\(^22\).

Comorbidity-index:

a) Reimbursed prescription of the following drugs during the last four years prior to diagnosis (each ATC-code \textbf{increases} the index by one, except that “Platelet” counts as one):

- A10AB01, A10BA02, A10BB01, A10BB12, A12BA01, B01AA03, Platelet (B01AC04, B01AC05, B01AC22, B01AC16, B01AC24 or B01AC25), B01AC06, B01AC07, C01AA05, C03CA01, C03EA01, C07AB02, C07AB03, C07AB07, C07AG02, C08CA01, C08CA05, C09AA02, C09AA03, D07AC17, H05BA01, N02AX02, N04BA02, N05AA02, N05AD01, N05BA01, N05CF01, N06AB04, N06AX03, N06DA02, N06DX01, R03BB01, N05BA04, N05AB03, N05AX08, N06DA03, R03AC02, R03BB04, R03DA04

b) Reimbursed prescription of the following drugs during the last four years prior to diagnosis (each ATC-code \textbf{decreases} the index by one):

- C10AA01, C10AA05, C10AA07, N05BA06, N05CD08, N06AA09, N06AX11, R03AC03

After constructed, age-adjusted Cox regression was used to validate the association with all-cause mortality. As a numeric variable the index was associated with all-cause mortality (HR 1.3, 95% CI 1.3-1.4) and as a categorised variable, there was a clear increase in risk of death with the increasing index:

| Index values | HR  | 95% CI    |
|--------------|-----|-----------|
| <0           | 0.9 | 0.8-1.0   |
| 0            | 1.0 | Ref       |
| 1-4          | 1.8 | 1.7-2.0   |
| 5+           | 5.3 | 4.4-6.3   |
Supplemental C. Androgen deprivation treatments used in this study along with recommended duration for a single prescription used to determine total duration.

| Drug name, route, dosage                 | Frequency | Percent (%) | Recommended duration in one prescription |
|------------------------------------------|-----------|-------------|------------------------------------------|
| Eligard 2care4 inj subst 45mg            | 46        | 0.06        | 6 months                                |
| Eligard inj subst 7.5mg                  | 49        | 0.07        | 1 month                                 |
| Eligard inj subst 22.5mg                 | 6069      | 8.17        | 3 months                                |
| Eligard inj subst 45mg                   | 790       | 1.06        | 6 months                                |
| Enantan DepDu injsu 3.75mg sp            | 8         | 0.01        | 1 month                                 |
| Enantan DepDu injsu 11.25mg sp           | 461       | 0.62        | 3 months                                |
| Enantan DepDu injsu 30mg spr             | 63        | 0.08        | 6 months                                |
| Enantan DepotSet injsu 3.75mg            | 8         | 0.01        | 1 month                                 |
| Enantan DepotSet injsu 11.25mg           | 2751      | 3.70        | 3 months                                |
| Enantan DepotSet injsu 30mg              | 565       | 0.76        | 6 months                                |
| Firmagon inj subst 80mg                  | 6354      | 8.55        | 1 month                                 |
| Firmagon inj subst 120mg                 | 627       | 0.84        | 1 month                                 |
| Leuprolelin aur injsu 11.25mg            | 46        | 0.06        | 3 months                                |
| Leuprolelin san impl 5mg/spr             | 26        | 0.03        | 3 months                                |
| Procren Depot inj subs 3.75mg            | 26        | 0.03        | 1 month                                 |
| Procren Depot inj subs 11.25mg           | 3026      | 4.07        | 3 months                                |
| Procren Depot inj subs 30mg              | 100       | 0.13        | 6 months                                |
| Vantas implantat 50mg                    | 17        | 0.02        | 12 months - very rare                   |
| Zoladex abacus impl 3.6mg/spr            | 4         | 0.01        | 1 month                                 |
| Zoladex farm implan 10.8mg/spr           | 5399      | 7.27        | 3 months                                |
| Zoladex implantat 3.6mg/spr              | 688       | 0.93        | 1 month                                 |
| Zoladex implantat 10.8mg/spr             | 46048     | 61.98       | 3 months                                |
| Zoladex orif implan 10.8mg/spr           | 1044      | 1.41        | 3 months                                |
| Zoladex orif implantat 3.6mg             | 74        | 0.10        | 1 month                                 |
| **Total**                                | **74289** |             |                                          |