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ORIGINAL ARTICLE

Influence of metformin use on PSA values, free-to-total PSA, prostate cancer incidence and grade and overall survival in a prospective screening trial (ERSPC Aarau)

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Abstract
Purpose To analyze the effect of the oral antidiabetic drug metformin on PSA level, free-to-total PSA ratio (f/t-ratio), PCa incidence and grade as well as mortality in men participating in a population-based screening trial.
Methods Data from 4,314 men aged 55–70 years from a population-based PSA-screening trial (ERSPC Aarau) were analyzed. Information on metformin exposure was obtained by a self-administered questionnaire. Serum PSA threshold at ≥3 ng/ml triggered prostate biopsy. Data on PCa incidence and mortality were obtained through registry linkages.
Results Median follow-up time was 7.6 years. Mean age at baseline was 65.5 years (±SD 4.4). In all, $n = 150$ (3.5 %) men used metformin [metf+]. Mean baseline PSA levels were comparable between both groups ([metf+] 1.6 ng/ml ± 2.4 vs. [metf−] 1.8ug/l ± 2.2, $p = 0.4$) while f/t-ratio was slightly higher in metformin users ([metf+] 30.7 % ± 10.9 vs. [metf−] 27.3 % ± 10.9, $p = 0.01$). Overall, $n = 372$ (8.6 %) PCa cases were detected. Neither cumulative PCa incidence ($n = 11$; 7.3 % [metf+] vs. $n = 361$ 8.7 % [metf−]; $p = 0.5$) nor d`Amico risk groups were significantly different between both groups. One man in each group (metf+ 0.7 % and metf− 0.02 %) died from PCa ($p < 0.0001$), respectively. All-cause mortality was significantly higher among met + compared to met- (adjusted OR 2.50, 95 %CI 1.59–3.82; $p = 0.0001$).
Conclusion No significant differences in PSA levels or PCa incidence and grade were observed. The slightly higher f/t-ratio did not result in lower PCa detection rate. Metformin users were at significantly higher risk of all-cause mortality. The relatively small number of men on metformin is a main limitation of the study.

Keywords Hypoglycemic agents · Metformin · Prostate cancer · Prostate-specific antigen · Screening · Survival

Introduction

Prostate cancer (PCa) remains the most frequently diagnosed malignant tumor among men in the Western world [1]. Irrespective of that, the global prevalence of type 2 diabetes mellitus is constantly rising [2]. The effect of diabetes mellitus in oncological patients [3] and, in particular, antidiabetic medication on the incidence and clinical course of PCa is a matter of ongoing discussion. While a recent large meta-analysis found a 21 % decreased risk of PCa incidence in diabetic men using insulin treatment in the USA [4], others found that preexisting diabetes mellitus itself was associated with more aggressive recurrence

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following treatment such as radical prostatectomy [5] as well as increased risk of PCa mortality [6].

The oral biguanide metformin is the most widely prescribed insulin sensitizer used as first-line therapy that aside from its antihyperglycemic properties has also been linked to decreased cancer risk [7]. The mechanisms for the antitumoral activity is postulated to be an antiproliferative effect on PCa cells such as induction of the cell growth regulating protein mammalian Target of Rapamycin (mTOR) [8]. More importantly, metformin is a potent activator of the adenosinmonophosphate-activated protein kinase (AMPK) in epithelial cells [8]. A recent report found a significant PSA response to metformin exposure in men with castration-resistant PCa [9] possibly through disruption of the androgen receptor protein synthesis [10]. Although the molecular mechanism of metformin to hamper PCa growth seems to be plausible, case–control studies found mixed results [11–14]. In addition, type 2 diabetes has been shown to be associated with a decreased risk of PCa, with longer duration of diabetes associated with greater decrease in PCa risk [4]. However, indication to prostate biopsy relays predominantly if not exclusively upon PSA levels of the man.

Surprisingly, data on metformin impact on PSA levels, subsequent PCa incidence and grade in a population-based screening setting are lacking. To address this void, we investigated the association of metformin on PSA levels, PCa detection and—cancer grade in our prospective population-based screening cohort during a median follow-up time of 7.6 years. Furthermore, we evaluated the effect of metformin on overall survival of men in our screening cohort.

Materials and methods

Study protocol and population

The study protocol has been previously described [15]. From September 1998 to August 2003, 10,311 Swiss men aged 55–70 years were randomized 1:1 to the screening or control group, respectively. Overall, 4,932 men were screened during the initial screening round. Metformin exposure [metf+] was assessed from the second screening round onwards (present study baseline). Thus, $n = 4{,}314$ men who participated at study baseline were included. Prostate-specific antigen (PSA) screening took place after years (follow-up visit), and PSA tests were performed in a centralized labor. Free-to-total PSA (f/t-ratio) was assessed if PSA was >0.99 ng/ml. PSA velocity (PSAV) was calculated by using the rate of PSA change during two PSA measurements at screening visits. Information on continuation of [metf+] use was likewise collected at follow-up visit. As was the case in other European Randomized Study of Screening for Prostate Cancer (ERSPC) study centers, prostate biopsy was performed if the PSA value was ≥3.0 ng/ml [16]. Usually, a six (8 if prostate volume was >40 ccm) core laterally directed transrectal ultrasound guided biopsy was taken. PSA screening was offered every 4 years until 74 years of age. Primary endpoint was PCa diagnosis among men on [metf+] and nonusers [metf−], the secondary endpoint was PCa grade between both groups. Central pathology review of specimens was performed at the Department of Pathology, University Hospital of Basel, Switzerland. All PSA tests have been determined in a centralized laboratory (responsible A.H., Centre of Laboratory Medicine, Cantonal Hospital in Aarau). Data gathering has been supervised by safeguards such as Epidemiology Committee, Pathology Committee, PSA Committee and Causes of Death Committee with an independent Data Monitoring Committee and the Scientific Committee overlooking the study as a whole [16]. Through registry linkages of all men, information on incidence and mortality was obtained (because of registry delay, causes of death were limited to the end of 2010 [17]). PCa risk profile was defined according to d`Amico criteria [18]. The study protocol was accepted by the ethical committee.

Baseline questionnaire

Information about current [metf+] therapy and family history (FH) was collected by questionnaires during each clinical visit. Men who reported one or more first-degree relative(s) (father or brother) diagnosed with PCa were considered as having a positive FH.

Statistical evaluation

Mann–Whitney U test was used for comparison of continuously coded variables. Cross-tables and Chi-square test were applied for comparison of categorical variables. Univariate and multivariate Cox regression analysis was used to examine the relationship between FH and time to PCa diagnosis during follow-up, with age and baseline PSA value as covariates. The hazard ratio (HR) was calculated with 95 % confidence interval (95 % CI). Kaplan–Meier curves were used to estimate the cancer-free survival function. The Statistical Package for Social Sciences (SPSS) version 20 (IBM Corporation, NY, USA) was used. To investigate the effect of all-cause mortality on PCa incidence, a competing risk analysis was performed. Subhazard ratio (SHR) was calculated with 95 % CI. The Stata statistical software Version 13.1 was used (StataCorp, Texas, USA). All tests were two-sided with a significance level set at 0.05.

Results

Baseline characteristics of metformin users and nonusers

All men gave information on [metf+] medication and FH (completeness 100 %). Table 1 depicts baseline characteristics of the study cohort. Among 4,314 screened men, 150 (3.5 %) were taking [metf+] as oral antidiabetic drug at the time of invitation. Of those, 80 % (88 of 110) who were actively screened during follow-up visit (<75 years of age) were still on metformin after 4 years. At follow-up visit, 105 men had new [metf+] exposure.

Changes of PSA, PSAV and f/t-PSA over time

Mean PSA levels at baseline and during follow-up were comparable between both groups (at baseline: [metf+] 1.6 ng/ml (±standard deviation) 2.4 vs. [metf−] 1.8 µg/l ± 2.2, $p = 0.4$; follow-up visit: [metf+] 2.2 ng/ml ± 2.9 vs. [metf−] 2.3 ± 2.6, $p = 0.2$). The mean PSAV between both groups was [metf+] 0.097 ± 0.31 vs. [metf−] 0.086 ± 0.38, $p = 0.53$, respectively. Overall, [metf+] men had slightly higher calculated f/t-ratio at baseline as compared to [metf-] men ([metf+] 30.7 % ± 10.9 vs. [metf−] 27.3 % ± 10.9, respectively; $p = 0.01$; follow-up visit: 28.4 % ± 13.6. [metf−] vs. 25.4 % ± 12.3 [metf−], respectively; $p = 0.3$). The biopsy compliance between both groups in case of PSA conversion to ≥3 ng/ml was comparable (baseline screening round [metf+] 63.2 % vs. [metf−] 76.0 %; $p = 0.2$ and follow-up screening round [metf+] 100 % vs. [metf−] 95.9 %; $p = 0.4$, respectively).

PCa detection rate and risk factor analysis

During follow-up, the PCa detection rate was comparable between both groups ([metf+] $n = 11$ [7.3 %] vs. [metf−] $n = 361$ [8.7 %]; $p = 0.6$, Table 2). D'Amico risk groups distribution was not significantly different between both groups. Figure 1 depicts the unadjusted PCa-free survival among [metf+] and [metf−] ($p = 0.6$, log rank test). On univariable Cox regression analysis increasing age (HR 1.03, 95 % CI 1.00–1.05; $p = 0.04$), higher baseline PSA (HR 1.18, 95 % CI 1.16-1.19; $p < 0.0001$), but not [metf+] (HR 0.86, 95 % CI 0.47–1.56; $p = 0.62$) were associated with PCa detection during follow-up (Table 3A). A higher free-to-total PSA was inversely associated with PCa detection (HR 0.94, 95 % CI 0.93–0.96; $p < 0.0001$). When new [metf+] exposure at follow-up visit ($n = 105$) was analyzed separately, there was no significant difference with respect to PCa incidence or PCa-specific/all-cause mortality between both groups (data not shown).

On multivariate analysis, only increasing baseline PSA (HR 1.11, 95 % CI 1.09–1.13; $p < 0.0001$) achieved an independent predictor status for PCa detection. An increasing free-to-total PSA ratio was an independent predictor for a decreased risk of PCa detection during follow-up (HR 0.95, 95 % CI 0.94–0.96; $p < 0.0001$).

PCa-specific mortality and all-cause mortality among metformin users and nonusers

Among 150 [metf+] and 4,164 [metf−] men, 1 (0.7 %) and 1 (0.02) died from PCa (OR 27.94, 95 % CI 1.73–448.84; $p < 0.0001$), whereas 26 (17.3 %) and 329 (7.9 %) (unadjusted OR 2.50, 95 % CI 1.59–3.82; $p < 0.0001$) died from other causes during follow-up, respectively (Table 4; Fig. 2). The leading causes of death among [metf+] men were cancer at different sites ($n = 10$ [37.0 %)] and cardiovascular diseases ($n = 6$ [22.2 %]). Among [metf−] men, these numbers were 42 (12.7 %) (cardiovascular diseases) and 22 (6.7 %) (cancer at different sites), respectively. Baseline PSA, age and metformin use were predictors for overall death on univariate (HR 1.09, 95 % CI 1.06–1.11; $p < 0.0001$; HR 1.05, 95 % CI 1.00–1.09; $p = 0.03$; HR

Table 1 Baseline characteristics of 4,314 men who were prospectively observed according to metformin use

Characteristics at baseline	Overall	Metformin use	No metformin use	*p* value
Number of patients (%)	4,314	150 (3.5)	4,164 (96.5)	–
Age at baseline, years (±SD)	65.5 (±4.4)	67.1 (±4.6)	65.4 (±4.4)	**<0.0001**
Age at death, years (±SD)	70.7 (±5.0)	72.0 (±5.3)	70.6 (±4.9)	0.1
PSA value, ng/ml	1.8 (±2.8)	1.6 (±2.4)	1.8 (±2.2)	0.4
Free-to-total PSA*, % (±SD)	27.4 (±10.9)	30.7 (±10.9)	27.3 (±10.9)	**0.01**
IPSS (%)				
Mild (0–7)	2,729 (64.6)	90 (60.0)	2,639 (63.4)	0.2
Intermediate (8–19)	1,362 (32.3)	52 (34.7)	1,310 (31.4)	
Severe (20–35)	135 (3.2)	8 (5.3)	127 (3.0)	

SD standard deviation. In 88 (2.0 %) men, IPSS was not calculated because of use of diuretics

* Free-to-total PSA was only measured in men with PSA >0.99 ng/ml. Continuous variables are given with mean ± standard deviation (SD)

Table 2 PSA levels ± SD during baseline and follow-up visit and numbers of detected PCa as well as d′Amico risk classification for disease progression among metformin users and nonusers

	Overall $n = 4{,}314$	Metformin use $n = 150$	No Metformin use $n = 4{,}164$	p value
PSA during baseline visit (ng/ml)	1.8 (±2.8)	1.6 (±2.4)	1.8 (±2.2)	0.4
PCa detected at baseline screening (% of group)	181 (4.2)	4 (2.7)	177 (4.3)	0.3
D'Amico risk group				
Low risk, no (%)	120 (66.3)	0 (0)	120 (67.8)	0.02*
Intermediate risk, no (%)	36 (19.9)	2 (50)	34 (19.2)	
High risk, no (%)	25 (13.8)	2 (50)	23 (13.0)	
PSA during follow-up visit (ng/ml)	2.3 (±2.6)	2.2 (±2.9)	2.3 (±2.6)	0.2
PCa detected during follow-up visit (% of group)	191 (4.4 %)	7 (4.7)	184 (4.4)	0.9
D′Amico risk group				
Low risk, no (%)	87 (45.5)	4 (57.1)	83 (45.1)	0.5
Intermediate risk, no (%)	72 (37.7)	3 (42.9)	69 (37.5)	
High risk, no (%)	32 (16.8)	0 (0)	32 (17.4)	
Overall PCa detected (% of group)	372 (8.6)	11 (7.3)	361 (8.7)	0.6
D'Amico risk group				
Low risk, no (%)	207 (55.6)	4 (36.4)	203 (56.2)	0.4
Intermediate risk, no (%)	108 (29.0)	5 (45.5)	103 (28.5)	
High risk, no (%)	57 (15.3)	2 (18.2)	55 (15.2)	

* Due to the small numbers, these results should be interpreted with caution

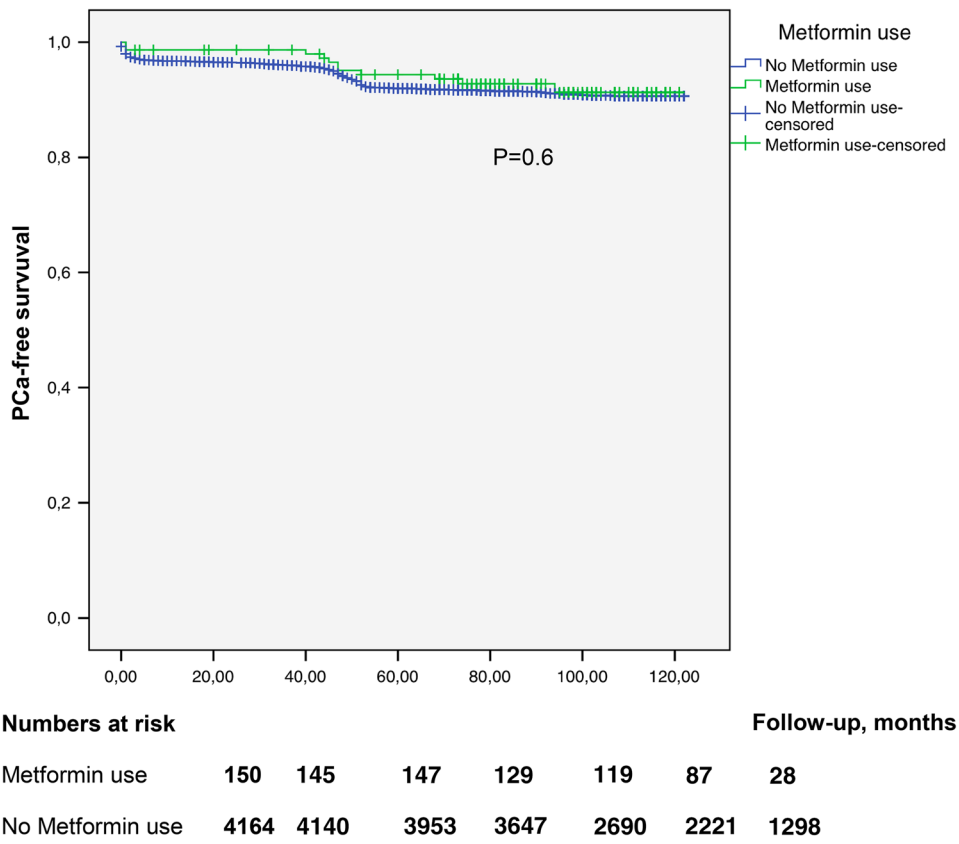

Fig. 1 Kaplan–Meier estimate for PCa-free survival of 4,314 men according to metformin use

2.34, 95 % CI 1.58–3.46; $p < 0.0001$) as well as on multivariate Cox regression analysis (HR 1.10, 95 % CI 1.06–1.14; $p < 0.0001$; HR 1.05, 95 % CI 1.01–1.10; $p = 0.03$; HR 2.14, 95 % CI 1.19–3.87; $p = 0.01$), respectively. When taking into account [metf+] men with insulin and sulfonylurea exposure, there was a nonsignificant trend

Table 3 Univariate and multivariate Cox regression proportional hazard analysis for prostate cancer detection (A) and all-cause mortality (B)

Characteristics	Univariate			Multivariate		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
(A) predicting prostate cancer detection during follow-up						
Age, years	1.03	1.00–1.05	**0.04**	1.01	0.99–1.04	0.26
PSA, ng/ml	1.18	1.16–1.19	**<0.0001**	1.11	1.09–1.13	**<0.0001**
Free-to-total PSA	0.94	0.93–0.96	**<0.0001**	0.95	0.94–0.96	**<0.0001**
Family history	1.19	0.81–1.76	0.38	1.10	0.73–1.65	0.65
IPSS	1.02	1.00–1.04	0.09	0.99	0.97–1.00	0.20
Metformin use	0.86	0.47–1.56	0.62	1.02	0.54–1.91	0.96
(B) predicting all-cause mortality during follow-up						
Age, years	1.09	1.06–1.11	**<0.0001**	1.10	1.06–1.14	**<0.0001**
PSA, ng/ml	1.05	1.00–1.09	**0.03**	1.05	1.01–1.10	**0.03**
Free-to-total PSA	1.01	0.99–1.02	0.12	1.00	0.99–1.02	0.62
Family history	1.01	0.65–1.55	0.98	1.21	0.68–2.12	0.52
IPSS	1.00	0.98–1.02	0.71	0.98	0.95–1.01	0.15
Metformin use	2.34	1.58–3.46	**<0.0001**	2.14	1.19–3.87	**0.01**

Table 4 Prostate cancer-specific mortality and all-cause mortality rates according to metformin use

	Metformin use ($n = 150$)	No metformin use ($n = 4164$)	OR (95 % CI)	*p* value
Death from other cause (%)	26 (17.3)	329 (7.9)	2.50 (1.59–3.82)	**<0.0001**
Death from PCa (%)	1 (0.7)	1 (0.02)	27.94 (1.73–448.84)	

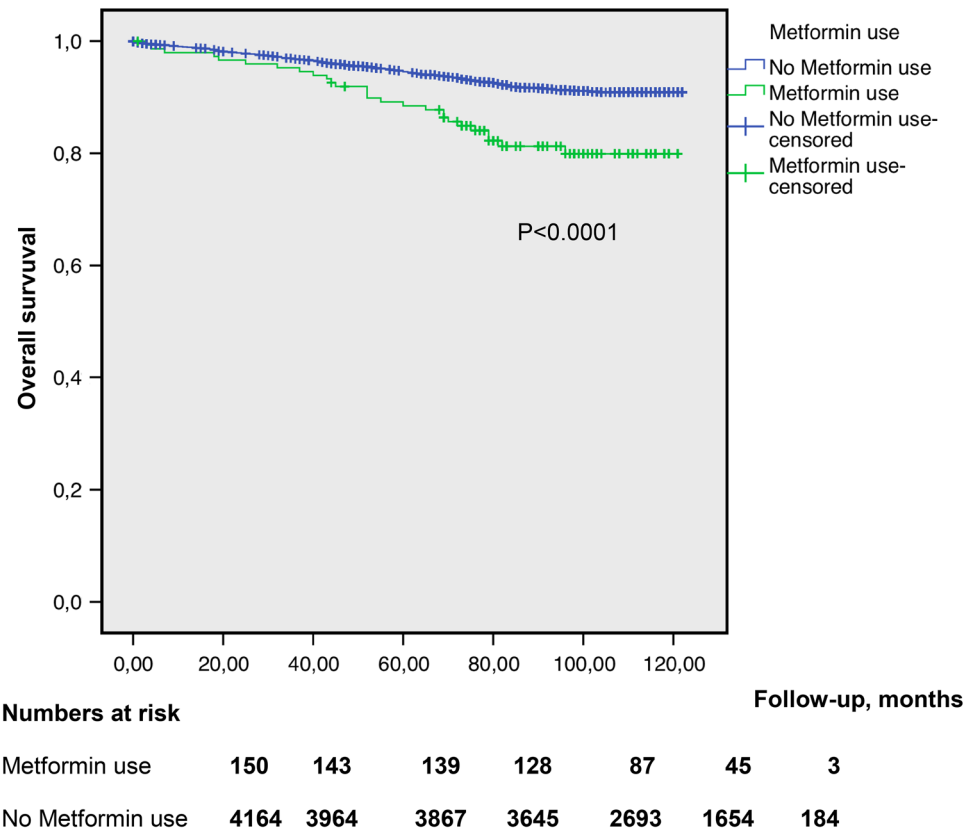

Fig. 2 Kaplan–Meier estimate for overall survival of 4,314 men according to metformin use

for higher all-cause mortality (HR 2.22, 95 % CI 0.90–5.44; $p = 0.08$). When taking into account [metf+]-only users, HR was comparable (HR 2.05, 95 % CI 0.96–4.40; $p = 0.07$). Overall, [metf+] men who died were slightly but not significantly older than [metf−] men (Table 1). In a competing risk analysis, [metf+] exposure among men who died during follow-up had no influence on PCa incidence (SHR 0.91, 95 % CI 0.50–1.66; $p = 0.77$).

Discussion

Several studies have shown a reduced risk of cancer incidence among patients on metformin [4]. The reason for this antineoplastic effect is thought to be an activation of the cellular "metabolic master" adenosine monophosphate-activated protein kinase (AMPK), which reduces glucose production and induces additional cell cycle arrest [8].

Interestingly, case–control studies investigating the association of metformin exposure and PCa incidence yielded mixed results. Wright et al. [11] found a 44 % risk reduction for PCa and stated that metformin use was associated with a borderline significant decrease in the relative risk of PCa. In contrast, Azoulay et al. [12] found no decrease in risk of PCa. A recently published large case–control study found no association between metformin use and PCa incidence and grade [13]. Importantly, this study had a median time of metformin exposure limited to 18 months. The same group published a study showing lower rates for PCa mortality during a follow-up time of 4.64 years [19], but had been criticized because of the statistical methods that were applied [20]. More recently, a Danish case–control study found a decreased risk of PCa diagnosis [14]. Interestingly, no association of diabetes mellitus or metformin use on PCa features and recurrence rate after radical prostatectomy have been found [21]. Regrettably, many of these studies looked at men exceeding 70 years—thus above the so-called core age for PSA screening and were lacking information on PSA levels [12, 19]. To our knowledge, the influence of metformin on PSA as well as PCa detection in a population-based PCa screening setting has never been investigated so far.

In the present population study, there was no significant effect of metformin exposure on overall PCa during 7.6 years on median. In addition, both, baseline and follow-up PSA levels, known to be highly predictive for future PCa development [22] were not significantly different between both groups; it might therefore be hypothesized that this lack of difference will remain in the future. Interestingly, there was a slightly higher proportion of intermediate and high risk PCa at baseline screening according to d`Amico risk groups among men on metformin ($p = 0.02$). However, the number of PCa detected in men on metformin was small. Therefore, these findings need to be interpreted with caution.

Men on metformin had slightly higher free-to-total PSA ratios at baseline (30.7 vs. 27.3 %). Lower ratios have been shown to indicate risk of PCa among men with elevated serum PSA [23] as well as below 3 ng/ml [24]. If lower ratios indicate increased risk of PCa, one should assume that higher ratios are associated with reduced risk of PCa, which is not supported by our data. One explanation might simply be the slightly higher age in men on metformin leading to higher free-to-total PSA ratio due to benign prostatic hyperplasia. Another explanation might be that this observed difference, although statistically significant, is still too small to produce a difference in tumor growth between both groups.

Type 2 diabetes has been shown to be associated with a decreased risk of PCa, with longer duration of diabetes associated with greater decrease in PCa risk [25]. This effect is believed to represent an intervention bias depending on lower PSA levels of diabetic men. Indeed, a significantly lower mean PSA levels in diabetics than in nondiabetics have been reported [26]. Similarly, a more severe diabetes mellitus was shown to be associated with 16 % lower PSA levels as compared to men without diabetes [27]. Reason for this seems to be a higher body mass index in diabetic men. This in turn might lead to delayed diagnosis of prostate cancer and possibly more aggressive prostate cancer. In the current study, there was no significant difference of PSA level at baseline or during follow-up. In addition to that, there was no significant difference in biopsy compliance between both groups in both screening rounds. As our study design did not differentiate between diabetic and nondiabetic men, the above mentioned intervention bias was less likely to occur.

Overall, only two men have died from PCa during follow-up. This very low number is to be expected as the observation time is too short for PCa-specific mortality evaluation. Therefore, any conclusions would be premature in this regard. Another even more important point to mention is the significantly higher overall mortality among men with metformin exposure. The all-cause mortality rate was more than twice as high among men on metformin compared to nonusers. Moreover, metformin exposure was an independent predictor for overall mortality after adjusting for other risk factors. The 2-year probability of non-PCa-specific death was 4.2 % and increased to 13.3 % at 5 years, respectively.

Although this did not influence the PCa incidence in the competing risk analysis, the higher overall mortality rate is of particular interest and contrary to a recently published large retrospective cohort study [19]. However, because of a shorter follow-up than in the current study, we hypothesize that this effect might decrease during follow-up.

There are several explanations for the higher all-cause mortality, such as the additional use of insulin and sulfonylurea to metformin, which has been associated with an 44 % increased risk of all-cause mortality among diabetic men [28]. On the other hand, the distribution of underlying causes of death suggests that it might simply be the higher rate of complications and morbidity caused by diabetes. This in turn confirms the need to recognize (severe) diabetes and pay even more attention to associated comorbidities in the daily routine practice when performing PSA testing. In other words, only those men who really will benefit should indeed be screened.

Several limitations of our study deserve mention. First, we rejected the null hypothesis for influence of metformin exposure on PCa detection based on a relatively small sample size in a subgroup of a screening population with relatively short follow-up. Second, we did not use validated classification of existing comorbidities, nor had we information on the rate of diabetes mellitus in nonmetformin users. Third, although featuring the strength of a population-based and randomized design and therefore reducing selection bias, a "healthy user bias" cannot be excluded [29]. Our findings are derived from a screening cohort with a mean age of 65.5 years and might therefore not be comparable to other populations with other age distributions. Fourth, PSA levels are known to be slightly influenced by body mass index which is known to be higher in diabetic men [30]. Last but not least, we did not have data on the duration of metformin exposure *before* men were included in our study. However, if metformin exposure was longer then assumed—this would even strengthen the conclusions of our study.

The strength of the present study is the prospective design with a median follow-up duration of 7.6 years, which is longer than in recent published studies [12, 13, 19]. Moreover, we focused on a relevant population in the screening core age that was highly compliant to the drug and adhered strictly to the screening protocol. Furthermore, our study provides complete data on baseline PSA levels, f/t-ratio levels and PSA kinetics as well as PCa incidence, grade and mortality rates including causes of death referring to metformin exposure. In contrast to other studies [14], metformin exposure was not assessed by a registry but was gathered by self-administered questionnaires and further confirmed by personal inquiry during the screening visit by experienced staff.

In conclusion, our study demonstrates lack of influence of metformin exposure on PSA levels, PSAV and PCa incidence in a prospective population-based screening trial during a median follow-up time of 7.6 years. Interestingly, metformin users had slightly higher free-to-total PSA ratio, but this finding had no effect on overall PCa incidence and grade. Metformin exposure was associated with a significantly higher risk of all-cause mortality reflecting the higher morbidity of diabetic men. Urologist and healthcare providers might need to incorporate this higher morbidity for a risk-adapted screening in order to test only those men who will benefit. This study is the first one in the literature providing insights into the impact of metformin use on early and follow-up PSA kinetics, prostate cancer incidence as well as mortality rates in a population-based setting.

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Conflict of interest None.

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