**Drugs for metabolic conditions and prostate cancer death in men on GnRH agonists**

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**Abstract**

**Background**: It is unclear whether metabolic syndrome and its related drugs is affecting treatment response in men with prostate cancer (PCa) on Gonadotropin releasing Hormone (GnRH) agonists. We aimed to evaluate whether drugs for metabolic conditions influence PCa-specific mortality in men starting GnRH agonists.

**Methods:** We selected all men receiving GnRH agonists as primary treatment in PCBaSe Sweden (n=9,267). Use of drugs for metabolic conditions (i.e. anti-diabetes, anti-dyslipidaemia, and anti-hypertension) in relation to all cause, cardiovascular disease (CVD), and PCa-specific death was studied using multivariate Cox proportional hazard and Fine and Gray competing regression models.

**Results:** 6,322 (68%) men used at least one drug for a metabolic condition at GnRH agonist initiation: 46% on antihypertensive drugs only, 32% on drugs for dyslipidaemia and hypertension and about 10% on drugs for more than two metabolic conditions. Cox models indicated a weak increased risk of PCa death in men who are on drugs for hypertension only (HR: 1.12 (95%CI: 1.03-1.23)) or drugs for hyperglycaemia (HR: 1.19 (95%CI: 1.06-1.35)) at GnRH agonist initiation. However, upon taking into account competing risk from CVD death, none of the drugs for metabolic conditions were associated with an increased risk of PCa death.

**Conclusion**: We did not find evidence for a better or worse response to GnRH agonists in men with PCa who were also on drugs for hypertension, dyslipidaemia, or hyperglycaemia.

**Introduction**

A recent meta-analysis estimated that the risk of prostate cancer (PCa) is 1.54 times (95%CI:1.23-1.94) higher for those with metabolic syndrome (MetS), as compared to those without MetS (1). Recent studies also suggest that the presence of MetS or some of its features is associated with higher grade disease in men with PCa and can lead to more rapid progression (2, 3). In contrast, drugs that treat components of MetS (e.g. metformin for diabetes or statins for dyslipidemia) have also been associated with a reduced risk and progression of PCa (4-7). However, the underlying biological mechanisms for these observations have not been fully elucidated (8) .

Gonadotropin-releasing hormone (GnRH) agonists are associated with an increased risk of type 2 diabetes as well as other components of the MetS in men with PCa who are treated with androgen deprivation therapy (ADT) (9). Moreover, one recent study found that that having MetS may shorten time to castrate resistant PCa and overall survival (3), whereas another study did not find any statistically significant associations between baseline MetS and PCa death (10).

Given this complex interaction between MetS, its related drugs, and PCa progression, the current study aimed to evaluate how use of drugs for metabolic conditions (below referred to as “metabolic drugs”) at time of GnRH agonist initiation may affect response to treatment by studying time to PCa death.

**Methods**

***Study population***

We selected all men with PCa who received primary GnRH agonists between 2007 and 2013 (n=9,267), as registered in Prostate Cancer data Base Sweden (PCBaSe) Traject – which is described in detail elsewhere (11, 12). Briefly, PCBaSe was created by linking the Swedish National Prostate Cancer Register (NPCR) with a number of other population-based registers using the Swedish personal identity number for record linkage. The Research Ethics Board at Umea University approved this study (12).

Based on the underlying causes of death registered in the Cause of Death Register, the following main outcomes were defined for this study: death from PCa (International Classification of Diseases [ICD]-10:C61), death from cardiovascular disease (CVD) (ICD-10: I10 to I99), as well as other deaths (remaining ICD 10 codes), and overall mortality (13).

The main exposure variables for this study were newly filled prescriptions, prescribed prior to GnRH agonist initiation, for treatment of diabetes (metformin, sulphonylurea, insulin), dyslipidaemia (statins), hypertension (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, or thiazide and thiazide-like diuretics), or anti-obesity agents in the Prescribed Drug Register. As only 20 men received anti-obesity agents, exposure to these drugs was not considered as part of the analysis a priori. As many men often take drugs for more than one of the metabolic conditions listed above, we looked at each metabolic drug group individually as well as the most common combinations: dyslipidaemia only (n=241), hyperglycaemia only (n=67 – 38 on insulin and 29 on metformin or sulphonylurea), hypertension only (n=2,933), dyslipidaemia and hyperglycaemia (n=41), dyslipidaemia and hypertension (n=1,996), hyperglycaemia and hypertension (n=333), and treated for more than two metabolic conditions (n=651). The analyses focused on the four most common groups of drugs: hypertension only, hypertension and dyslipidaemia, any hyperglycaemia, dyslipidaemia only (Figure 1).

The following information on potential covariates was also obtained: age, tumour grade and stage and educational level. PCa risk category was defined according to a modification of the National Comprehensive Cancer Network Guideline (14): low risk: T1–2, Gleason score 2–6 and PSA < 10 ng/mL; intermediate risk: T1–2, Gleason score 7 and/or PSA 10– 20 ng/mL; high risk: T3 and/or Gleason score 8–10 and/or PSA 20–50 ng/mL; regionally metastatic/locally advanced: T4 and/or N1 and/or PSA 50–100 ng/mL in the absence of distant metastases (M0 or MX); and distant metastases: M1 and/or PSA > 100 ng/mL. In addition, we collected information on history of CVD, defined by any CVD hospital admission (ICD-10 codes: I20-I25, I50, I60-I69, I70-I79) as primary diagnoses in the National Patient Register. Comorbidities were also measured using the Charlson comorbidity index (CCI), which assigns weights to a number of medical conditions. Each condition was assigned a score of 1, 2, 3 or 6, and the final CCI was the sum of these scores (15). Individuals were grouped into CCI categories for final scores of 0, 1, 2 or 3+. History of CVD and CCI were included for descriptive purposes, as careful assessment of the causal pathway did not indicate that these covariates need to be included in multivariate models (Figure 2) (16). The use of a directed acyclic graph (DAG) helps represent causal relations among variables to determine which ones need to be controlled for in the estimation of causal effects (17).

***Statistical analysis***

We conducted univariate and multivariate Cox proportional hazard regression models to assess the association between individual metabolic drugs as well as common combinations (Figure 2) and death from PCa, CVD and overall mortality. Multivariate models were adjusted for age, education level, disease stage and civil status. Adjustment for age were done using natural cubic splines with four degrees of freedom. To consider competing risks, we repeated the analyses using Fine and Grays competing risk regression (18). As all men were on primary GnRH agonists and disease stage was taken into account, all analyses are based on the intention to treat assumption – i.e. all men stayed on ADT, which was the standard drug for advanced PCa in Sweden at the time of data collection.

To further illustrate the associations between metabolic drugs and causes of death, stacked cumulative incidence proportion functions for all-cause, CVD, and PCa-specific death were displayed by categories of metabolic drug use.

Data management was performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and data analysis was conducted with R version 2.13.2 (R Foundation for Statistical Computing, Wien, Austria).

**Results**

A total of 6,322 (68%) men used at least one drug for a metabolic condition at the time they started GnRH agonists. The majority of these men were on antihypertensive drugs only (46%), followed by men on drugs for dyslipidemia and hypertension (32%). About 10% of men were on drugs for more than two metabolic conditions. Table 1 shows the baseline characteristics of all men included in the study based on the type of metabolic drugs they were taking at time of GnRH agonist initiation.

Multivariate Cox proportional hazards regression adjusted for age, education, and prostate cancer risk category showed that use of most metabolic drugs were associated with an increased risk of CVD death and hence also overall death (Table 2). For instance, those men on anti-hypertensive drugs only were 1.87 times more likely to die of CVD than men not taking any metabolic drugs (95%CI: 1.56-2.24) and this increased to 2.46 times if these men were also taking drugs for dyslipidaemia (95%CI: 2.03-2.98). With respect to PCa death, a small increased risk was observed for those on drugs for hypertension only or any hyperglycemia (HR: 1.12 (95%CI: 1.03-1.23) and 1.19 (95%CI: 1.06-1.35), respectively).

Given the strong association with death from CVD, competing risk regression showed little impact on the association between metabolic drugs and death from CVD (Table 2). However, the associations observed for PCa death disappeared and even became inverse for those on drugs for hypertension and dyslipidaemia, though not statistically significant (HR: 0.92 (95%CI: 0.83-1.02)).

Figure 3 illustrates these findings using stacked cumulative incidence proportions. The largest proportion of CVD-deaths (red) can be observed amongst those on metabolic drugs, with the biggest proportion for those who are on drugs for both hypertension and statins. The proportion of PCa-deaths (blue) was fairly similar across all the groups studied.

**Discussion**

Traditional Cox proportional hazards model indicated a weak increased risk of PCa death in men who are on drugs for hypertension or hyperglycaemia at the time they start GnRH agonists. However, upon taking into account competing risk from CVD death none of the drugs for metabolic conditions were associated with an increased risk of PCa death – and a trend towards an inverse association was observed for those who were on drugs for both hypertension and dyslipidaemia.

To our knowledge, few studies have investigated the effect of drugs for metabolic conditions in relation to response to treatment for men on GnRH agonists (19). Most studies to date have explored the effect of single drugs, predominantly metformin, statins, or beta-blockers, in relation to PCa death (5, 20-27). Moreover, these existing observational studies have found contradicting results – and they did not specifically study those men on GnRH agonists, a drug that in itself is also associated with an increased risk of metabolic conditions (9). Some reasons for these contrasting findings have been summarised previously (7), but by investigating several drugs for metabolic conditions in a specifically defined group of men with PCa, the current study aims to improve our understanding of possible metabolic drug effects in the context of PCa progression.

Thus, to our knowledge this is the first study to specifically investigate the overall use of drugs for metabolic conditions and PCa death in men on GnRH agonists. Our results are in line with a small study (n=273) investigating the effect of metabolic syndrome (without looking at the related drugs) on PCa death in men on ADT using data from the Health Professionals Follow-up Study and the Veteran’s Administration (10). The authors concluded that there was no association of PCa-specific death and metabolic syndrome, but the latter was associated with an increased risk of death from all causes. However, there was a weak positive association between hypertension only and PCa-specific death (HR: 1.59 (95%CI: 0.89-2.84)). Even though the exposure assessment in this study is different from what we have done here, none of the studies support a strong association between metabolic aberrations and PCa-specific death in men on GnRH agonists. The latter is relevant from a clinical point of view and could inform future studies looking into how development and treatment of metabolic syndrome following initiation of GnRH agonists (as an adverse event) may affect response to hormonal treatment or PCa progression.

A major strength of our study is the use of comprehensive data in PCBaSe Sweden, a large nationwide population-based register from which information on complete follow-up, PCa treatment, PCa risk category, comorbidities and socio-economic status can be retrieved. As with other currently published studies, our follow-up was rather short and a follow-up study might provide more power to investigate risk of PCa death in a competing risk setting (e.g. death from CVD (28)). Another limitation of the current study is the lack of direct measures of metabolic syndrome (e.g. serum glucose and cholesterol levels (7)) and information on ethnicity or lifestyle factors. However, the latter could be approximated by the CCI – which was not needed as a covariate in the statistical models (Figure 2).

**Conclusion**

Despite the suggested complex interaction between metabolic syndrome, metabolic drugs, and PCa progression, the current study did not find any evidence for a better or worse response to GnRH agonists in men who were also on drugs for hypertension, dyslipidaemia, or hyperglycaemia. These findings suggest that treatment of metabolic syndrome is important in men on GnRH agonists, but not a contraindication for their PCa treatment.

**Figures**

**Figure 1.** Combinations of metabolic drugs studied.

No metabolic drugs

Drugs for hyperglycaemia

(with or without drugs for hypertension or dyslipidaemia)

Drugs for dyslipidemia only

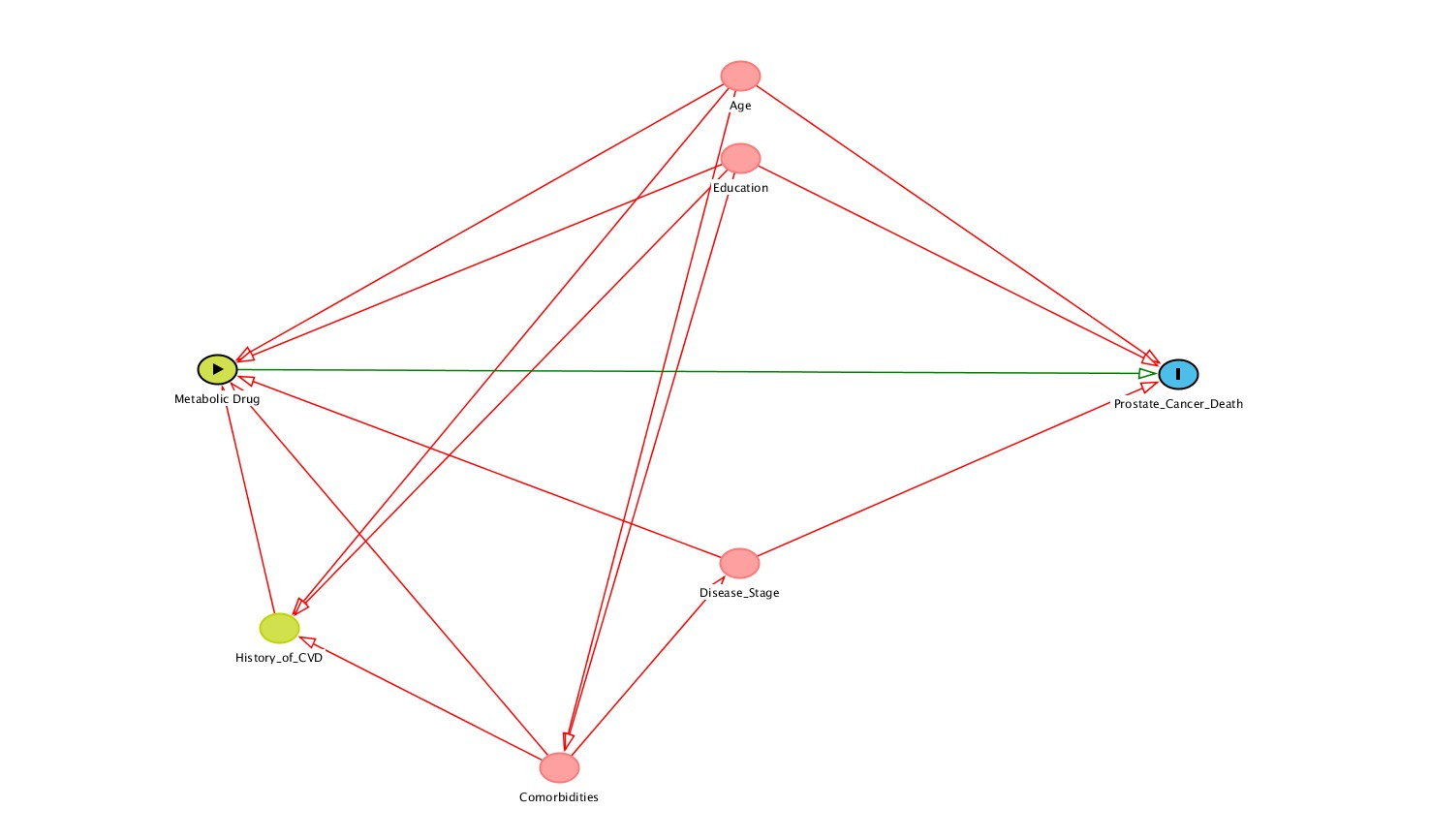
Drugs for hypertension only only

Drugs for dyslipidaemia and hypertension

(no hyperglycaemia drug)

**Figure 2.** Directed acyclic graph for the association between metabolic drugs and prostate cancer death in men who start on GnRH agonists.

*(CVD=Cardiovascular Disease)*

****

**Figure 3.** Stacked cumulative incidence of PCa-specific, CVD, and other deaths based on exposure to metabolic drugs.

*(CVD= Cardiovascular Disease; DM=Diabetes Mellitus)*

Only Hypertension

0

0.2

0.4

0.6

0.8

0

0.2

0.4

0.6

0.8

0

0.2

0.4

0.6

0.8

0

0.2

0.4

0.6

0.8

0

0.2

0.4

0.6

0.8

Proportion

Proportion

3002

2672

2224

1619

1140

746

398

174

2936

2512

2010

1442

983

626

347

137

2000

1761

1438

1052

702

403

204

76

1088

932

742

521

323

198

104

35

241

218

176

141

97

67

36

15

DM drugs

Hypertension

and Statins

No Drug

Only Statins

Prostate cancer death

CVD- death

Other death

0

1

2

3

4

5

6

7

Years

0

1

2

3

4

5

6

7

Years

No at risk

No at risk

No at risk

**Tables**

**Table 1.** Baseline characteristics according to use of drugs for metabolic conditions at time of GnRH agonist initiation.

*(SU=sulphonylurea; CCI=Charlson Comorbidity Index)*

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All men**  **(n=9267)** | | **Only**  **Dyslipidaemia**  **(n=241)** | | **Only**  **Hyperglycaemia**  **(n=67)** | | **Only Hyperglycaemia with insulin**  **(n=38)** | | **Only**  **Hyperglycaemia with Metformin/SU**  **(n=29)** | | **Only**  **Hypertension**  **(n=2,933)** | | **Dyslipidaemia**  **and Hyperglycaemia**  **(n=41)** | | **Dyslipidaemia**  **and Hypertension**  **(n=1,996)** | | **Hyperglycaemia and Hypertension**  **(n=333)** | | **≥2 Metabolic conditions(n=651)** | |
| **Age, n (%)** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <65 | 896 | (9.7) | 15 | (6.2) | 7 | (10.4) | 2 | (5.3) | 5 | (17.2) | 175 | (6.0) | 5 | (12.2) | 112 | (5.6) | 19 | (5.7) | 40 | (6.1) |
| 65-74 | 2599 | (28.0) | 76 | (31.5) | 28 | (41.8) | 18 | (47.4) | 10 | (34.5) | 651 | (22.2) | 12 | (29.3) | 548 | (27.5) | 76 | (22.8) | 217 | (33.3) |
| 75-84 | 4209 | (45.4) | 133 | (55.2) | 29 | (43.3) | 17 | (44.7) | 12 | (41.4) | 1368 | (46.6) | 21 | (51.2) | 1068 | (53.5) | 173 | (52.0) | 319 | (49.0) |
| 85+ | 1563 | (16.9) | 17 | (7.1) | 3 | (4.5) | 1 | (2.6) | 2 | (6.9) | 739 | (25.2) | 3 | (7.3) | 268 | (13.4) | 65 | (19.5) | 75 | (11.5) |
| **CCI, n (%)** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 0 | 5755 | (62.1) | 150 | (62.2) | 33 | (49.3) | 24 | (63.2) | 9 | (31.0) | 1857 | (63.3) | 17 | (41.5) | 827 | (41.4) | 124 | (37.2) | 179 | (27.5) |
| 1 | 1683 | (18.2) | 55 | (22.8) | 18 | (26.9) | 8 | (21.1) | 10 | (34.5) | 545 | (18.6) | 12 | (29.3) | 607 | (30.4) | 77 | (23.1) | 151 | (23.2) |
| 2 | 983 | (10.6) | 25 | (10.4) | 10 | (14.9) | 5 | (13.2) | 5 | (17.2) | 313 | (10.7) | 6 | (14.6) | 278 | (13.9) | 57 | (17.1) | 133 | (20.4) |
| 3+ | 846 | (9.1) | 11 | (4.6) | 6 | (9.0) | 1 | (2.6) | 5 | (17.2) | 218 | (7.4) | 6 | (14.6) | 284 | (14.2) | 75 | (22.5) | 188 | (28.9) |
| **Educational level, n (%)** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| High | 1411 | (15.2) | 52 | (21.6) | 9 | (13.4) | 4 | (10.5) | 5 | (17.2) | 425 | (14.5) | 9 | (22.0) | 283 | (14.2) | 30 | (9.0) | 78 | (12.0) |
| Low | 4551 | (49.1) | 104 | (43.2) | 34 | (50.7) | 22 | (57.9) | 12 | (41.4) | 1507 | (51.4) | 21 | (51.2) | 999 | (50.1) | 194 | (58.3) | 333 | (51.2) |
| Middle | 3172 | (34.2) | 81 | (33.6) | 24 | (35.8) | 12 | (31.6) | 12 | (41.4) | 960 | (32.7) | 9 | (22.0) | 699 | (35.0) | 104 | (31.2) | 229 | (35.2) |
| Missing | 133 | (1.4) | 4 | (1.7) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 41 | (1.4) | 2 | (4.9) | 15 | (0.8) | 5 | (1.5) | 11 | (1.7) |
| **Civil status, n (%)** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Married | 5664 | (61.1) | 157 | (65.1) | 33 | (49.3) | 17 | (44.7) | 16 | (55.2) | 1776 | (60.6) | 28 | (68.3) | 1284 | (64.3) | 183 | (55.0) | 411 | (63.1) |
| Not married | 3603 | (38.9) | 84 | (34.9) | 34 | (50.7) | 21 | (55.3) | 13 | (44.8) | 1157 | (39.4) | 13 | (31.7) | 712 | (35.7) | 150 | (45.0) | 240 | (36.9) |
| **Risk category** **, n (%)** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Low risk | 98 | (1.1) | 6 | (2.5) | 1 | (1.5) | 1 | (2.6) | 0 | (0.0) | 33 | (1.1) | 2 | (4.9) | 26 | (1.3) | 2 | (0.6) | 9 | (1.4) |
| Intermediate risk | 778 | (8.4) | 33 | (13.7) | 5 | (7.5) | 4 | (10.5) | 1 | (3.4) | 263 | (9.0) | 1 | (2.4) | 200 | (10.0) | 29 | (8.7) | 68 | (10.4) |
| High risk | 2976 | (32.1) | 80 | (33.2) | 22 | (32.8) | 14 | (36.8) | 8 | (27.6) | 1018 | (34.7) | 17 | (41.5) | 708 | (35.5) | 122 | (36.6) | 223 | (34.3) |
| Regionally metastatic | 1438 | (15.5) | 32 | (13.3) | 14 | (20.9) | 6 | (15.8) | 8 | (27.6) | 442 | (15.1) | 4 | (9.8) | 309 | (15.5) | 63 | (18.9) | 91 | (14.0) |
| Distant metastases | 3977 | (42.9) | 90 | (37.3) | 25 | (37.3) | 13 | (34.2) | 12 | (41.4) | 1177 | (40.1) | 17 | (41.5) | 753 | (37.7) | 117 | (35.1) | 260 | (39.9) |

**Table 2.** Cox proportional Hazard Ratios and Competing risks regression Ratios with 95% confidence intervals (CI) for the associations between drugs for metabolic conditions and PCa death, other deaths, CVD deaths and overall death.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Univariate**  **Cox** | | **Multivariate Cox\*** | | | **Competing risk regression\*** | | | |
|  | **No of events** | **HR** | **95% CI** | **HR** | **95% CI** | | **HR** | | **95% CI** | |
| **PCa death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 1117 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 986 | 0.97 | 0.89 - 1.06 | **1.12** | **1.03-1.23** | | 1.03 | | 0.94-1.13 | |
| Hypertension+ Dyslipidaemia | 578 | 0.81 | 0.74 - 0.90 | 1.02 | 0.93-1.14 | | 0.92 | | 0.83-1.02 | |
| Hyperglycaemia | 336 | 0.93 | 0.82 - 1.05 | **1.19** | **1.06-1.35** | | 1.00 | | 0.89-1.14 | |
| Only Statins | 73 | **0.78** | **0.62 - 0.99** | 1.06 | 0.83-1.34 | | 1.01 | | 0.80-1.29 | |
| **Other death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 294 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 394 | **1.48** | **1.27 - 1.72** | **1.23** | **1.05 - 1.43** | | **1.12** | | **0.96 - 1.31** | |
| Hypertension+ Dyslipidaemia | 238 | **1.29** | **1.09 - 1.53** | **1.20** | **1.01 - 1.43** | | **1.07** | | **0.90 - 1.27** | |
| Hyperglycaemia | 185 | **1.97** | **1.64 - 2.37** | **1.85** | **1.53 - 2.22** | | **1.59** | | **1.32 - 1.91** | |
| Only Statins | 31 | 1.26 | 0.87 - 1.82 | 1.23 | 0.85 - 1.79 | | 1.19 | | 0.83 - 1.72 | |
| **CVD Death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 174 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 385 | **2.45** | **2.05 - 2.93** | **1.87** | **1.56 - 2.24** | | **1.71** | | **1.43 - 2.05** | |
| Hypertension+ Dyslipidaemia | 283 | **2.59** | **2.14 - 3.13** | **2.46** | **2.03 - 2.98** | | **2.26** | | **1.87 - 2.74** | |
| Hyperglycaemia | 149 | **2.69** | **2.16 - 3.35** | **2.53** | **2.03 - 3.16** | | **2.15** | | **1.72 - 2.69** | |
| Only Statins | 15 | 1.03 | 0.61 - 1.74 | 1.06 | 0.63 - 1.80 | | 1.01 | | 0.59 - 1.71 | |
| **Overall Death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 1585 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 1765 | **1.23** | **1.15 - 1.31** | **1.22** | **1.14-1.31** | | N/A | | N/A | |
| Hypertension+ Dyslipidaemia | 1099 | **1.10** | **1.02 - 1.18** | **1.23** | **1.14-1.33** | | N/A | | N/A | |
| Hyperglycaemia | 670 | **1.32** | **1.20 - 1.44** | **1.49** | **1.36-1.63** | | N/A | | N/A | |
| Only Statins | 119 | 0.90 | 0.74 - 1.08 | 1.08 | 0.89-1.30 | | N/A | | N/A | |
| \*Adjusted for education, PCa risk category, civil status, and age. | | | | | |  | |  | |  | |  |

**Table 3.** Cox proportional Hazard Ratios and Competing risks regression Ratios with 95% confidence intervals (CI) for the associations between drugs for metabolic conditions and PCa death, other deaths, CVD deaths and overall death – stratified by metastatic status.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Univariate**  **Cox** | | **Multivariate Cox\*** | | | **Competing risk regression\*** | | | |
| **METASTATIC DISEASE ONLY** | | | | | | | | | | |
|  | **No of events** | **HR** | **95% CI** | **HR** | **95% CI** | | **HR** | | **95% CI** | |
| **PCa death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 820 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 614 | 1.12 | 1.01 - 1.24 | 1.07 | 0.96 - 1.2 | | 0.99 | | 0.88 - 1.1 | |
| Hypertension+ Dyslipidaemia | 361 | 0.98 | 0.87 - 1.11 | 1.01 | 0.89 - 1.14 | | 0.91 | | 0.81 - 1.04 | |
| Hyperglycaemia | 204 | 1.13 | 0.97 - 1.32 | 1.16 | 0.99 - 1.36 | | 0.97 | | 0.83 - 1.14 | |
| Only Statins | 48 | 1.07 | 0.8 - 1.43 | 1.11 | 0.83 - 1.49 | | 1.05 | | 0.78 - 1.42 | |
| **Other death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 105 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 124 | **1.78** | **1.37 - 2.30** | **1.41** | **1.08 - 1.84** | | 1.30 | | 0.99 - 1.70 | |
| Hypertension+ Dyslipidaemia | 69 | **1.48** | **1.09 – 2.00** | 1.34 | 0.98 - 1.82 | | 1.22 | | 0.90 - 1.67 | |
| Hyperglycaemia | 50 | **2.20** | **1.57 - 3.09** | **1.95** | **1.39 - 2.75** | | **1.63** | | **1.16 - 2.30** | |
| Only Statins | 0 | 1.40 | 0.68 - 2.86 | 1.28 | 0.62 - 2.63 | | 1.18 | | 0.58 - 2.43 | |
| **CVD Death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 59 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 118 | **2.99** | **2.19 - 4.09** | **2.06** | **1.50 - 2.83** | | **1.90** | | **1.38 - 2.61** | |
| Hypertension+ Dyslipidaemia | 78 | **2.97** | **2.12 - 4.16** | **2.58** | **1.83 - 3.64** | | **2.38** | | **1.69 - 3.35** | |
| Hyperglycaemia | 50 | **3.90** | **2.67 - 5.68** | **3.31** | **2.26 - 4.85** | | **2.77** | | **1.90 - 4.06** | |
| Only Statins | 6 | 1.86 | 0.80 - 4.32 | 1.64 | 0.71 - 3.81 | | 1.57 | | 0.69 - 3.54 | |
| **Overall Death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 984 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 856 | **1.30** | **1.19 - 1.43** | **1.18** | **1.07 - 1.29** | | N/A | | N/A | |
| Hypertension+ Dyslipidaemia | 508 | **1.15** | **1.04 - 1.28** | **1.14** | **1.03 - 1.28** | | N/A | | N/A | |
| Hyperglycaemia | 304 | **1.41** | **1.24 - 1.61** | **1.40** | **1.23 - 1.59** | | N/A | | N/A | |
| Only Statins | 62 | 1.15 | 0.89 - 1.49 | 1.16 | 0.90 - 1.50 | | N/A | | N/A | |
| **NON-METASTATIC DISEASE ONLY** | | | | | | | | |  | |
| **PCa death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 297 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 372 | **1.16** | **1.00 - 1.36** | **1.22** | **1.05 - 1.43** | | 1.14 | | 0.97 - 1.32 | |
| Hypertension+ Dyslipidaemia | 217 | 0.96 | 0.81 - 1.15 | 1.08 | 0.9 - 1.29 | | 0.96 | | 0.81 - 1.14 | |
| Hyperglycaemia | 132 | 1.14 | 0.93 - 1.40 | 1.26 | 1.03 - 1.55 | | 1.09 | | 0.89 - 1.34 | |
| Only Statins | 25 | 0.79 | 0.53 - 1.20 | 0.96 | 0.64 - 1.44 | | 0.95 | | 0.64 - 1.42 | |
| **Other death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 189 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 270 | **1.32** | **1.10 - 1.59** | 1.15 | 0.95 - 1.38 | | 1.04 | | 0.86 - 1.26 | |
| Hypertension+ Dyslipidaemia | 169 | 1.17 | 0.95 - 1.44 | 1.14 | 0.92 - 1.40 | | 1.00 | | 0.81 - 1.23 | |
| Hyperglycaemia | 135 | **1.81** | **1.45 - 2.26** | **1.78** | **1.43 - 2.22** | | **1.55** | | **1.25 - 1.94** | |
| Only Statins | 23 | 1.15 | 0.74 - 1.77 | 1.20 | 0.77 - 1.85 | | 1.17 | | 0.76 - 1.79 | |
| **CVD Death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 115 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 267 | **2.15** | **1.73 - 2.68** | **1.77** | **1.42 - 2.21** | | **1.63** | | **1.30 - 2.03** | |
| Hypertension+ Dyslipidaemia | 205 | **2.33** | **1.86 - 2.93** | **2.37** | **1.88 - 2.98** | | **2.19** | | **1.73 - 2.76** | |
| Hyperglycaemia | 99 | **2.19** | **1.67 - 2.86** | **2.22** | **1.69 - 2.91** | | **1.90** | | **1.45 - 2.50** | |
| Only Statins | 9 | 0.74 | 0.38 - 1.46 | 0.84 | 0.43 - 1.67 | | 0.79 | | 0.40 - 1.57 | |
| **Other death** |  |  |  |  |  | |  | |  | |
| No metabolic drugs | 601 | 1.00 | Ref | 1.00 | Ref | | 1.00 | | Ref | |
| Only Hypertension | 909 | **1.40** | **1.26 - 1.55** | **1.30** | **1.17 - 1.44** | | N/A | | N/A | |
| Hypertension+ Dyslipidaemia | 591 | **1.29** | **1.15 - 1.45** | **1.35** | **1.20 - 1.51** | | N/A | | N/A | |
| Hyperglycaemia | 366 | **1.55** | **1.36 - 1.77** | **1.62** | **1.42 - 1.84** | | N/A | | N/A | |
| Only Statins | 57 | 0.90 | 0.68 - 1.18 | 1.02 | 0.78 - 1.34 | | N/A | | N/A | |
| \*Adjusted for education, PCa risk category, civil status, and age. | | | | | |  | |  | |  | |  |

**References**

1. Hsing AW, Sakoda LC, Chua S, Jr. Obesity, metabolic syndrome, and prostate cancer. The American journal of clinical nutrition. 2007;86(3):s843-57.

2. Neuhouser ML, Till C, Kristal A, Goodman P, Hoque A, Platz EA, et al. Finasteride modifies the relation between serum C-peptide and prostate cancer risk: results from the Prostate Cancer Prevention Trial. Cancer prevention research. 2010;3(3):279-89.

3. Flanagan J, Gray PK, Hahn N, Hayes J, Myers LJ, Carney-Doebbeling C, et al. Presence of the metabolic syndrome is associated with shorter time to castration-resistant prostate cancer. Ann Oncol. 2011;22(4):801-7.

4. Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: results from a population-based case-control study. Cancer causes & control : CCC. 2009;20(9):1617-22.

5. Margel D, Urbach D, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, et al. Association between metformin use and risk of prostate cancer and its grade. J Natl Cancer Inst. 2013;105(15):1123-31.

6. Gandini S, Puntoni M, Heckman-Stoddard BM, Dunn BK, Ford L, DeCensi A, et al. Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. Cancer prevention research. 2014;7(9):867-85.

7. Melvin JC, Garmo H, Daniel R, Shanmugalingam T, Stattin P, Haggstrom C, et al. An investigation into the relationship between statins and cancer using population-based data. BJU Int. 2015;116(5):681-3.

8. Penney KL, Stampfer MJ. The time is ripe for a randomized trial of metformin in clinically localized prostate cancer. J Clin Oncol. 2013;31(25):3054-5.

9. Bosco C, Crawley D, Adolfsson J, Rudman S, Van Hemelrijck M. Quantifying the evidence for the risk of metabolic syndrome and its components following androgen deprivation therapy for prostate cancer: a meta-analysis. PLoS One. 2015;10(3):e0117344.

10. Rudman SM, Gray KP, Batista JL, Pitt MJ, Giovannucci EL, Harper PG, et al. Risk of prostate cancer-specific death in men with baseline metabolic aberrations treated with androgen deprivation therapy for biochemical recurrence. BJU Int. 2016;118(6):919-26.

11. Van Hemelrijck M, Wigertz A, Sandin F, Garmo H, Hellstrom K, Fransson P, et al. Cohort Profile: the National Prostate Cancer Register of Sweden and Prostate Cancer data Base Sweden 2.0. Int J Epidemiol. 2013;42(4):956-67.

12. Van Hemelrijck M, Garmo H, Wigertz A, Nilsson P, Stattin P. Cohort Profile Update: The National Prostate Cancer Register of Sweden and Prostate Cancer data Base-a refined prostate cancer trajectory. Int J Epidemiol. 2016;45(1):73-82.

13. Van Hemelrijck M, Adolfsson J, Garmo H, Bill-Axelson A, Bratt O, Ingelsson E, et al. Risk of thromboembolic diseases in men with prostate cancer: results from the population-based PCBaSe Sweden. Lancet Oncol. 2010;11(5):450-8.

14. Mohler J, Bahnson RR, Boston B, Busby JE, D'Amico A, Eastham JA, et al. NCCN clinical practice guidelines in oncology: prostate cancer. J Natl Compr Canc Netw. 2010;8(2):162-200.

15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

16. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology. 2011;22(5):745.

17. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37-48.

18. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American statistical association. 1999;94(446):496-509.

19. Grytli HH, Fagerland MW, Fossa SD, Tasken KA, Haheim LL. Use of beta-blockers is associated with prostate cancer-specific survival in prostate cancer patients on androgen deprivation therapy. Prostate. 2013;73(3):250-60.

20. Bensimon L, Yin H, Suissa S, Pollak MN, Azoulay L. The use of metformin in patients with prostate cancer and the risk of death. Cancer Epidemiol Biomarkers Prev. 2014;23(10):2111-8.

21. Chan JM, Kenfield SA, Paciorek A, Platz EA, Giovannucci EL, Stampfer MJ. Postdiagnostic Statin Use and the Risk of Lethal Prostate Cancer in the Health Professionals Follow-up Study. Cancer Epidemiol Biomarkers Prev. 2015;24(10):1638-40.

22. Chao C, Jacobsen SJ, Xu L, Wallner LP, Porter KR, Williams SG. Use of statins and prostate cancer recurrence among patients treated with radical prostatectomy. BJU Int. 2013;111(6):954-62.

23. Margel D, Urbach DR, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. J Clin Oncol. 2013;31(25):3069-75.

24. Yu O, Eberg M, Benayoun S, Aprikian A, Batist G, Suissa S, et al. Use of statins and the risk of death in patients with prostate cancer. J Clin Oncol. 2014;32(1):5-11.

25. Cardwell CR, Coleman HG, Murray LJ, O'Sullivan JM, Powe DG. Beta-blocker usage and prostate cancer survival: a nested case-control study in the UK Clinical Practice Research Datalink cohort. Cancer Epidemiol. 2014;38(3):279-85.

26. Grytli HH, Fagerland MW, Fossa SD, Tasken KA. Association between use of beta-blockers and prostate cancer-specific survival: a cohort study of 3561 prostate cancer patients with high-risk or metastatic disease. Eur Urol. 2014;65(3):635-41.

27. Poch MA, Mehedint D, Green DJ, Payne-Ondracek R, Fontham ET, Bensen JT, et al. The association between calcium channel blocker use and prostate cancer outcome. Prostate. 2013;73(8):865-72.

28. O'Farrell S, Garmo H, Holmberg L, Adolfsson J, Stattin P, Van Hemelrijck M. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. J Clin Oncol. 2015;33(11):1243-51.