

# Influence of concurrent medications on outcomes of men with prostate cancer included in the TAX 327 study

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## Abstract

**Objectives:** The TAX 327 trial was pivotal in establishing docetaxel in castration refractory metastatic prostate cancer. Various commonly prescribed and over-the-counter co-administered medications are thought to exhibit anti-neoplastic properties and/or could potentially have pharmacokinetic interactions with docetaxel lessening the effectiveness of chemotherapy.

**Methods:** To examine the effect of on prostate cancer outcomes within this trial, we examined overall survival, prostate-specific antigen (PSA) response, percent PSA reduction, pain response and QOL responses for 14 families of medications including metformin, digoxin, verapamil, proton pump inhibitors, nitrates, statins, cox-2 inhibitors, warfarin, heparins, ascorbic acid, selenium, tocopherol, antidepressants and erythropoietin.

**Results:** Our findings did not reveal any medication that had a significant additive or synergistic effect with docetaxel. We did note, however, that patients on digoxin or verapamil had poorer overall survival, possibly due to a trend of fewer cycles of administered chemotherapy being administered to the verapamil group, consistent with a pharmacokinetic interaction.

**Conclusions:** These data are only hypothesis-generating given the statistical limitations, but may form a basis for similar future analysis in other malignancies. The data suggest the need to be aware of pharmacokinetic interactions with medications that may interact with docetaxel.

## Introduction

Patients with advanced cancer receiving chemotherapy generally require multiple medications for concurrent illnesses, treatment-related toxicities or for pain control. There is growing interest in potential anti-tumour properties of some prescription drugs; conversely, there is that these same drugs may increase the likelihood of adverse drug interactions. The most recent analysis of concomitant medications taken by cancer patients suggests that patients take

an average of 4.8 prescription drugs, 1.6 non-prescription drugs and 1.6 other remedies within the 3 days before chemotherapy.<sup>1</sup>

The large database (n = 1006) of the TAX 327 study provided us with an opportunity to evaluate concomitant medications taken by the patients at baseline and their influence on treatment outcomes. TAX 327 was a landmark study showing survival advantage in men treated with docetaxel 3 times weekly compared to docetaxel once a week and mitoxantrone as initial chemotherapy for castrate-resistant, metastatic prostate cancer.<sup>2</sup>

## Methods

We identified patients taking selected concomitant medications while receiving study treatment as part of the TAX 327 study. We examined 14 types of medications (metformin, digoxin, verapamil, proton pump inhibitors, nitrates, statins, cox-2 inhibitors, warfarin, heparins, ascorbic acid, selenium, tocopherol, antidepressants and erythropoietin) taken concurrently with chemotherapy and prednisone and analyzed them for their association with overall survival (primary endpoint), PSA-response rate, percent PSA-reduction from baseline to on-treatment nadir, pain-response and quality of life (QOL)-response. Each of these measures was defined as per the TAX 327 study,<sup>2</sup> aside from PSA shrinkage (Appendix 1). Each of these selected medications was taken by at least 20 men in the study. Medications were selected because of their putative anti-neoplastic effects (Table 1). We detailed selected data suggesting that specific concurrent medications have an effect on outcome measures in Table 2 and Table 3 (greater details in Appendix 2 to 9). For all outcomes, both unadjusted tests and adjusted tests were examined. Unless otherwise specified, the adjusted test results are discussed in the text with both sets of results presented in the online supplementary tables. Overall survival was estimated using the Kaplan-Meier method, and is based on the updated survival analysis.<sup>3</sup> Cox proportional hazards models were used to estimate the hazards ratio (HR) and *p*-value comparing

**Table 1. Rationale for selection of some of the concomitant medications in the TAX 327 database, with putative mechanisms of action and pharmacokinetic interactions with docetaxel**

Agent	Purported mechanism of anti-cancer action and references	Overview of evidence
<b>Metformin</b>	AMPK activation, <sup>9</sup> cyclin D1 inhibition. <sup>10</sup>	Population-based study has shown decreased prostate cancer risk with use of metformin. <sup>11</sup>
<b>Digoxin</b>	Inhibition of HIF1. <sup>4,5</sup>	Digitalis inhibits proliferation of prostate cancer cell lines. <sup>12</sup>
<b>Nitrates</b>	Attenuates hypoxia induced tumour growth/drug-resistance. <sup>13</sup>	Prolonged PSA doubling time with use of glyceryl trinitrate in recurrent prostate cancer patients in a phase II study. <sup>14</sup>
<b>PPI</b>	Tumour alkalinization, inhibition of autophagy and P-glycoprotein antagonist. <sup>15</sup>	Limited evidence.
<b>Verapamil</b>	Reversal of multidrug resistance, inhibition of voltage-gated K <sup>+</sup> channel. <sup>16,17</sup> However, CYP3A4 inhibitor, potentially increasing docetaxel concentration. <sup>18</sup>	Inhibition of proliferation in LNCaP. <sup>6</sup>
<b>Statins</b>	Inhibitory effects on angiogenesis, cell proliferation and invasion. <sup>19</sup> However, may possibly compete for CYP3A4 metabolism (atorvastatin, lovastatin, simvastatin).	Reduced risk of prostate cancer and of biochemical recurrence after prostatectomy. <sup>20,21</sup>
<b>Cox-2 inhibitors</b>	Converts arachnoidic acid to prostaglandins which inhibit apoptosis, stimulate cell proliferation and facilitate angiogenesis. <sup>22</sup>	Decreased tumour cell proliferation, microvessel density, angiogenesis and HIF-1 and increased apoptosis associated with celecoxib. <sup>23</sup>
<b>Warfarin</b>	Inhibition of fibrin formation, reduction of urokinase receptor expression, and inhibition of thrombin generation, release of metalloproteinase-2 from subendothelial matrix. <sup>24</sup> Also may compete for CYP3A4 with docetaxel for metabolism.	Warfarin showed anti-metastatic activity in pre-clinical prostate cancer models <sup>25</sup> and showed antitumour activity in prostate cancer in a population based study. <sup>8,26</sup>
<b>Ascorbic acid</b>	Ascorbic acid: direct cytotoxicity by hydrogenperoxide <sup>27</sup> and antioxidant properties.	Limited evidence.
<b>Lycopene</b>	Lycopene thought to act through Ras and mevalonate. <sup>28</sup>	A prospective study of tomato products (lycopene) was associated with decreased prostate cancer risk. <sup>30</sup>
<b>Tocopherol</b>	Induces apoptosis via caspase dependent and independent mechanisms <i>in vitro</i> and <i>in vivo</i> . <sup>29</sup> Possibly by affecting interrupting sphingolipid synthesis. <sup>31</sup> May also affect NF-Kb activation. <sup>32</sup>	Effects found in prostate cancer cell lines and xenografts. <sup>34</sup>
<b>Selenium</b>	May contribute to elevation of the endogenous inhibitor of angiogenesis, platelet factor-4, <sup>41</sup> inhibiting nuclear translocation of the NF-Kb and the subsequent production of the immunosuppressive cytokine TGF-beta, VEGF and IL-6, <sup>42</sup> increases the activity of PTEN. <sup>43</sup>	Evidence from mouse and rat prostate models. <sup>33,44</sup> Early human evidence of a benefit in preventing carcinogenesis not validated.
<b>Heparins</b>	Possible role in decreasing metastases formation via decreasing adhesion. <sup>35</sup>	<i>In vitro</i> models and rat prostate models. <sup>36</sup>
<b>Antidepressants</b>	Selective serotonin reuptake inhibitors and monoamine oxidase inhibitors may decrease prostate cancer growth. <sup>38</sup>	<i>In vitro</i> proliferation experiments. <sup>37</sup>
<b>Erythropoietin</b>	May promote growth of prostate cancer cells. <sup>39</sup>	Experiments in prostate cancer cell lines and indirect evidence from human tumours. <sup>40</sup>

PSA: prostate-specific antigen; PPI: proton pump inhibitors; LNCaP: Human prostate adenocarcinoma cell line; NF-Kb: nuclear factor kappaB; TGF-beta: Transforming Growth Factor-beta; VEGF: Vascular endothelial growth factor; IL-6: interleukin-6; PTEN: phosphatase and tensin homologue.

patients who received each concomitant medication to those who did not receive it. The proportion of patients having a PSA-response, differences in PSA reduction, pain-response and QOL-response were calculated for patients receiving (or not) each concomitant medication. The unadjusted *p*-value was calculated using Fisher's exact test, and adjusted *p*-values using the Cochran-Mantel-Haenszel test, adjusted for treatment group. The homogeneity of odds ratios was tested using the Breslow-Day test and used to determine whether the

estimated odds ratio is different between the three treatment groups. Duration of intravenous chemotherapy was compared using Wilcoxon rank sum tests (unadjusted analysis) and linear regression (adjusted analysis). The median and inter-quartile range was calculated for patients receiving (or not) each concomitant medication, and these were compared using the Wilcoxon rank sum test. Statistical significance was set at *p* = 0.05 and no *p*-value adjustment was performed for multiple hypothesis testing. All tests were two-sided.

**Table 2. Probability values for selected results of interest with results in bold indicating significance**

Outcome	Concomitant medication	N	Total patients	Groups		
				(D3W/D1W/M)	D3W	D1W
OS	Digoxin	10:14:11	35	<b>0.023</b>	<b>0.3</b>	<b>0.7</b>
	Verapamil	16:11:16	43	0.062	0.14	0.29
PSA decline	Warfarin	22:23:24	69	0.047	0.35	0.52
Pain response	Antidepressants	27:21:17	65	0.61	0.018	0.46
	Epoetin	16:26:19	61	0.009	0.79	0.68
QOL response	Digoxin	10:14:11	35	0.096	0.38	0.58
	Cox-2 inhibitors	37:34:29	80	0.27	0.48	0.06
	Statins	28:21:33	82	0.021	0.26	0.36

OS: overall survival; PSA: prostate-specific antigen; QOL: quality of life; D3W: docetaxel 3 weekly; D1W: docetaxel weekly; M: mitoxantrone; N: number of patients in each group.

## Results

Patients taking verapamil and digoxin had worse overall survival than patients who did not (adjusted analysis using data from all 3 treatment cohorts: digoxin HR 1.43 (1.01-2.03),  $p = 0.046$ ; verapamil HR 1.51 (1.10-2.08),  $p = 0.011$ ). These differences in survival were consistent within each of the 3 treatments, but were most pronounced in the docetaxel 3-weekly treatment group. Interestingly, the duration of intravenous chemotherapy comparing the median duration for those on verapamil with the median duration of those not on verapamil approached statistical significance (unadjusted  $p = 0.080$  and adjusted  $p = 0.070$ ). Those on verapamil appeared to have reduced weeks on chemotherapy compared with those not on verapamil.

No concomitant medication had a statistically significant effect on PSA-response rate, although men taking warfarin had greater PSA reduction than those not taking it (PSA reduction 49.0% [-5.5, 85.3] vs. 69.2% [20.3, 90.8], unadjusted  $p = 0.047$ , adjusted  $p = 0.035$ ). Men taking antidepressants had lower rates of pain-response than those not taking antidepressants (unadjusted  $p = 0.045$ ; Cochran-Mantel-Haenszel [CMH] test  $p = 0.028$ ; homogeneity of odds ratios  $p = 0.19$ ). The QOL response rates were significantly higher (unadjusted  $p = 0.032$ ; CMH  $p = 0.031$ ; homogeneity of odds ratios  $p = 0.49$ ) among patients who received cox-2 inhibitors than those who did not.

## Discussion

Our analysis revealed a number of possible associations between concomitant medications and outcome measures in the TAX-327 trial. The use of digoxin was associated with poorer overall survival within all three treatment groups. Pre-clinical studies have shown digoxin to be a potential anticancer agent,<sup>6,7</sup> but its effects here are likely due to the influence of comorbidity from the cardiac condition for which it was prescribed, an effect that would only be partially accounted for by the stratification for the Karnofsky performance status. Patients who took verapamil also had poorer

overall survival, although other efficacy outcomes were not substantially different between those who did and did not take verapamil. This result is contrary to previous suggestions that verapamil can inhibit the proliferation of many tumour types, including prostate cancer,<sup>6</sup> and, in higher doses, can block the multi-drug resistance drug efflux pump. Patients receiving digoxin or verapamil probably represented a group of people who were more likely to have death related to cardiovascular disease; although, it is possible that competition for CYP3A4 and the inhibitory ability of verapamil on CYP3A4 also lead to more toxicity, abrogating the length of chemotherapy, a hypothesis supported by the trend to a decreased treatment duration in patients on verapamil. Unfortunately, it is not possible to extract causes of mortality from the trial records to clarify this issue.

Our analysis revealed that the degree of PSA reduction in men taking warfarin was higher than in those not taking this medication. Data are sparse on the effects of warfarin in prostate cancer treatment; a Canadian case-control study showed that 4 years of warfarin use was associated with an adjusted incidence rate ratio of 0.80 (95% CI 0.65-0.99) for prostate cancer compared with that in people who never used warfarin; little research has been carried out subsequently.<sup>10</sup>

Patients concurrently taking antidepressants had poorer pain-response rates, and trends to poorer survival and PSA-response rates ( $p < 0.10$ ). The poorer pain response may be due to anxiety that was associated with conditions for which these medications were prescribed.

Our analysis of proton pump inhibitors and metformin, drugs with pre-clinical evidence to suggest potential antineoplastic activity (Table 1), also did not reveal any association with outcome measures, although we noted trends for QOL response (unadjusted  $p = 0.074$ ; CMH  $p = 0.074$ ; homogeneity of odds ratios 0.31) for metformin.

Despite pre-clinical, clinical and epidemiological observations that some of these medications are likely to exhibit anticancer properties, we were unable to detect sufficient activity to warrant testing with docetaxel in future studies. There are a number of potential reasons for this. It is impor-

**Table 3. Overall survival**

Drug	n (%)	Treatment D3W:D1W:M	Median (95% CI) survival, no concomitant medication	Median (95% CI) survival, concomitant medication	Unadjusted HR (95% CI) p-value	Adjusted HR (95% CI) p-value <sup>†</sup>
Metformin	38 (3.8)	17:10:11	17.3 (16.3-18.4)	18.2 (13.1-25.5)	1.00 (0.70-1.42) 1.00	0.99 (0.69-1.41) 0.96
PPI	223 (22.2)	74:92:57	17.2 (16.3-18.6)	17.8 (15.3-19.7)	0.96 (0.82-1.12) 0.60	0.92 (0.79-1.08) 0.31
Glyceryl	51 (5.1)	21:15:15	17.5 (16.6-18.7)	13.5 (10.3-17.2)	1.19 (0.88-1.60) 0.27	1.16 (0.86-1.57) 0.35
Digoxin	35 (3.5)	10:14:11	17.4 (16.5-18.6)	12.0 (7.3-17.5)	1.54 (1.09-2.17) 0.014	1.43 (1.01-2.03) 0.046
Verapamil	43 (4.3)	16:11:16	17.4 (16.5-18.6)	12.9 (8.1-17.5)	1.51 (1.10-2.07) 0.011	1.51 (1.10-2.08) 0.011
'Statin'	82 (8.2)	28:21:33	17.3 (16.3-18.4)	17.3 (14.8-22.6)	0.94 (0.74-1.19) 0.60	0.97 (0.76-1.23) 0.80
'Coxib'	100 (9.9)	37:34:29	17.3 (16.4-18.5)	16.5 (14.1-19.7)	1.05 (0.84-1.30) 0.69	1.02 (0.82-1.28) 0.85
Warfarin	69 (6.9)	22:23:24	17.3 (16.3-18.5)	17.3 (15.1-20.5)	1.04 (0.81-1.34) 0.76	1.01 (0.79-1.31) 0.91
'Parin'	57 (5.7)	21:17:19	17.5 (16.6-18.6)	15.1 (11.4-17.5)	0.13 (0.85-1.50) 0.41	1.14 (0.86-1.52) 0.36
Ascorbic acid	42 (4.2)	17:13:12	17.2 (16.3-18.4)	18.1 (15.1-22.8)	0.96 (0.69-1.34) 0.81	0.96 (0.69-1.34) 0.81
Selenium	24 (2.4)	9:6:9	17.3 (16.4-18.4)	19.7 (11.2-30.7)	0.87 (0.57-1.32) 0.51	0.91 (0.60-1.37) 0.64
Tocopherol	56 (5.6)	19:18:19	17.2 (16.3-18.4)	17.6 (14.6-28.4)	0.85 (0.63-1.13) 0.26	.87 (0.65-1.16) 0.33
Antidepressants	65 (6.5)	27:21:17	17.4 (16.6-18.7)	15.1 (11.3-17.7)	1.34 (1.03-1.74) 0.028	1.27 (0.97-1.64) 0.079
Epoetin	61 (6.1)	16:26:19	17.5 (16.6-18.7)	14.3 (12.3-17.3)	1.42 (1.09-1.85) 0.010	1.23 (0.94-1.61) 0.13
Aspirin	170 (16.9)	49:61:60	17.1 (16.2-18.6)	17.6 (15.5-19.2)	1.02 (0.85-1.21) 0.87	.01 (0.85-1.20) 0.91

CI: confidence interval; HR: hazard ratio; D3W: docetaxel 3 weekly; D1W: docetaxel weekly; M: mitoxantrone; PPI: proton pump inhibitors; † adjusted for treatment group, and stratified by baseline pain and baseline Karnofsky performance status.

tant to note that most preclinical (and clinical) data supporting the potential anti-cancer properties of most of the agents included in these studies were based on reports excluding combinations with chemotherapy; the current analysis, however, focused on the possibility of combined effects. Additionally, our analyses was restricted by the limited data on the pharmacokinetic interactions with docetaxel and the medications listed other than theoretical interactions with verapamil, diltiazem (inhibitors of CYP3A4), numerous SSRIs (selective serotonin reuptake inhibitors) (including citalopram, sertraline, which may compete for CYP 3A4) and some statins (atorvastatin, lovastatin and simvastatin, which may also compete for CYP3A4).

Finally, there are a number of limitations of secondary analyses, such as multiple hypothesis testing, patient comorbidities, and small numbers of patients taking individual drugs to the extent that we were unable to confidently exclude the effect of any concomitantly taken medication given the confidence intervals surrounding them. Future efforts may

concentrate on recent large clinical trials with patients at earlier stages of disease (and with fewer comorbidities), such as those with asymptomatic metastatic castrate refractory disease. These efforts will allow us to examine these issues in combination with either pharmacogenetic or physiological data to refine an hypothesis (e.g., does the presence of the insulin resistance syndrome portend a shorter response to hormonal therapies that can be reversed with metformin?).

## Conclusion

Our data are hypothesis-generating and contain a number of important clinical research negative findings, such as the lack of benefit of metformin and the potentially concerning data about verapamil. This data is the only one of its kind available for prostate cancer. Aside from some case-control analyses of breast cancer populations examining the use of SSRIs and tamoxifen,<sup>45-47</sup> there are no similar analyses in the literature for any malignancy. Therefore, our study provides

a basis for evaluating other trials for similar effects, which may reveal unanticipated findings that would warrant further research.

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This paper has been peer-reviewed.

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**Appendix 1. PSA-decline, a measure of the maximum fall of PSA from the starting value to its nadir**

Drug	Median (IQR) % PSA-shrinkage, no concomitant medications	Median (IQR) % PSA-shrinkage; concomitant medications	Wilcoxon RS <i>p</i> -value	Adjusted <i>p</i> -value <sup>†</sup>
Metformin	50.2 (-3.3, 85.9)	35.1 (-27.4, 83.3)	0.14	0.25/0.25
PPI	49.3 (-5.9, 85.9)	55.3 (3.8, 85.2)	0.52	0.76/0.67
Glyceryl	49.6 (-5.1, 85.5)	50.4 (14.6, 86.4)	0.84	0.70/0.68
Digoxin	49.5 (-4.3, 85.5)	55.1 (14.1, 86.5)	0.96	0.97/0.90
Verapamil	50.2 (-4.7, 85.5)	46.1 (9.4, 90.6)	0.57	0.29/0.25
'Statin'	49.6 (-5.4, 85.9)	49.7 (12.1, 76.1)	0.77	0.64/0.70
'Coxib'	49.2 (-6.7, 85.2)	53.5 (18.2, 88.3)	0.11	0.058/0.057
Warfarin	49.0 (-5.5, 85.3)	69.2 (20.3, 90.8)	0.047	0.035/0.034
'Parin'	49.3 (-5.6, 85.3)	72.6 (28.3, 88.3)	0.10	0.14/0.16
Ascorbic Acid	50.0 (-4.7, 85.9)	48.2 (0, 78.9)	0.58	0.86/0.85
Selenium	50.0 (-4.3, 85.9)	24.8 (-3.0, 82.0)	0.61	0.91/0.88
Tocopherol	49.6 (-4.8, 85.6)	54.4 (0, 82.0)	0.85	0.96/0.93
Antidepressants	50.4 (-4.3, 85.6)	45.3 (-3.0, 85.9)	0.70	0.73/0.74
Epoetin	49.6 (-5.4, 85.8)	55.1 (18.3, 80.9)	0.41	0.19/0.15
Aspirin	49.9 (-5.4, 85.6)	49.6 (7.5, 85.5)	0.82	0.38/0.42

<sup>†</sup> adjusted for treatment group / treatment group and baseline pain and baseline Karnofsky performance status; IQR: interquartile range; PSA: prostate-specific antigen; PPI: proton pump inhibitors; RS: rank sum.

**Appendix 2. Overall survival by treatment for concomitant medications significantly different overall**

	D3W			D1W			M		
	Median (95% CI)	HR (95% CI)	<i>p</i> -value	Median (95% CI)	HR (95% CI)	<i>p</i> -value	Median (95% CI)	HR (95% CI)	<i>p</i> -value
Digoxin	7.6 (2.6-17.1)	2.10	0.023	15.3 (6.1-25.6)	1.35	0.30	14.9 (9.6-19.2)	1.14	0.70
No Digoxin	19.1 (17.3-21.2)	1.11-3.96		17.4 (15.9-18.8)	0.77-2.36		15.8 (14.1-17.5)	0.59-2.22	
Verapamil	11.7 (6.1-19.8)	1.68	0.062	9.9 (6.1-21.3)	1.59	0.14	15.8 (8.0-20.0)	1.33	0.29
No Verapamil	19.1 (17.3-21.2)	0.97-2.89		17.6 (16.1-19.0)	0.86-2.93		15.8 (13.5-17.3)	0.79-2.26	

CI: confidence interval; HR: hazard ratio; D3W: docetaxel 3 weekly; D1W: docetaxel weekly; M: mitoxantrone.

**Appendix 3. PSA-response**

Drug	n (%) PSA-response	Unadjusted <i>p</i> -value	CMH <i>p</i> -value	Homogeneity of odds ratios
Metformin	10/31 (32%)	0.35	0.24	0.071
PPI	83/188 (44%)	0.40	0.69	0.89
Glyceryl	16/43 (37%)	0.64	0.54	0.94
Digoxin	12/30 (40%)	1.00	0.79	0.78
Verapamil	15/39 (38%)	0.74	0.81	0.24
'Statin'	21/63 (33%)	0.19	0.28	0.97
'Coxib'	40/89 (45%)	0.50	0.56	0.23
Warfarin	30/59 (51%)	0.13	0.12	0.16
'Parin'	22/46 (48%)	0.44	0.38	0.49
Ascorbic Acid	10/33 (30%)	0.21	0.18	0.83
Selenium	6/21 (29%)	0.27	0.25	0.36
Tocopherol	18/45 (40%)	0.88	0.93	0.43
Anti-Depressants	19/59 (32%)	0.17	0.095	0.82
Epoetin	23/54 (43%)	0.89	0.88	0.21
Aspirin	54/147 (37%)	0.23	0.22	0.90
All patients	362/873 (41.5%)	-	-	-

PPI: proton pump inhibitors; PSA: prostate-specific antigen; CMH: Cochran-Mantel-Haenszel test. \*No further analyses performed due to small numbers.

**Appendix 4. PSA-decline for warfarin/no warfarin patients, by treatment group**

	No warfarin		Warfarin		p-value
	N	Median (IQR)	N	Median (IQR)	
D3W	258	56.0 (-0.5, 87.6)	17	83.3 (62.5, 93.0)	0.047
D1W	239	68.1 (17.6, 89.1)	20	76.5 (41.1, 91.3)	0.35
M	265	23.9 (-17.2, 73.5)	21	29.2 (-7.2, 69.9)	0.52

PSA: prostate-specific antigen; D3W: docetaxel 3 weekly; D1W: docetaxel weekly; M: mitoxantrone; IQR: interquartile range.

**Appendix 5. Pain response**

Drug	n (%) pain-response	Unadjusted p-value	CMH p-value	Homogeneity of OR
Metformin	4/17 (23.5)	0.79	0.49	0.72
PPI	35/119 (29.4)	1.00	0.88	0.96
Glyceryl	9/25 (36.0)	0.50	0.50	0.37
Digoxin	3/17 (17.7)	0.42	0.24	0.037
Verapamil	7/23 (30.4)	1.00	0.93	0.71
'Statin'	7/35 (20.0)	0.25	0.20	0.42
'Coxib'	19/49 (38.8)	0.13	0.14	0.063
Warfarin	11/34 (32.4)	0.70	0.71	0.76
'Parin'	7/32 (21.9)	0.42	0.32	0.46
Ascorbic acid	3/20 (15.0)	0.21	0.15	0.41
Selenium	3/11 (27.3)	1.00	0.90	0.44
Tocopherol	7/26 (26.9)	1.00	0.72	0.042
Antidepressants	6/40 (15.0)	0.045	0.028	0.19
Epoetin	7/39 (18.0)	0.14	0.083	0.049
Aspirin	22/71 (31.0)	0.78	0.77	0.045
All patients	135/464 (29.1)			

PPI: proton pump inhibitors; CMH: Cochran-Mantel-Haenszel test; OR: odds ratio.

**Appendix 6. Pain-response rates by treatment group, based on non-homogenous OR or significance of OR**

	D3W		D1W		M	
	N (%)	p-value	N (%)	p-value	N (%)	p-value
Digoxin	0/7 (0.0)	0.096	3/6 (50.0)	0.38	0/4 (0.0)	0.58
No Digoxin	53/146 (36.3)		45/148 (30.4)		34/153 (22.2)	
Antidepressants	5/18 (27.8)	0.61	0/11 (0.0)	0.018	1/11 (9.1)	0.46
No antidepressants	48/135 (35.6)		48/143 (33.6)		33/146 (22.6)	
Tocopherol	6/11 (54.6)	0.19	0/8 (0.0)	0.058	1/7 (14.3)	1.00
No tocopherol	47/142 (33.1)		48/146 (32.9)		33/150 (22.0)	
Epoetin	0/12 (0.0)	0.009	6/18 (33.3)	0.79	1/9 (11.1)	0.68
No epoetin	53/141 (37.6)		42/136 (30.9)		33/148 (22.3)	

OR: odds ratio; D3W: docetaxel 3 weekly; D1W: docetaxel weekly; M: mitoxantrone.

**Appendix 7. Quality of life response**

Drug	n (%) QOL-response	Unadjusted p-value	CMH p-value	Homogeneity of OR
Metformin	11/34 (32.4)	0.074	0.074	0.31
PPI	39/184 (21.2)	0.53	0.74	0.21
Glyceryl	10/46 (21.7)	0.70	0.78	0.15
Digoxin	4/29 (13.8)	0.63	0.39	0.10
Verapamil	7/39 (18.0)	1.00	0.90	0.71
'Statin'	8/70 (11.4)	0.083	0.087	0.024
'Coxib'	25/88 (28.4)	0.032	0.031	0.49
Warfarin	10/60 (16.7)	0.73	0.59	0.085
'Parin'	5/49 (10.2)	0.097	0.078	0.42
Ascorbic acid	5/40 (12.5)	0.31	0.24	0.33
Selenium	3/21 (14.3)	0.78	0.58	0.25
Tocopherol	9/50 (18.0)	1.00	0.80	0.50
Antidepressants	12/48 (25.0)	0.35	0.48	0.32
Epoetin	8/51 (15.7)	0.59	0.42	0.72
Aspirin	23/147 (15.7)	0.21	0.20	0.14
All patients	159/815 (19.5)			

PPI: proton pump inhibitors; CMH: Cochran-Mantel-Haenszel test; OR: odds ratio.

**Appendix 8. Quality of life-response rates by treatment group, based on non-homogenous OR or significance of OR**

	D3W		D1W		M	
	N (%)	p-value	N (%)	p-value	N (%)	p-value
Statin	1/25 (4.0)	0.021	2/19 (10.5)	0.26	5/26 (19.2)	0.36
No statin	61/253 (24.1)		60/251 (23.9)		30/241 (12.5)	
Coxib	10/33 (30.3)	0.27	8/29 (27.6)	0.49	7/26 (26.9)	0.058
No coxib	52/245 (21.2)		54/241 (22.4)		28/241 (11.6)	

OR: odds ratio; D3W: docetaxel 3 weekly; D1W: docetaxel weekly; M: mitoxantrone.

**Appendix 9. Median number of cycles delivered and median weeks on chemotherapy, patients on concomitant medication**

	D3W	D1W	M	Median weeks
Metformin	6	4.5	7	20.6
'Prazole'	9	4	6	23.1
Glyceryl	6	4	5	15.9
Digoxin	3	4	7	16.1
Verapamil	4	4	4.5	11.1
Statin	7	5	5.5	18.1
'Coxib'	9	4.5	6	23.4
Warfarin	10	5	7	26.9
'Parin'	6	5	8	21.1
Ascorbic acid	6	5	6	19.4
Selenium	5	4	5	18.1
Tocopherol	6	4	6	18.1
Anti-depressants	10	5	6	24.1
Epoetin	10	4	7	24.1
Aspirin	9	4	7	21.1

D3W: docetaxel 3 weekly; D1W: docetaxel weekly; M: mitoxantrone.