Hypertension as a Predictive Marker for Bevacizumab in Metastatic Breast Cancer: Results from a Retrospective Matched-pair Analysis

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Abstract. *Background: Several phase-III studies have shown improvements in terms of progression-free survival (PFS) with bevacizumab when added to chemotherapy in advanced breast cancer. However, the extent of improvement varied and none of the trials showed benefit in terms of overall survival (OS). Patients and Methods: All patients with metastatic breast cancer treated with bevacizumab at our Institution between 2005 and 2011 were retrospectively analyzed. A control group was matched according to the following variables: receptor status, treatment line, type of chemotherapy, presence of visceral disease and age. Results: All 212 patients were evaluable for toxicity, and 198 for response; 430 controls allowed a complete matching for 85 bevacizumab-treated patients. The addition of bevacizumab to chemotherapy significantly prolonged PFS (9.3 vs. 7.6 months, hazard ratio [HR]=0.70, 95% confidence interval [CI]=0.51-0.97, p=0.031) and OS (28.9 vs. 22.6 months, HR=0.67, 95% CI=0.45-0.99, p=0.043). Clinical benefit rate (overall response rate + stable disease for at least six months) was significantly better in the bevacizumab group (75% vs. 59%, p=0.002), while ORR did not differ significantly (48% vs. 35%, p=0.21). Patients developing hypertension during treatment had a more favourable outcome (PFS 13.7 vs. 6.6 months, HR=0.34, 95% CI=0.23-0.49 p<0.001; 2-year OS 78% vs. 30%, HR=0.20, 95% CI=0.12-0.35, p<0.001). Conclusion: Bevacizumab in addition to chemotherapy prolonged PFS and OS in a non-selected, partly intensively pre-treated breast cancer population. Hypertension induced by bevacizumab predicted therapy efficacy.*

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For human epidermal growth factor receptor-2 (HER2)-negative metastatic breast cancer (MBC), bevacizumab in combination with paclitaxel or capecitabine is an European Medicines Agency (EMA)-approved treatment option. Several phase III trials demonstrated an improvement in terms of progression-free survival (PFS) when bevacizumab was added to standard chemotherapy. On the downside, the grade 3/4 toxicity rate was increased and no benefit in terms of overall survival (OS) was observed (E2100, AVADO, RIBBON-1/2, and AVEREL) (2, 7, 11, 13, 21). In consequence, in November 2011, the Food and Drug Administration of the US (FDA) decided to withdraw accelerated approval for bevacizumab as first-line treatment for MBC. Interestingly, in European countries such as Austria, a significant decline in bevacizumab prescriptions for MBC also became evident thereafter (19).

To reduce the number needed to treat in order to determine therapy benefits and effects, predictive markers for bevacizumab efficacy are urgently required. Clinical characteristics such as hormone receptor and HER2 status fail to identify patients deriving the most substantial

benefit, as the relative treatment effect is similar in all subgroups. Of the various biomarkers evaluated, only a high baseline vascular endothelial growth factor A (VEGFA) level seems to predict clinical benefit in MBC, but the level of evidence is low (7, 12). Data on the predictive value of single-nucleotide polymorphisms (SNPs) of *VEGF* or *VEGFR1/2* are inconsistent. Two SNPs in *VEGFA* (−2578 and −1154) correlated with OS in E2100 (23), but not in AVADO and in the ATHENA observational trial (6, 12). Furthermore, predictive markers seem to vary in different tumour entities. In pancreatic and renal cell cancer, only the rs9582036-A allele for *VEGFR1* predicted for bevacizumab activity (9). Interestingly, several retrospective evaluations suggest a positive correlation between treatment-induced hypertension and response to bevacizumab (4, 14, 18, 20, 22, 23).

We conducted a retrospective analysis of patients with MBC treated at a single centre in order to clarify the role of bevacizumab-based chemoimmunotherapy in a real-world scenario. In addition, we set out to analyze clinical and biological risk factors predicting response to the drug.

Patients and Methods

Study population. A retrospective analysis of all patients with locally advanced inoperable or MBC receiving bevacizumab-plus-chemotherapy between August 2005 and October 2011 at the Third Medical Department, Salzburg Cancer Research Institute of the Paracelsus Medical University Salzburg (Austria) was performed.

A control group was matched according to the following variables: receptor status ($HR^+/HER2^-$, $HER2^+$, and $HR^-/HER2^-$), treatment line (first-line, second-line, and third-line or greater), chemotherapy agent (paclitaxel, docetaxel, capecitabine, and taxane plus trastuzumab), visceral or non-visceral disease, and age (<50, 50-69, ≥70 years).

To increase the number of controls, patients treated at the Clinical Division of Oncology, Department of Medicine I, Medical University of Vienna, Austria, were also included.

Key inclusion criteria for both groups were histologically-confirmed adenocarcinoma of the breast, locally advanced inoperable or metastatic tumour stage, Eastern Cooperative Oncology Group (ECOG) performance status 0-3, and sufficiently documented source data. In the control group, no bevacizumab treatment was allowed prior to the matched line of therapy. All patients with at least three administrations of bevacizumab or control chemotherapy were included in the efficacy analysis.

The protocol and a sample of a written informed consent was submitted to the Ethics Committee of the Medical University Salzburg, which confirmed that this study does not fulfil the criteria of a clinical trial according to the Pharmaceutical Law or the Medicinal Devices Law and does not represent a new medical method according to the Hospital Law of Salzburg. Therefore, the Ethics Committee of the Medical University Salzburg approved the study and attested that no detailed appraisal was required and no written or verbal informed consent was needed (approval number: 415-EP/73/67-2011). The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

Treatment. Bevacizumab was administered in combination with chemotherapy at the following doses: 7.5 mg/kg or 15 mg/kg every three weeks or 10 mg/kg every two weeks. After stopping chemotherapy, bevacizumab maintenance therapy was allowed. Treatment was continued until disease progression, unacceptable toxicity, or patient's decision. Evaluation of therapy response was carried out by computed tomography (CT) or positron emission tomography (PET)-CT scan or by other imaging techniques if indicated, every 2-4 months, or at any time clinical signs of progression were present.

Blood pressure. Inclusion criterion for evaluation of hypertension was one or more available blood pressure values for at least 50% of all cycles. Due to the limited number of measurements, a very strict definition of hypertension was chosen: (i) increase of systolic blood pressure ≥40 mmHg or diastolic blood pressure ≥20 mmHg during the treatment period compared to baseline leading to values >140/90 mmHg; (ii) increase of systolic pressure ≥30 mmHg during bevacizumab infusion; or (iii) start or extension of anti-hypertensive medication.

Safety and efficacy. Toxic effects were graded according to the Common Terminology Criteria for Adverse Events (CTCEA) v4.0 (1). Grade 1 to 3 side-effects were recorded only if thought to be associated with bevacizumab. Other adverse events were reported only if exceeding grade 3. Assessment of toxicity was exclusively carried out within the bevacizumab group. Disease status was assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 (5).

End-points. The primary end-point of this evaluation was PFS, defined as time from treatment initiation until progression or death from any cause. Secondary end-points were OS, overall response rate (ORR), clinical benefit rate (CBR=complete response + partial response + stable disease for at least six months), and bevacizumab-induced toxicity.

Statistical methods. Differences in the baseline characteristics between the two study arms were examined by chi-square test, *t*-test or Wilcoxon Mann-Whitney *U*-test as appropriate. Differences in response rates were also assessed with chi-square testing and relative risk (RR) measures were calculated, together with their 95% confidence intervals (CI). Unadjusted, univariate survival probabilities of PFS and OS were calculated by the Kaplan–Meier method and compared by the log-rank test. In addition, the Cox proportional hazards regression model with all influential covariates was used to estimate adjusted, multivariate hazard ratios (HR) and their 95% confidence intervals. The significance level for all analyses was α=0.05. All *p*-values are two-sided. All analyses were performed with IBM SPSS software version 20, IBM Software Group, Chicago, IL, USA.

Results

A total of 212 patients fulfilled the inclusion criteria. All patients were evaluable for toxicity, 198 for response, and 147 for response and blood pressure evaluation; 430 potential controls allowed a complete matching for 85 patients (Figure 1).

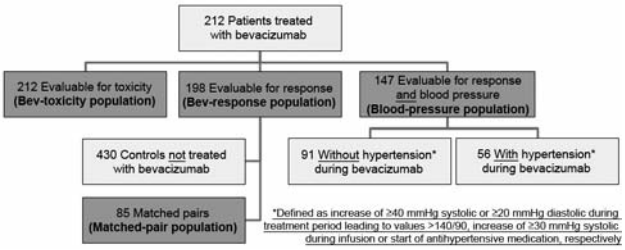

Figure 1. *Analysis populations*.

Matched pair analysis. Major characteristics of the matched-pair population (n=170) are shown in Table I. Notably, in 35 patients (41%) of the control group, the matched chemotherapy backbone was combined with a second chemotherapy agent, such as epirubicin or gemcitabine.

The addition of bevacizumab to chemotherapy significantly prolonged PFS from 7.6 to 9.3 months (HR=0.70, 95% CI=0.51-0.97, p=0.031) and OS from 22.6 to 28.9 months (HR=0.67, 95% CI=0.45-0.99, p=0.043; Figure 2). CBR was significantly higher in the bevacizumab group (75% *vs*. 59%, p=0.002, RR=1.28, 95% CI=1.02-1.59), while ORR did not differ significantly (48 *vs*. 35%, p=0.21, RR=1.25, 95% CI=0.85-1.86; (Table II). In patients receiving first-line therapy only (n=108), PFS was 10.8 and 8.0 months (HR=0.63, 95% CI=0.42-0.95, p=0.027) and OS was 34.8 and 25.6 months (HR=0.67, 95% CI=0.40-1.12, p=0.121), respectively.

To analyze the impact of potential prognostic factors on PFS and OS, we conducted a Cox regression model considering the following covariates: age, DFS, ECOG PS, histology, grade, receptor status, type of metastases, adjuvant therapy, line of treatment, and chemotherapy backbone. For both PFS and OS, the group difference assessed at univariate analysis with the log-rank test lost significance in the fully-adjusted multivariate model (PFS: HR=0.78 95% CI, 0.55-1.12, p=0.18; OS: HR=0.80, 95% CI, 0.52-1.24, p=0.31). However, hazard ratios did not change considerably indicating that the loss of significance is primarily due to a limited sample size.

We found no significant difference in PFS between different chemotherapy backbones, except for the addition of trastuzumab (PFS 7.9 months for paclitaxel, 8.0 months for docetaxel, 7.3 months for capecitabine, and 16.0 months for trastuzumab in combination with taxanes; p=0.005).

Hypertension as a predictive marker. Out of all patients evaluable for response and blood pressure (blood-pressure population, n=147), 56 patients (38%) developed hypertension while on bevacizumab treatment. These patients had a more favourable outcome (PFS 13.7 *vs*. 6.6 months, HR=0.34, 95% CI=0.23-0.49 p<0.001; OS NR *vs*. 18.4 months, HR=0.20, 95% CI=0.12-0.35, p<0.001). After a median follow-up of 20 months (range 2-65 months) the median OS in the bevacizumab group was not reached. The one- and two-year

Table I. *Patients' characteristics (matched-pair population, n=170).*

	Control (n=85)		Bevacizumab (n=85)		*p*-Value
Median age (range), years *	61	(39-86)	61	(29-79)	0.725
Median DFS (months)					
≤24	12	(14%)	15	(17%)	
>24	52	(61%)	41	(48%)	
M1 at diagnosis	21	(25%)	29	(34%)	0.233
ECOG PS					
0-1	72	(85%)	82	(97%)	
2-4 + unknown	13	(15%)	3	(3%)	0.009
Histology					
Ductal	59	(69%)	58	(69%)	
Lobular	16	(19%)	19	(22%)	
Other + unknown	10	(12%)	8	(9%)	0.784
Grade					
1	2	(2%)	2	(2%)	
2	52	(61%)	54	(64%)	
3	26	(31%)	25	(29%)	
Unknown	5	(6%)	4	(5%)	0.983
Receptor status*§					
$HR^+/HER2^-$/G1-2	44	(50%)	44	(50%)	
$HR^+/HER2^-$/G3	12	(14%)	15	(17%)	
$HR^+/HER2^+$	5	(6%)	3	(3%)	
$HR^-/HER2^+$	4	(5%)	6	(7%)	
triple negative	18	(21%)	17	(19%)	
$HR^+/HER2^-$/G unknown	5	(6%)	3	(3%)	0.881
Metastases*					
Visceral	60	(68%)	60	(68%)	
Non-visceral	28	(32%)	28	(32%)	1.000
Adjuvant therapy					
Anthracycline	17	(19%)	8	(9%)	
Taxane	2	(2%)	0	(0%)	
Anthracycline- and taxane	4	(4%)	22	(25%)	
Non	36	(42%)	16	(19%)	
M1 at diagnosis	21	(25%)	29	(34%)	0.001
Line of treatment*					
First-line	54	(64%)	54	(64%)	
Second-line	11	(13%)	11	(13%)	
Third-line	12	(14%)	11	(13%)	
Fourth-line or more	8	(9%)	9	(20%)	0.992
Chemotherapy backbone*					
Paclitaxel	40	(47%)	40	(47%)	
Docetaxel	10	(12%)	10	(12%)	
Capecitabine	29	(34%)	29	(34%)	
Taxane + trastuzumab	6	(7%)	6	(7%)	1.000
Second chemotherapy backbone					
Epirubicin	20	(24%)	0	(0%)	
Gemcitabine	6	(7%)	0	(0%)	
Capecitabine	3	(4%)	0	(0%)	
Other	6	(7%)	0	(0%)	0.001

*Matching criteria. §For matching,the following criteria were used: $HR^+/HER2^-$, $HER2^+$, triple negative. DFS, disease-free survival; ECOG PS, M1; metastatic disease; Eastern Cooperative Oncology Group Performance Score; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; G1-3, grading.

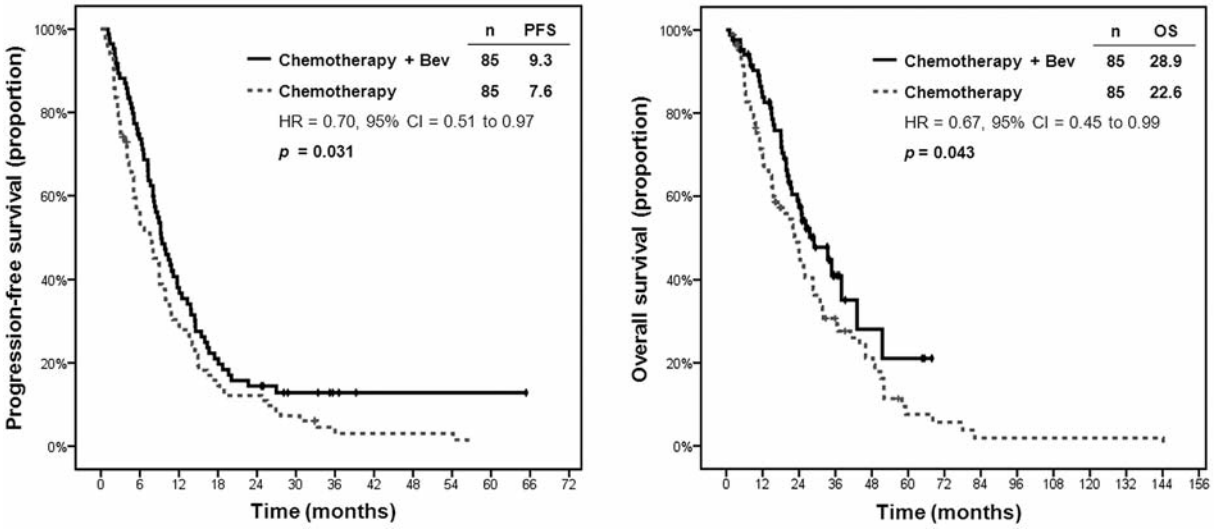

Figure 2. *Progression-free and overall survival according to treatment group (matched-pair population, n=170).*

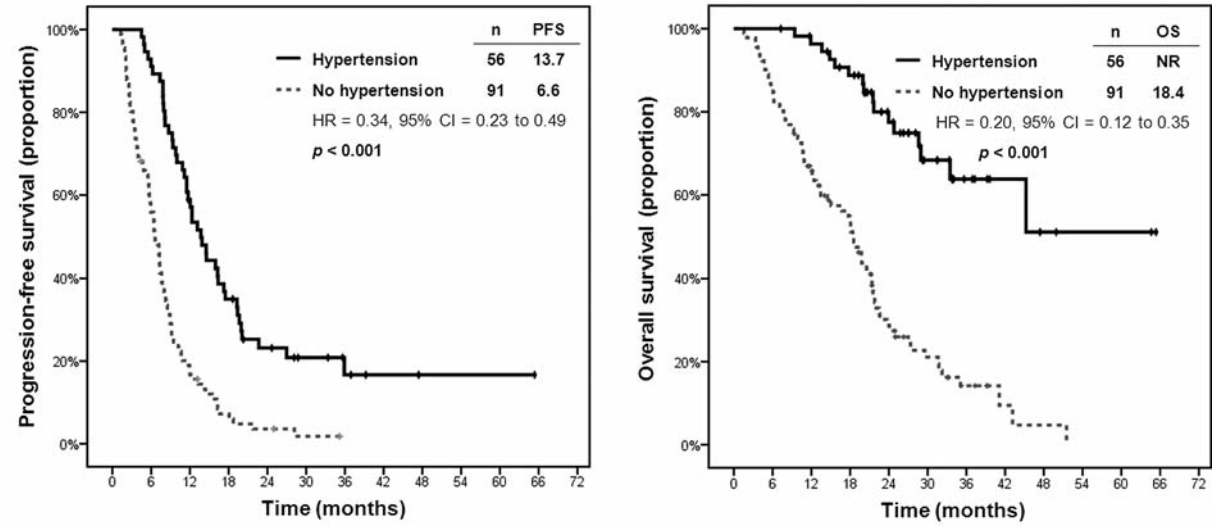

Figure 3. *Progression-free and overall survival according to hypertension (blood pressure population, n=147).*

survival rates were 96% *vs*. 65% ($p<0.001$) and 78% *vs*. 30% ($p<0.001$), respectively. In the matched-pair population this effect was reproducible, showing that only patients with treatment-induced hypertension benefit from the addition of bevacizumab to conventional chemotherapy (PFS with hypertension 16.0 months, without hypertension 7.3 months, matched controls 6.7 months; $p=0.001$; Figure 4). In the multivariate analysis hypertension was an independent predictor of PFS (HR=0.42, 95% CI=0.27-0.64, $p<0.001$) and OS (HR=0.24, 95% CI=0.13-0.44, $p<0.001$). CBR in the population for which blood pressure values were available was also superior whenever hypertension was diagnosed (95% *vs*. 62%, RR=1.54, 95% CI=1.28-1.67, $p<0.001$). The median time until occurrence of hypertension was 2.8 months.

Toxicity. The most common grade 3/4 toxicities related to bevacizumab were hypertension (26%), thromboembolism (5%), bleeding events (2%) and proteinuria (1%). No case of grade 4 hypertension was observed. One case of myocardial infarction, 2 cases of congestive heart failure and one case

Table II. *Response according to RECIST 1.1 (matched-pair population, n=170).*

	Control (n=85)		Bevacizumab (n=85)		Relative risk	*p*-Value
CR	1	(1%)	8	(9%)		
PR	29	(34%)	33	(39%)		
ORR (CR+PR)	30	(35%)	41	(48%)	1.25 (95% CI=0.85-1.86)	0.210
SD ≥6 months	20	(24%)	23	(27%)		
CBR (ORR+SD≥6 months)	50	(59%)	64	(75%)	1.28 (95% CI=1.02-1.59)	0.002
SD <6 months	9	(11%)	9	(11%)		
PD	25	(29%)	12	(14%)		
NA	1	(1%)	0	(0%)		

RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; ORR, overall response rate; SD, stable disease; PD, progressive disease; NA, not available; CI, confidence interval.

Table III. *Toxicity according to CTCAE version 4.0 (bevacizumab-toxicity population, n=212).*

	All grades		Grade 1		Grade 2		Grade 3		Grade 4	
Hypertension*	107	(50.5%)	13	(6.1%)	38	(17.9%)	56	(26.4%)	0	-
Proteinuria	14	(6.6%)	4	(1.9%)	8	(3.8%)	2	(0.9%)	-	-
Bleeding event	25	(11.8%)	21	(9.9%)	-	-	4	(1.9%)	-	-
Thromboembolism	16	(7.5%)	1	(0.5%)	3	(1.4%)	10	(4.7%)	2	(0.9%)
GI perforation	1**	(0.5%)	-	-	-	-	1*	(0.5%)	-	-
Anaphylaxis	-	-	-	-	-	-	-	-	-	-
Congestive heart failure	2	(0.9%)	-	-	-	-	2	(0.9%)	-	-
Myocardial infarction	1	(0.5%)	-	-	-	-	1	(0.5%)	-	-
Sepsis	1	(0.5%)	-	-	-	-	-	-	1	(0.5%)
Renal failure	1	(0.5%)	-	-	-	-	1	(0.5%)	-	-

*Grade 1: >120/90 mmHg; Grade 2: >140/90 mmHg or increase ≥20 mmHg diastolic or increase of ≥30 mmHg systolic during infusion or start of antihypertensive medication; Grade 3: >160/100 or start of second antihypertensive medication; Grade 4: >230/130 mmHg. **Patient with bowel metastasis. CTCAE, Common Terminology Criteria for Adverse Events.

of acute renal failure occurred. In one patient with bowel metastases a gastrointestinal perforation was recorded. Detailed toxicity information is shown in Table III.

Discussion

In this matched-pair analysis, the addition of bevacizumab to chemotherapy significantly prolonged PFS and OS. These results are in contrast to published phase III trials, in which despite a prolongation of PFS, no statistically significant difference in median OS was seen (2, 7, 11, 13, 21). Because post-progression survival is influenced by subsequent therapies and crossover, OS may not be an adequate end-point in MBC trials. Notably, in the AVADO and RIBBON-1 trials, crossover was frequent (40% and 60%, respectively), while the rate in our analysis was only 15%.

Concerning first-line treatment, our results (PFS 10.6 *vs*. 8.0 months) are comparable to those of the AVADO trial, where PFS was 10.1 months and 8.2 months in the bevacizumab- and docetaxel-only group, respectively (11).

Considering the chemotherapy backbone our study revealed no difference in terms of PFS between paclitaxel and capecitabine, the EMA-approved combination partners for bevacizumab in MBC (7.9 *vs*. 7.3 months, p=0.721). Again, these data are in contrast to the results of the TURANDOT trial, where the combination of paclitaxel with bevacizumab showed better PFS than capecitabine-plus-bevacizumab (11.0 *vs*. 8.1 months, p=0.0052) (10).

Importantly, this retrospective analysis suggests a strong predictive value of hypertension for bevacizumab effectiveness (Figure 3). Hypertension is a well-known side-effect of anti-VEGF therapy and occurs at grade 3 in about 10% of patients with MBC (3). The underlying mechanism is not completely understood, but several models are discussed. Activation of VEGFR2 by VEGF induces nitric oxide (NO) synthase in endothelial cells, leading to higher levels of vasodilatory NO (17). Additionally, the production of prostacycline (prostaglandin I2, PGI2) is increased by activation of COX-1 and PGI2 synthase after heterodimerisation of VEGFR1 and 2 (16). Blocking VEGF signaling therefore reduces the

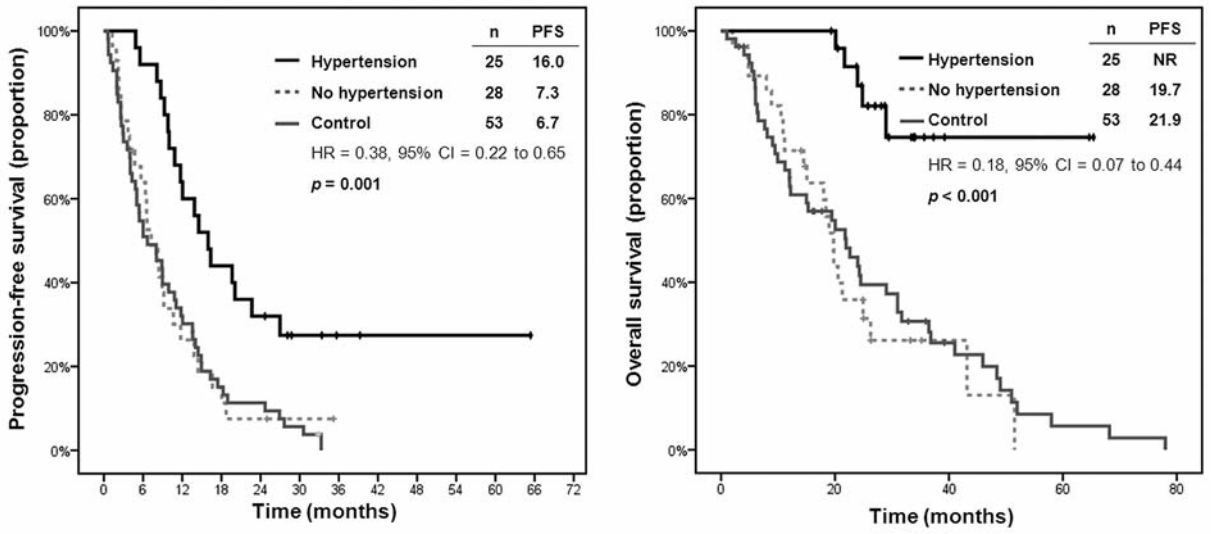

Figure 4. *Progression-free and overall survival according to hypertension (matched-pair population, n=170).*

expression of NO and PGI2, leading to vasoconstriction and hypertension. Further pathophysiological mechanisms may involve the loss of parallel capillary circulation in non-tumour tissues, increase of endothelin-1 and aortic stiffness (15, 25).

Similarly to our study, the E2100 trial reported superior outcomes in terms of OS in patients with grade 3/4 hypertension (39 *vs*. 25 months, p=0.002) (23). The same phenomenon was observed in colorectal (4, 14, 18, 22), renal cell (20), non-small cell lung, and ovarian (14) cancer. In contrast, the RIBBON-1 trial revealed only a trend towards better OS (HR=0.62, p=0.0505), while in the AVADO trial, hypertension was not predictive at all (HR=0.72, p=0.28) (8). Furthermore, the ATHENA trial, evaluating 2,264 patients receiving first-line bevacizumab-containing therapy in routine oncology practice, detected no relationship between hypertension and OS (24).

In order to exclude a bias caused by hypertension as a potential late event occurring only in patients remaining on bevacizumab for a long period of time, time-until-onset of hypertension is of great importance. In our evaluation, this time frame was 2.7 months, making that kind of bias unlike. Due to the retrospective design, blood pressure measurements were available on treatment days only. Therefore, an even earlier onset could not be detected. In an observational trial, home-based measurements detected significantly higher rates of early hypertension than in-clinic assessments (14).

Establishing predictive markers for bevacizumab is of urgent need. These data should be confirmed in a prospective trial in order to determine whether hypertension can be used as a simple biologic biomarker for bevacizumab efficacy. However, bevacizumab appears to be a relevant addition to conventional chemotherapy in patients with MBC.

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