# Statin Drugs Effect on Life Expectancy of Patients with Advanced Prostate Cancer that Received Primary Castration Treatment

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**University of Iceland**
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HÁSKÓLI ÍSLANDS

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## Abstract

**Background:** Statins are cholesterol-lowering drugs proven to prevent cardiovascular disease. They are among the most prescribed drugs worldwide. Conflicting evidence suggest that statins may have anticancer activities against prostate cancer. Prostate cancer is the fifth leading cause of cancer death in men worldwide. The aim of this retrospective cohort study is to examine whether statin use affects the life expectancy of men with advanced prostate cancer who had castration as a primary treatment.

**Material and methods:** The study population consists of 269 men who received castration as a primary treatment to prostate cancer in the years 2007 and 2008. These patients were collected from an existing quality database that belongs to the Urology department at Sahlgrenska University hospital in Gothenburg, Sweden. The database contains information from the Swedish cancer registry and patients' medical journals. We collected additional information from medical journals on patients' drug use and PSA nadir levels. Patients that had been taking statin drugs prior to castration were classified as statin users. The last day of follow-up was December 31$^{st}$ 2012.

**Results:** Of the 269 men 56 (20,8%) were taking statin drugs prior to castration. Statin users (56) were compared to the non-users (213). Statin use was not found to be a prognostic factor for survival when all-cause mortality was used. However statin users had statistically lower PSA at castration and also lower PSA nadir value after castration compared to non-users.

**Discussion:** In this study no significant difference was found in life expectancy between the two groups. We used all-cause mortality and that most likely affected our results. Patients taking statin drugs have more comorbidities than the non statin-users. Statin-users had lower PSA values but we cannot know whether this is a direct effect of statins on the tumors or if there are confounding factors causing this. To reach a conclusion that has to be studied further.

**Key words:** Statins; prostate cancer; castration

## Abbrevations

| | |
|---|---|
| ACE-Is | Angiotensin-converting enzyme inhibitors |
| ADT | Androgen deprivation therapy |
| ARBs | Angiotensin II receptor blockers |
| CT | Computed tomography |
| cT stage | Clinical tumor stage |
| DRE | Digital rectal examination |
| GnRH | Gonadotropin releasing hormone |
| GS | Gleason score |
| HMG-CoA | 3-hydroxy-3-methylglutaryl-coenzyme A |
| HR | Hazard ratio |
| LDL | Low density lipoprotein |
| MRI | Magnetic Resonance Imaging |
| PCa | Prostate cancer |
| PCSM | Prostate cancer specific mortality |
| PSA | Prostate specific antigen |
| TMN | Tumor metastasis nodes |
| TRUS | Transrectal ultrasound |
| TURP | Transurethral resection of the prostate |

# 1 Background

## 1.1 The prostate gland

The prostate is one of the male accessory sex glands. The prostate surrounds the urethra at the neck of the bladder and is the size of a chestnut. The prostate gland is divided in three histologically different zones; central, transition and peripheral zones.

The prostate gland secretes alkaline fluid that forms approximately 60% of the ejaculate. This fluid is involved in fertility primarily by liquefying the semen after ejaculation has occurred to improve the motility of the sperm cells.

Androgens control growth and function of the gland. The testes are the largest source of most androgens but the adrenal glands play a role in androgen synthesis as well. The adrenal glands' androgen production counts for 5-10% of the overall androgen production.[1]

## 1.2 Prostate cancer

Prostate cancer (PCa) is the fifth leading cause of cancer death in males worldwide (2012).[2] It is the most common cancer in men in both Iceland and Sweden and the leading cause of cancer related deaths in Swedish men and second in Icelandic men after lung cancer. The mean incidence rate in Iceland is 91,7 per 100.000 per year (average between 2007 and 2011)[3] and 103,3 per 100.000 in Sweden (2011).[4]

As mentioned above the prostate gland is composed of three different zones, approximately 70% of all prostate cancers are located in the peripheral zone of the prostate. Cancers located in this zone can sometimes be detected with digital rectal examination (DRE) if the tumor is 0,2 ml or larger. If something unusual is detected during DRE, prostate biopsy is often necessary.[5,6]

### 1.2.1 Prostate specific antigen (PSA)

PSA is an organ-specific glycopeptide that is only produced in prostate gland cells. It is a proteolytic enzyme that dissolves coagulated semen. PSA can rise in the serum for various reasons; it is not a tumor-specific marker.[7,8] PSA can rise for example when there is infection or inflammation, injury to the prostate, benign prostatic hyperplasia or prostate cancer. PSA level of 4,0 ng/mL or lower is considered normal. PSA is currently the only serological marker routinely used in the diagnosis, staging and monitoring of treatment response or failure in prostate cancer.[9] PSA screening has increased the detection of the disease and therefore we are now detecting the disease earlier than before. Prostate cancer has been

increasing during the past years and that is most likely because of increased detection because of screening procedures[10] and also because of ageing population.[11]

#### *1.2.1.1 Screening*

Prostate cancer incidence has been increasing and many men undergo curative treatment. Prostate cancer mortality rate has started to decrease in some countries, for example in the United Kingdom and USA but in other countries the mortality rate is unaffected even though detection and treatment with curative intention is increasing. The reason for this might be increased detection of insignificant tumors and not the aggressive ones that would be beneficial to treat.[12] This has raised questions whether mass PSA screening is appropriate for PCa or if it might only increase the detection of less aggressive tumors.[13] Overdiagnosis of prostate cancer in screening has been calculated to be as high as 60%. Recent studies on PSA screening show however that to save one man from dying from prostate cancer you will make four men impotent and less than one man incontinent.[14]

### 1.2.2 Diagnosis

The diagnosis of PCa is based on histological evaluation of prostate tissue according to the Gleason score system. There are two ways to get out the prostate tissue; using transrectal ultrasound guided biopsies (TRUS) or transurethral resection of the prostate (TURP).

A transrectal ultrasound (TRUS) is an ultrasound technique used to view a man's prostate and surrounding tissues through the rectum. This technique can be used for diagnosis of nonpalpable cancer, for staging of cancer or for guidance when a prostate biopsy sample is needed.[15] When a biopsy sample is needed TRUS helps to guide the doctor, who uses a special biopsy needle, to take samples from different areas of the prostate. The biopsy samples are then evaluated histologically, under a microscope, according to the Gleason score system.[16]

Transurethral resection of the prostate (TURP) is a surgical procedure that removes portions of the prostate through the urethra. A resectoscope, which is a surgical and a visual instrument, is inserted into the urethra and samples of the prostate tissue are trimmed away and evaluated histologically. General anaesthesia or spinal anaesthesisa are used for this kind of procedure.[17,18]

### 1.2.3 Gleason grading system

The Gleason grading system is one of the most powerful prognostic factors for prostate cancer. The system was updated at consensus conference of international experts in urological

pathology in 2005 held by the International Society of Urological Pathology. The tumors were originally graded microscopically on a scale, according to morphological pattern, from 1 to 5 but the grading system was modified in 2005 to a scale of 2 to 5. The reason for this was that patterns 1 and 2 are very seldom applicable for cancer diagnosis. The grading in the clinic now goes from 2 to 5 and in biopsies from 3 to 5.[19]

In one biopsy sample you can have different grades of cancer. The most common grade is added together with the most aggressive grade and this gives you the Gleason score that ranges between 6 and 10 according to the updated Gleason score system. If only one pattern is observed the grade is doubled. The higher the Gleason score the worse the prognosis.[20] Gleason scores 2-4 are considered well-differentiated, 5-7 are moderately-differentiated and 8-10 is poorly-differentiated (see figure 1).

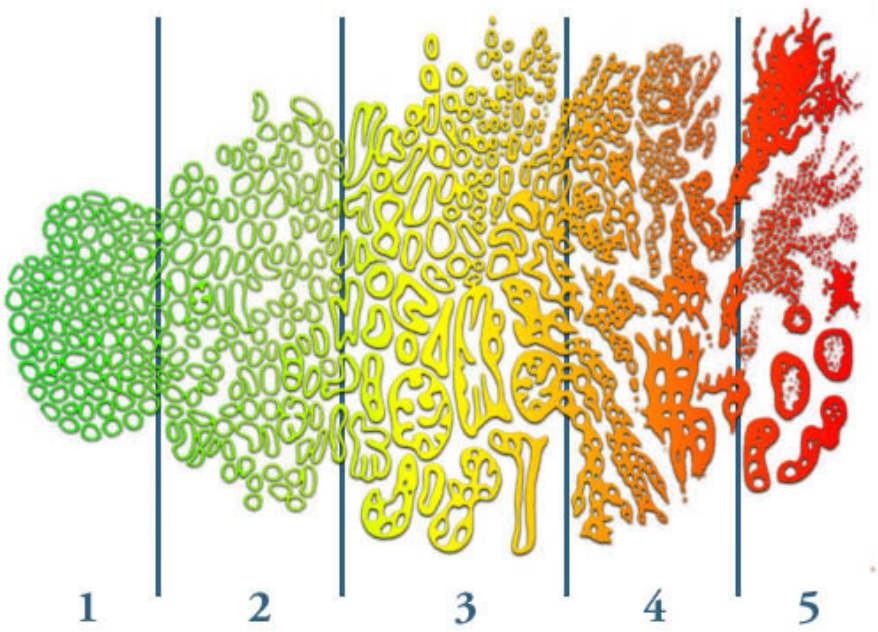


**Figure 1: Gleason grading system. The higher the Gleason score the worse the prognosis.**[20,21]

### 1.2.4 TNM staging

The TNM staging system is an internationally accepted system for classification and staging of all cancers. The system is based on the extent of the primary tumor, whether the cancer has spread to nearby lymph nodes and the absence or presence of distant metastasis. The clinical T (cT) stage is assessed by digital rectal examination and imaging (TRUS, MRI). The T stage ranges from T1-T4. The N stage is assessed by imaging (for example MRI and CT) or biopsy, most commonly of the pelvic lymph nodes. N stage is either N0 which means that the lymph nodes are free of cancer or N1 which means that they are not. The M stage is assessed by

physical examination (bone scan, CT or MRI) and states whether the patients has metastasis, M1 or not, M0. The most common symptomatic metastasis from prostate cancer is to bone but metastasis to lungs, liver and brain are also common. The NXMX means that neither lymph node staging nor metastatic staging was performed (see table 1).[22]

**Table 1: TNM classification for prostate cancer.[22]**

| TNM | | |
|---|---|---|
| Primary tumor | | |
| Tx | Primary tumor cannot be assessed | |
| T0 | No evidence of primary tumor | |
| T1 | Clinically inapparent tumor not palpable or visible by imaging | |
| | T1a | Tumor incidental; histological finding in less than 5% of resected tissue |
| | T1b | Tumor incidental; histological finding in over 5% of resected tissue |
| | T1c | Tumor identified by needle biopsy because of elevated PSA |
| T2 | Tumor confined to the prostate | |
| | T2a | Tumor involved in one lobe |
| | T2b | Tumor involved in both lobes |
| T3 | Tumor extends through the prostatic capsule | |
| | T3a | Extracapsular extension |
| | T3b | Tumor invades seminal vesicles |
| T4 | Tumor is fixed or invades other adjacent structures | |
| Regional Lymph Nodes | | |
| Nx | Not assessed | |
| N0 | No regional lymph node metastasis | |
| N1 | Regional lymph node metastasis | |
| Distant metastasis | | |
| Mx | Not assessed | |
| M0 | No distant metastasis | |
| M1 | Distant metastasis | |
| | M1a | Non regional lymph nodes |
| | M1b | Bone |
| | M1c | Other sites |

### 1.2.5 Risk Factors

There are two well established risk factors for prostate cancer, they are genetics and increasing age.[11]

Hereditary susceptibility is now considered the strongest risk factor for PCa.[23] Men with one first degree relative affected with prostate cancer are at least twice as likely to develop PCa when compared to men with no relatives affected and the risk increases with more effected relatives.[24,25] Only a small percentage of individuals with PCa have true hereditary prostate cancer. The hereditary form of prostate cancer does not differ clinically from sporadic prostate cancer except that the hereditary form is on average diagnosed 6 to 7 years earlier. Because of this early onset a greater proportion of men with hereditary prostate cancer die of the disease than those with nonhereditary prostate cancer.[23]

### 1.2.6 Epidemiology

The incidence for prostate cancer varies between countries and that is partially because of lack of screening procedures in some countries. In Western populations PCa is the most common cancer among men, but when you look at the world it is the second most common.[26]

Epidemiological studies have shown that Asian countries have much lower cancer incidence compared to the USA and Europe. Prostate cancer incidence and mortality in most native Asian populations are about one third lower than in corresponding Asian-American cohorts, which are themselves lower than the rates observed in other American cohorts.[27] Asian men moving to the USA will experience a much higher PCa prevalence. This is partially thought to be because of different diet. The Western diet lacks vegetables when compared to Asian diet and the Western diet is also rich in meat, fat and dairy products.[28] These products may increase the risk of prostate cancer but lower exposure to PSA screening in Asian men might be a contributing factor.[27] Another thing to keep in mind is for example that the Western population is generally older than the population in some of the Asian countries and PCa is a disease of older men.[11]

Prostate cancer has the highest incident rates in African American men.[11,29] Studies have shown that education is a prognostic factor for prostate cancer death and that African Americans with less than 12 years of education have greater risk of prostate cancer death than those African Americans with college degrees.[29] Lack of health insurance has also been connected to disease severity.[30]

### 1.2.7 Treatment

Prostate cancer can be treated in many different ways depending on whether it has metastasized or not.

#### *1.2.7.1 Localized prostate cancer*

Localized prostate cancer can be treated in various ways. Treatment with curative intention is either surgery or radiotherapy while some patients are monitored by active surveillance. Only patients with at least ten year life expectancy are considered for therapy with curative intent.[18] There are a few surgery options; which are open retro-pubic radical prostatectomy, laparoscopic prostatectomy or robotic assisted laparoscopic prostatectomy. There are also a few radiation therapy options; they are seed implantation, external beam radiotherapy and/or internal brachytherapy.

Side effects to curative treatments include impotence, incontinence and urethral strictures. Impotence is the most common side effect with 80-90% of pre-operative potent men classified as impotent 18 months post operation but 14-20% incontinent.[31]

Non-curative treatment can also be used, sometimes called watchful waiting. Watchful waiting is suitable for older patients, with a life expectancy of less than 10 years and good predictive factors.[32] Patients are monitored regularly for PSA levels and hormonal treatment is given only if there is clear evidence of disease progression or if symptoms occur.[18,33]

#### *1.2.7.2 Metastasized prostate cancer*

If the prostate cancer has metastasized it is treated with direct hormonal treatment such as androgen deprivation therapy (ADT). Castration levels of testosterone can be achieved surgically with bilateral orchiectomy or medically by stopping testosterone productions with drugs, such as gonadotropin-releasing hormone (GnRH) agonists or antagonist or with estrogen injections.[1,34] Bilateral orchiectomy is the most cost-effective way of inducing permanent androgen deprivation. The morbidity for bilateral orchiectomy is low but many patients find the concept worrisome.[18]

Side effects of androgen deprivation can include reduced or absent libido, impotence[35], hot flashes[36], osteoporosis[37], weight gain[38], fatigue and depression.[39]

## 1.3 Statin drugs

Statins are cholesterol-lowering drugs proven to prevent cardiovascular disease. They are among the most prescribed drugs worldwide.[40] They have minimal side effects and are relatively inexpensive.[41] Statin inhibit 3-hydroxy-3-methylglutaryl-coenzyme A reductase

(HMG-CoA reductase), the enzyme that controls conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, an essential precursor of cholesterol.[42] This results in an increased expression of low density lipoprotein (LDL)-receptors in the liver which increases clearance of LDL from the blood.[43]

The pleomorphic effects of the HMC-CoA reductase inhibition is that it impedes the activation of important cell-cycle regulators such as Ras and Rho family proteins. Dysregulation of these proteins has been linked to carcinogenesis.[44,45] Statins regulation of cholesterol might also indirectly affect prostate carcinogenesis through pathways partially regulated by cholesterol like Akt and androgen production.[42,46] This suggests that statins may have anticancer activities and numerous in vitro and in vivo studies support that. Statins appear to have antineoplastic activity such as induction of apoptosis[47-49], angiogenesis suppression[50], suppression of tumor growth[51] and inhibition of metastatic potential.[52,53]

### 1.3.1 Different types of statin drugs

There are a few types of statin drugs available (see table 2). Lovastatin was the first statin drug, commercialized in 1987. After lovastatin came simvastatin but both are closed-ring lactone pro-drugs.[54] Simvastatin is more lipophilic than lovastatin and simvastatin is therefore a more potent cholesterol synthesis inhibitor.[54,55] The closed ring lactone makes the drugs inactive pro-drugs so the ring has to be opened in the liver (or GI tract) for the drugs to work.[56] Development of newer agents led to a preference for open ring structure. Atorvastatin and rosuvastatin both have an open ring structure.[57] Atorvastatin is a second generation statin but rosuvastatin a third generation statin. Of all the statin drugs atorvastatin and rosuvastatin have the longest half-lives, about 20 hours but simvastatin has a 12 hour half-live.[58] Rosuvastatin is hydrophilic and differs from atorvastatin and simvastatin which both are lipophilic. Therefore rosuvastatin undergoes minimal metabolic handling compared to the other two which both are metabolized by the cytochrome P450 (CYP) system.[57] This raises the question whether different statin drugs could be having different effects on carcinogenesis.

**Table 2: Different types of statin drugs.**

| | |
|---|---|
| Hydrophilic statins | Rosuvastatin*, pravastatin |
| Lipophylic statins | Lovastatin, simvastatin*, atorvastatin*, fluvastatin, cerivastatin |

### 1.3.2 Statin drugs and other factors that might affect prostate cancer

Conflicting evidence suggest that statins may have chemopreventive properties against prostate cancer.[59,60] A recent prospective study (2013) by Geybels et al. showed a significant decrease in risk of prostate cancer specific mortality (PCSM) associated with statin use.[61]

Many other factors have been thought to play a role in prostate cancer, for example antihypertensive drugs[62], metformin[63], vitamin D, omega 3[64], diet, amiloride and 5-alfa reductase inhibitors.

Some experimental studies have shown that the renin angiotensin II system plays a role in regulation of cell proliferation, angiogenesis and tumor progression. This has raised questions whether drugs affecting the renin angiotensin system could modify cancer risk. A recent study by Morote et al. showed that use of angiotensin-converting enzymes inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) do not affect prostate cancer incidence and aggressiveness.[65] Some studies have shown otherwise including a study by Bhaskaran et al. which showed a slight increase in prostate cancer for patients using ARBs.[62,65]

Metformin has shown to decrease both all cause and prostate cancer specific mortality among diabetic men.[63,66]

These factors must be kept in mind when analysing the data.

## Aim of this study

The aim of this study is to examine whether statin use could be affecting the life expectancy of men with advanced prostate cancer who had castration as a primary treatment to prostate cancer.

# 2 Material and methods

## 2.1 Database

The database consists of 1905 prostate cancer patients who either received a prescription for GnRH-analog or antagonists or had a surgical castration at the Sahlgrenska University hospital between 2007 and 2012. From this database we collected all men from 2007 and 2008 that had castration as a primary treatment to prostate cancer at the Sahlgrenska University hospital (see figure 2).

The study population consists of 269 patients with advanced prostate cancer who had primary castration treatment in 2007 or 2008. 144 patients had primary castration in 2007 and 125 in 2008. Patients were collected from an existing database that belongs to the Urology department at Sahlgrenska in Gothenburg, Sweden.

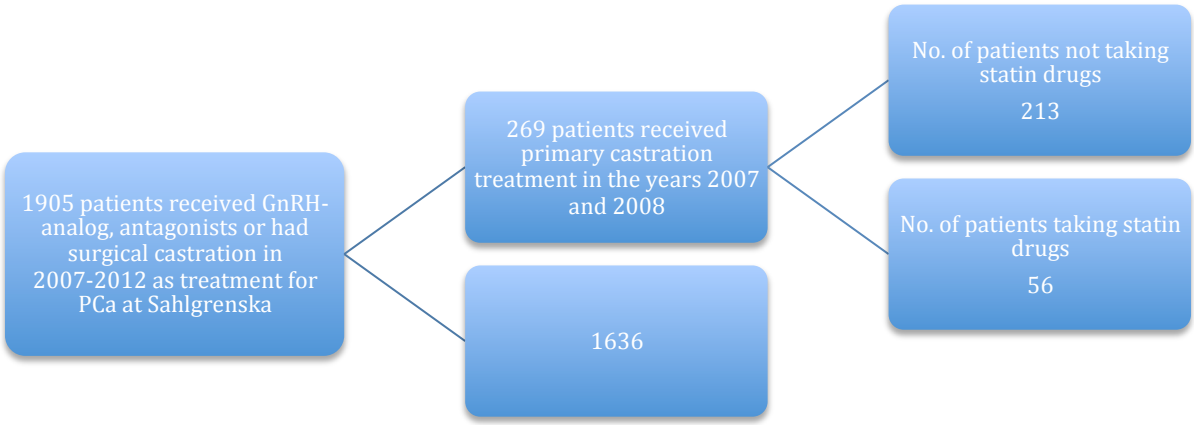


**Figure 2: Our study population was gathered from an existing database.**

In this historical cohort study we collected patients' information on drug use through Melior where we had access to medical journals. Information was collected from medical journals from the urology department and other departments such as medicine, geriatrics, emergency demand and more. In addition we also had access to scanned journals in Melior from all the hospital departments.

We read all the patients' journals and listed their drug use. We focused on their drug use before they had the castration treatment. We wanted to see whether statin use before castration could be affecting the patients' overall survival.

We also collected information on our patients' lowest PSA value after castration (PSA nadir levels). This information we also found in Melior in journals from the Urology department. In Sahlgrenska's database there already were information on patients' PSA levels at castration. We wanted to use the information to see whether statin drugs could be affecting patients PSA levels.

## 2.2 Statistics

T-test was used to compare continues variables in different groups and Chi-square test was used to test association of categorical variables in different groups. Kaplan-Meier curves were used to test for overall survival and statistical significance was tested using Log-Rank tests.

When analyzing data two kinds of errors must be kept in mind, type I and type II. When we reject a null hypothesis, when the null hypothesis is in fact true, it is called a type I error. It can be thought of as a false positive result. But on the other hand we can obtain non-significant result when the null hypothesis is in fact not true, this is called a type II error. Then we should have rejected the null hypothesis but did not because the data showed non-significant results. This can be thought of as a false negative finding.[67]

We try to minimize the risk of errors by focusing on the statin use before castration. We think that statin use before castration is of more clinical importance and for that reason it would increase the risk of type I error if we did not stratify the data for statin use before and after castration.

All the analysis was made in IBM SSPS statistics version 20.0.

# 3 Results

A total of 269 men received a primary castration treatment in the years 2007 and 2008, 56 (20,8%) of those men were taking statin drugs prior to surgery. The most commonly used statin drug was simvastatin. Of those 56 men, 47 were taking simvastatin, nine were taking atorvastatin and only one was taking rosuvastatin (see table 3). The last day of follow-up was December 31st 2012 for those men (102) who were still alive at that time, 167 men (62,1%) died before the last day of follow-up.

**Table 3: Distribution of statin drugs among the statin users.**

| | Statin use distribution (n=56) |
|---|---|
| Simvastatin | 47 |
| Atorvastatin | 9 |
| Rosuvastatin | 1 |

## 3.1 Compatible groups

The two groups, the statin user group and the group not taking statins, were very compatible. The groups had similar ratios of patients with metastasis at diagnosis; the difference between the two groups was not significant (see table 4).

Gleason score evaluation at diagnosis was also similar for both patients taking statins and those who were not, there was not a statistical difference (see table 4).

Age at castration was significantly lower in the group taking statins (P=0,016). The statin group was on average 2 years younger than the non-statin group (see table 4).

## 3.2 Findings

We found that the life expectancy, days from castration until death, was on average a little bit longer in the group taking statins but the difference was not significant (P>0,05). We did not however have information on prostate cancer specific mortality so we used all-cause mortality.

The mean PSA score at castration was 74,40 in the statin group and 395,48 for the group not taking statins. This difference was significant with a P value of 0,006 when a T-test was used.

The mean of the lowest PSA nadir value was also significantly lower in the statin group or 7,86 compared to 38,04 for the patients not taking statins (T-test was used, P=0,011).

The mean follow-up time from castration to death or last follow up (December 31st 2012) was 1378 days or 3,8 years. Of all the patients in the study 167 (62,1%) died before the last day of follow-up. For the patients dying within the follow-up time, the mean time from castration to death was 901 days or 2,5 years. A quarter of those patients died within 398 days or approximately one year.

We also looked at patients that died within six months after castration, this was a total of 21 (7,8% of the total population) patients and 72% of those patients had a PSA value before castration below 100. PSA nadir levels were missing for 62% of the patients in this group. Only a quarter of the patients who had a PSA nadir level evaluation after castration had a PSA nadir value below 10. Of these 21 patients that died within six months after castration, 11 (52,4%) had more than 10 drugs.

**Table 4: Characteristics of our total population (n=269).**

| | Patient taking statin drugs | | |
|---|---|---|---|
| | **Yes (n=56)** | **No (n=213)** | **P value** |
| **Age at castration, yrs** | | | |
| Mean | 76,88 (±6,94) | 78,84 (±9,29) | 0,016 |
| Age span | 59,75-90,25 | 40,92-95,25 | |
| **Gleason score at castration, no. of patients** | | | |
| GS 5-6 | 7 (12,5%) | 34 (16,0%) | |
| GS 7-8 | 25 (44,6%) | 94 (44,1%) | |
| GS 9-10 | 17 (30,4%) | 54 (25,4%) | NS* |
| GS missing | 7 (12,5%) | 31 (14,6%) | |
| **PSA at castration** | | | |
| Mean | 76,40 (±157,41) | 395,48 (±1413,85) | 0,006 |
| PSA span | 1-820 | 2-13000 | |
| Range | 819 | 12998 | |
| **PSA nadir** | | | |
| Mean | 7,86 | 38,04 | 0,008 |
| **M stage, no. of patients** | | | |
| M stage 0 | 9 (3,3%) | 48 (17,8%) | |
| M stage 1 | 12 (4,5%) | 51 (19,0%) | NS* |
| M stage missing | 35 (13,0%) | 114 (42,4%) | |
| **cT stage, no. of patients** | | | |
| cT stage 1 | 11 (19,6%) | 31 (14,6%) | |
| cT stage 2 | 23 (41,1%) | 64 (30,0%) | |
| cT stage 3, 4 | 17 (30,4%) | 81 (38,0%) | |
| cT stage missing | 5 (8,9%) | 37 (17,4%) | |
| **Days from castration until death** | | | |
| Mean | 1047,39 (±559,99) | 837,85 (±589,47) | NS* |

Chi-square test was used to test for statistical difference for all variables except age, PSA at castration and PSA nadir where T-test was used.

* Non significant

## 3.3 Prognosticators of overall survival

After analyzing the following variables we found that Gleason score, cT stage, metastasis at diagnosis, PSA at castration, PSA nadir and PSA decline of more than 90% after castration were all statistically significant prognostic factors for overall survival.

In a Kaplan-Meier analysis the Gleason score 9-10 had a significantly worse prognosis than Gleason score 7-8 that had a worse prognosis than Gleason score 5-6 (Log-Rank value 17,5 and p<0,001). (See figure 3)

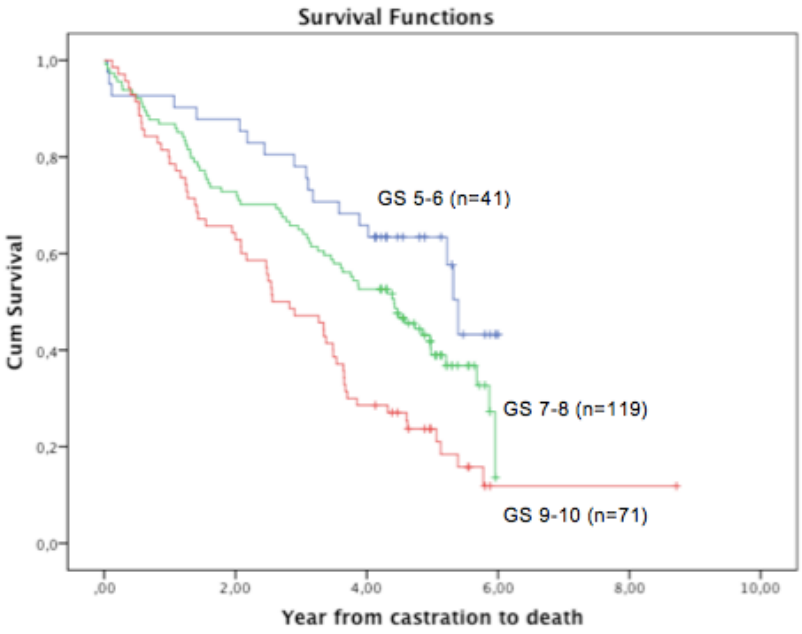


**Figure 3: High Gleason score is associated with shorter survival (n=231).**

Patients with a Gleason score of 5-6 all received castration treatment within 140 days of diagnosis. The highest value of PSA in this group at castration was 110 and 58% of the patients had a PSA value of less than 20.

Clinical t stage 3-4 had a significantly worse prognosis than cT stages 1 and 2 (Log-Rank value 23,6 and p<0,001).

The median survival for those patients without metastasis at diagnosis was 1685 days or 4,6 years. For patients with metastasis at diagnosis the median survival was 650 days or 1,8 years. The difference was statistically significant in a Kaplan-Meier analysis (Log-Rank value 45,8 and p<0,001). (See figure 4).

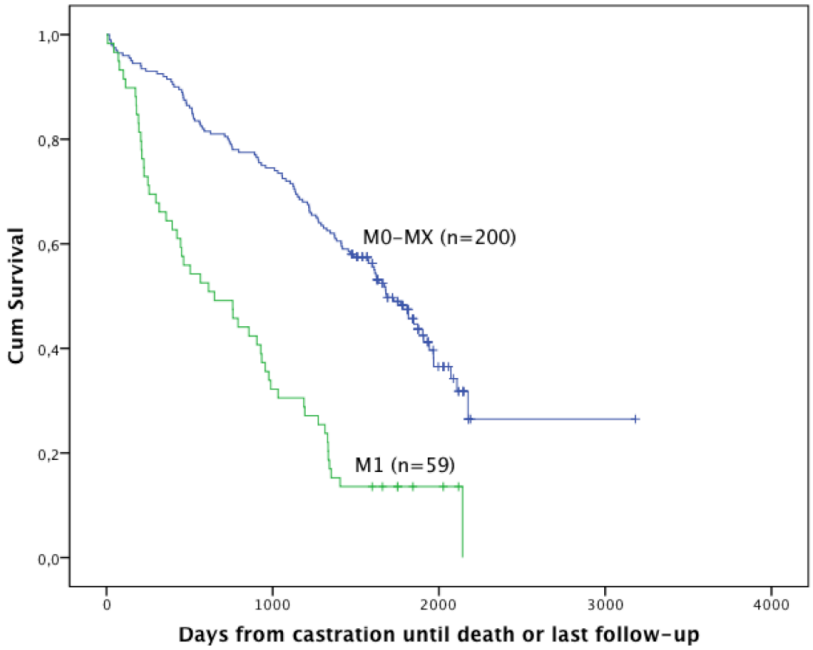


**Figure 4: M0-MX represents patients without metastasis at diagnosis. M1 represents the patients that had metastasis at diagnosis.**

PSA at castration was also a prognostic factor for overall survival. PSA value less than 50 at castration was a prognostic factor for overall survival in a Kaplan-Meier analysis (Log-Rank value 12,0 and p=0,001). Patients with a PSA value less than 50 at castration lived longer than the patients with PSA value over 50 at castration. 153 patients had a PSA value at castration less than 50. Median survival for those patients was 4,6 years and for patients with PSA above 50 it was 2,7 years.

Patients that responded to castration and had a PSA nadir value of 4 or less had a significantly better prognosis than those patients that had a PSA nadir value above 4 (Log-Rank value 30,7 and p = 0,001).

PSA decline of more than 90% after castration was a statistically significant prognostic marker for a longer survival (Log-Rank 7,5 and p=0,006).

Very few patients (<3%) were taking metformin so we did not evaluate whether metformin was a prognostic factor.

We found that statin use and age were not prognostic factors for survival.

## 3.4 Multivariate analysis

In a cox regression multivariate analysis only metastasis at diagnosis and PSA nadir value were independent prognostic markers of overall survival.

We divided the patients into a high risk group and a low risk group. The high risk group had both PSA nadir value above 4 and metastasis at diagnosis, the low risk group had neither.

Patients in the high risk group had a hazard ratio (HR) of 5 when compared to the low risk group that had neither of the risk factors, patients in the high risk group were 5 times more likely to die within the follow-up time when compared to the low risk group.

In the low risk group there were 133 patients and 33 in the high risk group. 31 of the 33 patients in the high risk group died within the follow-up time. The median survival time from castration to death in the high risk group was 424 days or approximately on year compared to 1630 days or 4,5 year in the low risk group.

The median PSA nadir value for the high risk group was 33,5 and in more than half of the patients more than 10% of the PSA value at castration. In the low risk group the median PSA nadir value was 0,5 and in 75% of those patients the PSA value dropped more than 94% after castration.

# 4 Discussion

In this study no significant difference was found in life expectancy between the group taking statins and the group not taking statins.

There was a difference in age between the statin-users and the non-statin users. The statin users were younger. The average age in the statin group was close to 77 years compared to 79 years in the non-user group. This however does not matter because age was not found to be a prognostic factor for survival in this study. Our population as a whole was relatively old and that might be the reason for age not being a prognostic factor.

We did however find out that statin-users had statistically significant lower PSA-level at castration when compared to the group of patients not taking statins before castration. Statin use was also associated with lower PSA nadir levels after castration.

Prognostic factors for overall survival in this study were Gleason score, cT stage, metastasis at diagnosis, PSA at castration, PSA nadir, cT stage and PSA decline of more than 90% after castration. These were all statistically significant prognostic factors for overall survival.

Patients with a Gleason score of 5-6 added up to a total of 42 patients. Patients with a Gleason score of 5-6 do not have very aggressive cancers. These kinds of patients would not receive a primary castration treatment today. It is also very interesting to see that all these patients, with such low Gleason scores, were castrated within 140 days of diagnosis. This treatment would not be offered to this group of patients today.

When we did a multivariate analysis metastasis at diagnosis and PSA nadir value were independent prognostic markers of overall survival. It was already known that metastasis at diagnosis is a prognostic factor for prostate cancer so our results support previous studies.[68]

## 4.1 Statins

The fact that we used all-cause mortality most likely affected our results so maybe the difference in life expectancy between the groups would have been significant if we would have had information on PCa specific mortality. The patient group taking statin drugs is more likely to have more comorbidities than the group not taking statins. Men taking statin drugs are for example more likely to have heart diseases[69] and diabetes.[70,71] There might have been more patients in the statin group dying from other causes than prostate cancer than in the other group but we cannot know.

Statins did have statistically significant effect on both PSA at castration and PSA nadir levels. Patients taking statin drugs had a significantly lower PSA at castration and lower PSA nadir levels than those who were not taking statins. Low PSA nadir level is a good prognostic factor for overall survival. We were not able to see these positive effects of statins in the patients' survival. The follow-up time is limited and maybe the higher risk of death of other causes is outperforming any cancer-preventive effects of statin-use in this small study of relatively short follow-up. If that is the case this would be called a type II error or false negative findings. The fact that the population is relatively small and the follow-up short could also be affecting our results. A larger study with longer follow-up is needed. In a larger study it would be interesting to compare different types of statins. Unfortunatly our study population was too small for us to be able to examine different effects of different statins. Only one patient was taking rosuvastatin and only nine were taking atorvastatin so we could only examine the effects of simvastatin. The effects of these different statin drugs on prostate cancer could be different. Rosuvastatin or atorvastatin might have more potent anticancer activities than simvastatin and that is something that would be interesting to study further.

## 4.2 PSA nadir value

PSA nadir value was an independent prognostic factor for overall survival in this study.

PSA nadir value was missing for 62% of the patients that died within 6 months of castration. This is likely because these patients died so soon after castration that there was not a chance for a PSA level evaluation after castration.

More than half of the patients that died so soon after castration were taking more than ten drugs. The comorbidity of these patients was probably substantial but we cannot know whether these patients were dying from prostate cancer or something else.

# 5 Conclusion

From this study we conclude that statin use is not a prognostic factor for survival but there are limitations to the study such as the population was small and shortage of information on prostate cancer specific mortality so there is a possibility that this is a false negative finding. A study with a larger population and longer follow-up is needed for conclusion.

Statin-users had lower PSA values but we cannot know whether this is a direct effect of statins on the tumors or if there are confounding factors causing this. To reach a conclusion that has to be studied further.

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