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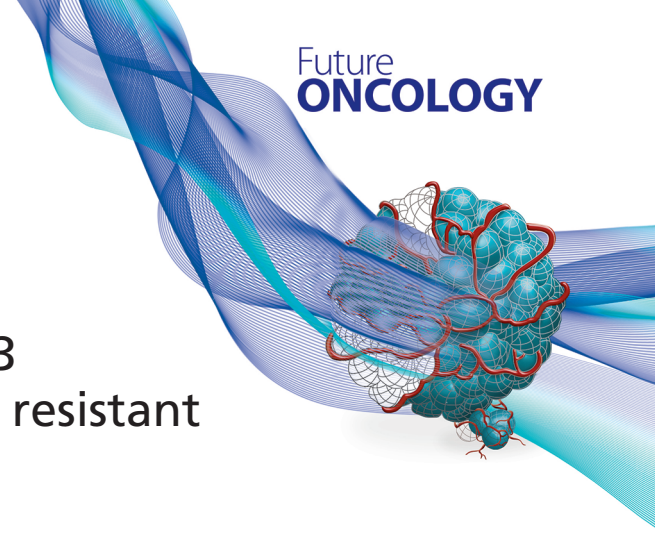

Real-world outcomes of radium-223 dichloride for metastatic castration resistant prostate cancer

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Aim: Timing of radium-223 (Ra-223) in metastatic castration-resistant prostate cancer (mCRPC) remains challenging due to alternative options and short window of opportunity. **Methods**: Ra-223 treated patients in the CAPRI-registry were included. Outcomes were evaluated based on treatment line of Ra-223. **Results:** Out of 285 patients, 49% received Ra-223 in line ≥3. 51% completed six Ra-223 injections and 34% had a symptomatic skeletal event after first Ra-223 without differences between subgroups. After correction of known prognostic factors Ra-223 in line ≥3 (HR: 3.267; 95% CI: 1.689–6.317; $p < 0.01$) remained associated with worse OS. **Conclusion**: In the Netherlands, Ra-223 was mainly started as second or third mCRPC-treatment in 2014–2018. Later timing of Ra-223 did affect OS, but not treatment completion and occurrence of symptomatic skeletal events.

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Keywords: metastatic castration-resistant prostate cancer • radium-223 • real-world outcomes • sequencing • skeletal-related events • survival

The management of metastatic castration-resistant prostate cancer (mCRPC) is palliative, but in recent years several new life-prolonging drugs (LPDs) have been developed, including taxane chemotherapy (docetaxel and cabazitaxel), AR-targeting therapies (abiraterone acetate plus prednisone and enzalutamide), and a targeted alpha-emitting isotope (radium-223 dichloride, Ra-223) [1,2].

Ra-223 has been registered for the treatment of mCRPC patients with symptomatic bone metastases, limited lymph node metastases and no visceral metastases since February 2014, based on the Phase III ALSYMPCA

trial [3]. An increased overall survival (OS) of Ra-223 compared with placebo has been established in both docetaxel pre-treated (median OS 14.4 months) and docetaxel untreated (median OS 16.1 months) patients [4]. Ra-223 also improved quality of life and reduced the risk of symptomatic skeletal event (SSEs) [5,6].

Optimal patient selection and timing of treatment for the best possible treatment in mCRPC is challenging with multiple treatment options available [7]. In general, there is a lack of prospective comparative data and data on sequencing of LPDs in mCRPC leading to unrestricted sequences. Recently in July 2018, after our database lock (in December 2017), the European Medicines Agency (EMA) has recommended restricting the use of Ra-223 to patients who received two prior systemic lines for mCRPC or to patients ineligible for other systemic treatments which is the only definitive restriction for sequencing in mCRPC patients [8]. However, especially for Ra-223 optimal timing of treatment is important, due to the short window of opportunity. After the occurrence of extensive nodal metastases or visceral disease, often later in the disease stage, patients are ineligible for Ra-223 [9].

Adequate monitoring of treatment efficacy in mCRPC should be based on a combination of PSA changes, clinical and radiological parameters [10,11]. Since Ra-223 is an isotope targeting bone metastases, monitoring is different from other LPDs due to the lack of reliability for PSA-changes as a marker of disease progression [12]. It has therefore been recommended to combine PSA changes with ALP and LDH changes in order to determine efficacy [11].

Results on treatment efficacy from randomized controlled trials are not easily translated to daily practice due to patient selection [13]. Therefore, real-world evidence on sequencing and outcomes is becoming more and more important. The aim of this study was to evaluate outcomes of Ra-223 treatment in a real-world setting in the Netherlands. We provide data on the use and experience with Ra-223 in a contemporary mCRPC cohort, treated prior to EMA restrictions.

Patients & methods

Study design & setting

CAstration-resistant Prostate cancer RegIstry (CAPRI) is an investigator-initiated, observational multicenter cohort study in 20 Dutch hospitals (11 large teaching hospitals, 5 general hospitals and 4 academic hospitals). The study design has been described before [14]. The study was approved by a central medical ethics committee and hospital board before the start of inclusion. Patients diagnosed with CRPC were included retrospectively from 1 January 2010 until 31 December 2015. CRPC was either defined by the criteria set by the European Association of Urology (EAU) [15] or defined by the treating physician. All data has been regularly updated for all patients until 31 December 2017. The study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

Participants

mCRPC patients that were treated with Ra-223 monotherapy during follow-up were included in this analysis. Outcomes were evaluated based on the position of Ra-223 in the treatment sequence: line 1 (no prior systemic treatment with docetaxel [DOC] and androgen-receptor targeting therapies [ART], i.e. abiraterone acetate plus prednisone or enzalutamide), line 2 (prior systemic treatment with one line of DOC or ART), and line ≥3 (prior systemic treatment with two or more systemic treatments).

Patients treated with DOC or ART for hormone-sensitive metastatic prostate cancer were excluded from the analysis.

Follow-up & data collection

Predefined and readily available data from medical records were retrospectively collected by trained data managers. Baseline characteristics were included in the analysis if they were documented six weeks prior to one week after the start of Ra-223. All patients were followed until death, lost-to-follow-up or 31 December 2017. Follow-up duration was calculated as time from first Ra-223 injection to last recorded date.

Outcomes

Primary outcomes were treatment duration, occurrence of SSEs and OS. Treatment duration was calculated as the number of Ra-223 injections. Reason for discontinuation included PSA, radiological and clinical progression and was collected retrospectively without protocol mandated progression assessment. Registration did not include ALP and LDH progression as reason for discontinuation. SSEs were defined as either radiotherapy to the bone, surgery to the bone, spinal cord compression and pathological fractures. SSE analyses included only patients with structured

SSE registration, which was performed from 2016 onward. All SSEs were clinically apparent and occurred after first Ra-223 injection to end of follow-up. Time to SSE was calculated as time in months from first Ra-223 injection to SSE and SSE-free survival as time to SSE or death. OS was measured as time in months from first Ra-223 injection to time of death from any cause. Patients alive or lost-to-follow-up at the end of study were censored at last recorded date.

Secondary outcomes were biochemical responses and serious adverse events (SAE). Biochemical responses (i.e., PSA and ALP) were calculated as maximum change in PSA and ALP up to 4 weeks after last Ra-223 injection and change per Ra-223 injection. Responses were not confirmed by a second value. Patients who did not finish Ra-223 treatment at end of follow-up (either due to early discontinuation or maximum of six injections), were excluded from biochemical response analyses. SAE were defined as hospital admission during Ra-223 treatment or within 30 days after last Ra-223 injection. Hematologic events were calculated as anemia grade 2 or higher (hemoglobin <6.2 mmol/l), thrombocytopenia grade 2 or higher (platelets $<75 \times 10^9$/l), and the need of blood transfusion during this time period. Other hematologic events as leukopenia or neutropenia were not evaluable. No distinction between SAE or hematologic events related to Ra-223 treatment, to underlying disease or to other conditions could be made.

Statistical analysis

Descriptive statistics were performed. To test significance between subgroups, χ^2 tests were used for categorical variables and Kruskall-Wallis and ANOVA for nonparametric continuous, and parametric continuous variables, respectively. Kaplan-Meier analysis was used to estimate OS, with log-rank test to test for differences between subgroups. Missing baseline characteristics were imputed using multiple imputations with Monte Carlo Markov Chain method. Binary logistic regression and Cox-proportional hazard analysis were performed on pooled data after multiple imputation for treatment completion and OS respectively. A p-value of 0.05 or less was considered statistically significant. IBM SPSS Statistics version 24.0 (IBM ®, NY, USA) was used for all analyses.

Results

At the end of the study, 3616 CRPC-patients were included in 20 hospitals. 14 patients were excluded due to docetaxel-treatment in hormone sensitive prostate cancer. In total, 285 patients (8%) treated with Ra-223 were included in this analysis.

Median follow-up from Ra-223 was 8.5 months (range 0.2–44.7 months). At the end of study, 161 deaths (57%) had occurred, 63 patients (22%) were lost to follow-up and 61 patients (21%) were still on follow-up with a median follow-up period from start of Ra-223 of 10.5 months (range 1.3–44.7 months).

Treatment sequence

29 patients (10%) were treated with Ra-223 as first line and 106 patients (37%) with Ra-223 as second line: 22 patients (8%) after DOC and 84 patients (29%) after ART. Overall, 150 patients (49%) were treated with Ra-223 in line ≥3: 92 patients (32%) in line 3 and 63 patients (22%) in line ≥4. Seven patients (2%) were retreated with Ra-223 (Supplementary Figure 1).

Baseline characteristics

Baseline characteristics of patients at start of Ra-223 are shown in Table 1. Patients treated with Ra-223 in line ≥3 were younger (median 72 vs 76 and 76 years; $p < 0.01$) and had lower hemoglobin (Hb; median 7.4 vs 8.1 and 7.8 mmol/l; $p = 0.02$) than patients treated with Ra-223 in line 1 and 2.

Bone health agents (i.e., bisphosphonates or denosumab) were given prior to or during Ra-223 in 16 patients in line 1 (55%), in 67 patients (63%) in line 2 and in 120 patients (80%) in line ≥3 ($p < 0.01$).

Biochemical response

In total, 267 patients had ended Ra-223 treatment at the end of follow-up and were included in response analyses (Figure 1). Eight patients (4%) had a ≥50% PSA decline and 122 patients (58%) had a ≥30% ALP decline during follow-up. Maximum ALP response during treatment was less in Ra-223 in line ≥3 (-34%) compared with line 1 and 2 (-48% and -39%, respectively; $p = 0.05$; Table 2).

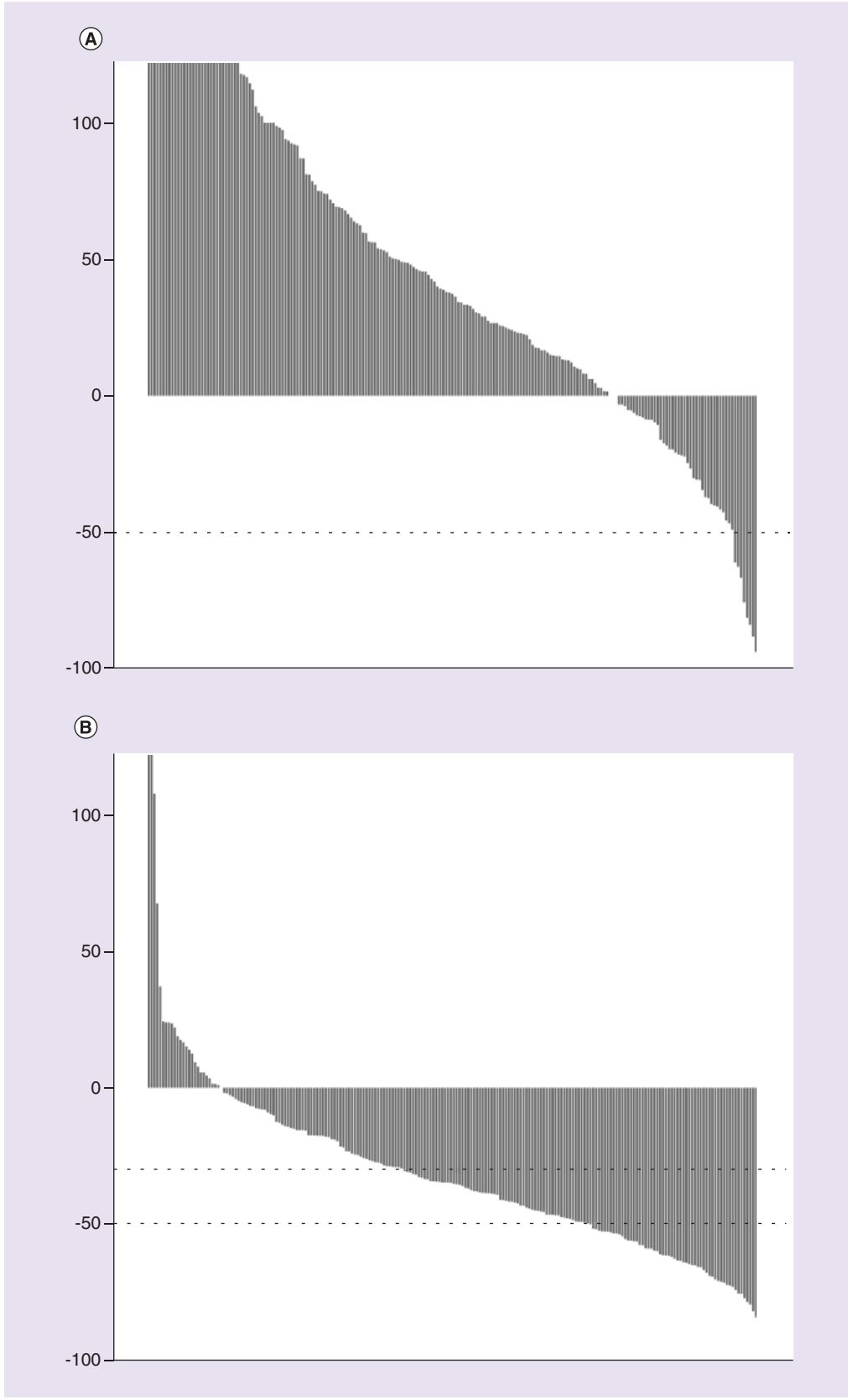

Figure 1. Waterfall plots of maximum percentage change from baseline up to end of treatment during radium-223 for PSA and ALP. Dotted lines indicate the threshold of ≥50% PSA decline **(1A)** and ≥30% and ≥50% ALP decline **(1B)**.

Table 1. Baseline characteristics at the start of radium-223.

Characteristics	Ra-223			p-value
	Line 1 (n = 29)	Line 2 (n = 106)	Line ≥3 (n = 150)	
Age (years), median	76	76	72	0.00
Range	58–80	51–92	54–89	
≥75 years, n (%)	16 (55)	62 (59)	52 (35)	
Charlson score, n (%):				0.822
– 6	21 (72)	68 (64)	93 (62)	
– 7–8	7 (24)	33 (31)	44 (29)	
– 9–10	1 (3)	4 (4)	11 (7)	
– >10	0 (0)	1 (1)	2 (1)	
– Missing	0 (0)	0 (0)	0 (0)	
ECOG performance status, n (%):				0.760
– 0	7 (24)	22 (21)	27 (18)	
– 1	12 (41)	52 (49)	71 (47)	
– ≥2	5 (17)	11 (10)	21 (14)	
– Missing	5 (17)	21 (20)	31 (21)	
Lymph node involvement, n (%):				0.990
– Yes	7 (24)	22 (21)	29 (19)	
– No	18 (62)	60 (57)	76 (51)	
– Missing	4 (14)	24 (23)	45 (30)	
Visceral disease, n (%):				0.549
– Yes	0 (0)	4 (4)	5 (3)	
– No	25 (86)	84 (79)	103 (69)	
– Missing	4 (14)	18 (17)	42 (28)	
Opioid use, n (%):				0.196
– Yes	7 (24)	16 (15)	38 (25)	
– No	12 (41)	39 (37)	48 (32)	
– Missing	10 (35)	51 (48)	64 (43)	
Time castration to mCRPC (months), median	15.6	16.9	12.6	0.239
IQR	7–29	10–29	8–22	
Period mCRPC to Ra-223 (months), median	12.6	25.8	34.0	<0.001*
IQR	5–42	18–36	21–46	
Hb (mmol/l), median	8.1	7.8	7.4	0.016*
IQR	7.4–8.6	7.0–8.3	6.6–8.2	
Missing, n (%)	4 (14)	10 (9)	15 (10)	
ALP (U/l), median	157	140	153	0.480
IQR	106–273	80–227	93–276	
Missing, n (%)	6 (21)	11 (10)	22 (15)	
LDH (U/l), median	233	240	248	0.517
IQR	202–309	205–277	197–335	
Missing, n (%)	11 (38)	37 (35)	46 (31)	
PSA (µg/l), median	141	84	155	0.006*
IQR	46–261	39–205	60–456	
Missing, n (%)	7 (24)	11 (10)	19 (13)	

† Significant at $p < 0.05$. Percentages may exceed 100% due to rounding.
ECOG: Eastern Cooperative Oncology Group; Hb: Hemoglobin; IQR: Interquartile range; mCRPC: Metastatic castration-resistant prostate cancer; Ra-223: Radium-223.

Adverse events

92 patients (32%) were admitted during Ra-223 or within 30 days after last Ra-223 injection without differences between treatment lines (Table 4). Anemia ≥grade 2 occurred in 74 patients (26%): 4 patients in line 1 (14%), 20 patients in line 2 (19%) and 50 patients (33%) in line ≥3 ($p < 0.01$). In total, 61 patients (21%) needed at least one blood transfusion during Ra-223, most frequently in line ≥3 (29 % in line ≥3 vs 7% in line 1 and 14% in line 2). Thrombocytopenia ≥grade 2 was also more prevalent in line ≥3, namely in 14 patients (9%) compared with 0 patients (0%) in line 1 and 2 patients (2%) in line 2 ($p = 0.02$).

Treatment completion

6% of patients were still on treatment at the end of follow-up and were excluded from analysis of treatment completion. Overall, 135 (51%) patients were treated with 6 Ra-223 injections and 128 (48%) with 1–5 Ra-223 injections. Median number of injections was 6 in Ra-223 as 1st or 2nd line and 5 in Ra-223 as 3rd line treatment (Table 3).

Table 2. Efficacy outcomes of radium-223.

Outcomes	Ra-223			p-value
	Line 1	Line 2	Line ≥3	
Treatment injections				
n	29	106	150	0.185
Median	6	6	5	
IQR	3–6	3–6	3–6	
Missing, n (%)	1 (3)	0 (0)	3 (2)	
On treatment, n (%)	1 (3)	8 (8)	9 (6)	
<6, n (valid %)	12 (44)	43 (44)	73 (53)	
6, n (valid %)	15 (56)	55 (56)	65 (47)	
Biochemical responses during Ra-223				
N‡	28	98	141	0.766
Max. PSA response				0.677
Median	+15%	+39%	+37%	
IQR	-20% to +137%	0% to +81%	+7% to +90%	
Missing, n (%)	10 (36)	19 (19)	33 (23)	
≥50% PSA decline (n, valid %)	1 (6)	4 (5)	3 (3)	
Max. ALP response				
N				0.046†
Median	-48%	-39%	-34%	
IQR	-63% to -28%	-53% to -18%	-50% to -5%	
Missing, n (%)	8 (29)	14 (14)	35 (25)	
≥30% ALP decline, n (valid %)	13 (65)	51 (61)	58 (55)	0.570
≥50% ALP decline, n (valid %)	7 (35)	25 (30)	26 (25)	0.537
SSEs				
N	28	96	124	
During Ra-223§, n (%):				
– Total	2 (7)	13 (14)	17 (14)	0.622
– Radiation to bone	2 (7)	13 (14)	17 (14)	0.622
– Orthopedic surgery	1 (4)	0 (0)	0 (0)	0.019†
– Spinal cord compression	0 (0)	1 (1)	3 (2)	0.541
– Pathologic fracture	0 (0)	0 (0)	1 (1)	0.595
During follow-up¶, n (%)				
Total	8 (29)	32 (33)	44 (36)	0.824
Radiation to bone	7 (25)	31 (32)	44 (36)	0.604
Orthopedic surgery	2 (7)	1 (1)	0 (0)	0.007†
Spinal cord compression	0 (0)	5 (5)	3 (2)	0.292
Pathologic fracture	0 (0)	2 (2)	2 (2)	0.741
Time to SSE (months)				
Median (IQR)	35.1 (13–35)	18.9 (7–22)	14.6 (6-NR)	0.124
Censored, n (%)	18 (64)	60 (63)	75 (60)	
Unknown, n (%)	2 (7)	5 (5)	6 (5)	
SSE-free survival (months)				
Median (IQR)	12.5 (6–35)	8.7 (5–18)	7.5 (4–11)	0.003†
Censored, n (%)#	9 (32)	36 (38)	30 (24)	
Unknown, n (%)	2 (7)	5 (5)	6 (5)	
Overall survival (months)				
N	29	106	150	<0.001†
Median (IQR)	23.8 (11–39)	17.0 (8–26)	10.4 (6–19)	
Censored, n (%)††	15 (52)	54 (51)	55 (37)	

†Significant at $p < 0.05$;
‡Patients still on treatment with Ra-223 at end of follow-up were excluded from response analyses;
§In time period from start of first Ra-223 injection to 30 days after last Ra-223 injection;
¶In time period from start of first Ra-223 injection to last recorded date;
#Patients alive without SSE were censored at end of follow-up date;
††Patients alive or lost-to-follow-up were censored at end of follow-up date.
IQR: Interquartile range; Ra-223: Radium-223; SSE: Symptomatic skeletal event.

Table 3. Univariable and multivariable binary logistic regression for treatment completion (6 injections vs 1–5 injections).

Characteristics	n‡	Univariable analysis of original data (n = 267)			Multivariable analysis of pooled data after imputation (n = 267)		
		OR	95% CI	p-value	OR	95% CI	p-value
Age (years)	263	0.984	0.954–1.016	0.328	0.974	0.938–1.012	0.181
Charlson score:							
– 6	165	REF	–	–	REF	–	–
– 7–8	79	1.180	0.698–2.020	0.546	1.224	0.652–2.299	0.530
– >9	19	0.889	0.344–2.301	0.809	1.154	0.384–3.462	0.799
ECOG PS:							
– 0	51	REF	–	–	REF	–	–
– 1	124	0.676	0.346–1.318	0.250	0.893	0.396–2.013	0.782
– ≥2	35	0.310	0.126–0.762	0.011†	0.793	0.265–2.369	0.676
Lymph node involvement Yes vs no	194	0.868	0.460–1.640	0.664	1.082	0.518–2.259	0.832
Visceral disease Yes vs no	194	0.505	0.117–2.175	0.359	0.625	0.166–2.352	0.480
Time castration to CRPC (months)	263	1.011	0.999–1.023	0.062	1.011	0.999–1.024	0.080
Hb (mmol/l)	240	1.778	1.351–2.338	<0.001†	1.464	1.082–1.982	0.014†
ALP (U/l)	227	0.999	0.998–1.000	0.074	1.000	0.999–1.002	0.728
LDH (U/l)	180	0.995	0.991–0.998	0.003†	0.996	0.992–1.000	0.029†
PSA (µg/l)	229	1.000	0.999–1.000	0.107	1.000	0.999–1.000	0.666
Prior treatment:							
– Line 1	27	REF	–	–	REF	–	–
– Line 2	98	1.023	0.434–2.412	0.958	0.999	0.377–2.648	0.998
– Line ≥3	138	0.712	0.311–1.633	0.423	0.866	0.332–2.260	0.768

†Significant at $p < 0.05$;
‡Number of patients included in univariate analysis.
CI: Confidence interval; Cont: Continuous; CRPC: Castration-resistant prostate cancer; ECOG: Eastern Cooperative Oncology Group; Hb: Hemoglobin; REF: Reference category.

Table 4. Hospital admissions and hematologic events of radium-223‡.

Characteristics	Ra-223			p-value
	Line 1 (n = 29)	Line 2 (n = 106)	Line ≥3 (n = 150)	
Hospital admission during Ra-223				
Yes	8 (28)	27 (26)	57 (38)	0.075
No	16 (55)	61 (58)	68 (45)	
Missing	5 (17)	18 (17)	25 (17)	
Anemia ≥grade 2[b]				
Yes	4 (14)	20 (19)	50 (33)	0.007†
No	16 (55)	53 (50)	56 (37)	
Missing	9 (31)	33 (31)	44 (29)	
Thrombocytopenia ≥grade 2[c]				
Yes	0 (0)	2 (2)	14 (9)	0.015†
No	20 (69)	71 (67)	91 (61)	
Missing	9 (31)	33 (31)	45 (30)	
Blood transfusion during Ra-223				
Yes	2 (7)	15 (14)	44 (29)	0.001†
No	26 (90)	90 (85)	100 (67)	
Missing	1 (3)	1 (1)	6 (4)	

Data represented as n (%).
†Significant at $p < 0.05$;
‡In time period from start of first Ra-223 injection to 30 days after last Ra-223 injection; [b] defined as hemoglobin <6.2 mmol/l according to CTCAE v3.0 [32]; [c] defined as platelets <75 × 109/l according to CTCAE v3.0 [32].
CTCAE: Common terminology criteria for adverse event; Ra-223: Radium-223.

Patients who completed 6 Ra-223 injections had better known prognostic factors at start of Ra-223 than patients who had 1–5 Ra-223 injections, namely higher Hb (7.9 vs 7.3 mmol/l; $p < 0.01$), lower ALP (122 vs 189 U/l; $p < 0.01$), lower LDH (231 vs 263 U/l; $p < 0.01$) and lower PSA (84 vs 165 µg/l; $p < 0.01$). Patients with 6 Ra-223 injections less frequently needed a hospital admission (21% vs 47%; $p < 0.01$) and blood transfusion (13 vs 32%; $p < 0.01$) during Ra-223 compared with patients with one to injections. After correction for known prognostic characteristics, higher Hb (OR: 1.464: 95% CI: 1.082–1.982; $p = 0.01$) was associated with higher odds and higher LDH (OR: 0.966, 95% CI: 0.992–1.000; $p = 0.03$) with lower odds for treatment completion (6 injections vs 1–5 injections; Table 3).

At the last Ra-223 injection, 20 patients (7%) had an ALP increase ≥25% and 105 patients (39%) a PSA increase ≥25% without differences between one and five or six Ra-223 injections. Recorded reasons for early discontinuation were progressive disease (PD) in 83 patients (65%) and toxicity in 14 patients (11%). PD was defined by one of the parameters (i.e. PSA, radiological or clinical deterioration) in 25% (n = 20), by a combination of two parameters in 54% (n = 44) and all three parameters in 21% (n = 17). Other reasons for discontinuation were death (n = 11, 9%), patient preference (n = 4, 3%) and unknown reasons (n = 16, 13%).

Symptomatic skeletal events

In total, 248 patients were available for SSE analyses. 84 patients (34%) had a SSE during total follow-up after 1st Ra-223 injection. SSE concerned mostly radiation therapy (n = 82, 33%). Eight patients (3%) had a spinal cord compression, 4 patients (2%) a pathologic fracture and 3 patients (1%) orthopedic surgery. During Ra-223 32 patients (13%) experienced a SSE. There were no differences in rate of SSE between treatment line of Ra-223, except for orthopedic surgery (Table 2).

Median time to first SSE was 16.0 months with SSE-free survival of 8.0 months (Figure 2A & B). SSE-free survival was longer in patients treated in line 1 (12.5 months), than line 2 (8.7 months) and line ≥3 (7.5 months).

Overall survival

In total, 161 deaths (57%) occurred during follow-up. Median OS was 12.2 months (IQR: 8–29 months). Median OS was shorter in patients treated in line ≥3 (10.4 months) and line 2 (17.0 months) compared with line 1 (23.8 months; $p < 0.01$; Figure 3).

In univariable analyses, Ra-223 in line 2 (HR: 1.744; $p = 0.07$) and line ≥3 (HR: 3.293; $p < 0.01$) were associated with shorter OS. After correction for known prognostic factors in multivariable analysis, this remained significant for Ra-223 treatment in line ≥3 (HR: 3.267; $p < 0.01$; Table 5). ECOG ≥2 (HR: 2.206; $p = 0.03$), higher ALP (HR: 1.001; $p = 0.03$) and higher LDH (HR: 1.002; $p = 0.02$) were also associated with worse survival, while higher Hb (HR: 0.796; $p = 0.02$) was associated with longer survival (Table 5).

Discussion

In this retrospective analysis, we report the outcomes of Ra-223 in the real world. To our knowledge, so far this is the largest multicenter population without strict patient selection criteria in which patients are treated according to the views and opinions of their treating physicians and outcomes therefore reflect current daily practice.

In our cohort, 79% was treated with Ra-223 prior to line 4, mostly in second (37%) or third (32%) line. Only 29 patients were treated with Ra-223 in line 1, since only part of our cohort could be treated with Ra-223 in first line due to the fact that Ra-223 was registered in the Netherlands in February 2014 and our patient population included patients with mCRPC diagnosis between 2010 and 2016. In the Netherlands, the start of Ra-223 tends to be earlier in the disease stage compared with an Italian retrospective study of 158 Ra-223-treated patients in 2013–2018 [16]. It has been proposed that earlier treatment utilization is related to higher treatment completion rates and better outcomes [17], but prospective data on the outcomes of treatments in third line or higher are lacking.

Median OS in our cohort was lower than in the ALSYMPCA trial (12.2 vs 14.9 months) [3], while previous retrospective cohorts of Ra-223 treated patients reported a wide range of OS (8.1 to 17.5 months) [7]. As we have shown before, outcomes from trials are not easily generalizable to the real-world mainly due to patient selection [14]. In our unselected patient cohort, patients were older than in the ALSYMPCA trial (46 vs 28% aged ≥75 years), but other known prognostic factors were comparable. In the ALSYMPCA trial with all patients treated in line 1 or 2 the OS differed between the docetaxel pre-treated (14.4 months) and docetaxel untreated (16.1 months) cohorts [3,4]. In our cohort positioning of Ra-223 was later in the disease trajectory (49% with Ra-223 in line 3 or higher). OS in patients with Ra-223 in line ≥3 was lower than in line 1 or 2 (respectively 10 vs 24 and 17 months). However, OS

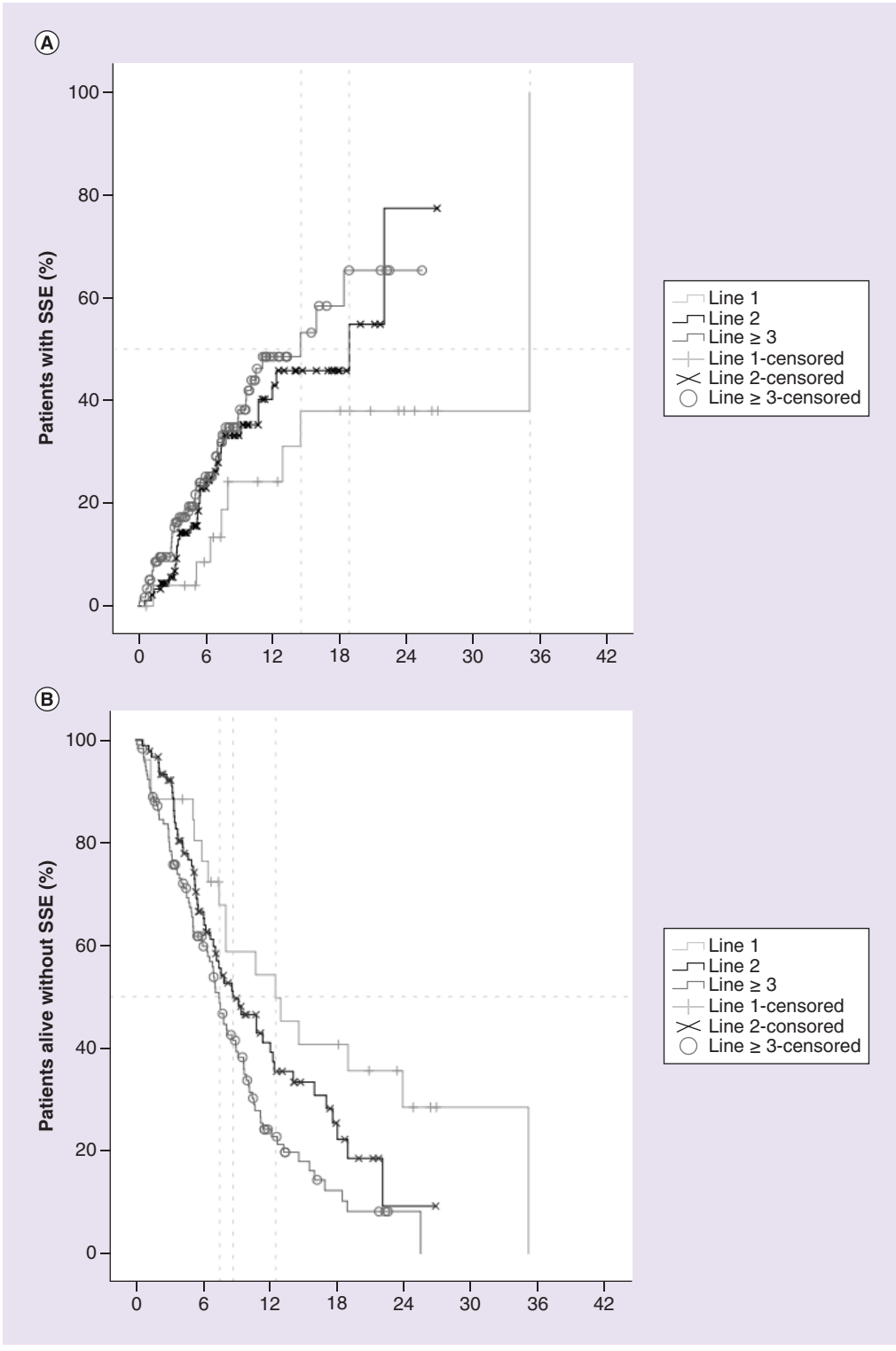

Figure 2. Kaplan-Meier curve showing time to first SSE (2A) and SSE-free survival (2B) from start of radium-223 (months).
Dotted lines indicate median time to SSE and SSE-free survival for different lines.
SSE: Symptomatic skeletal event.

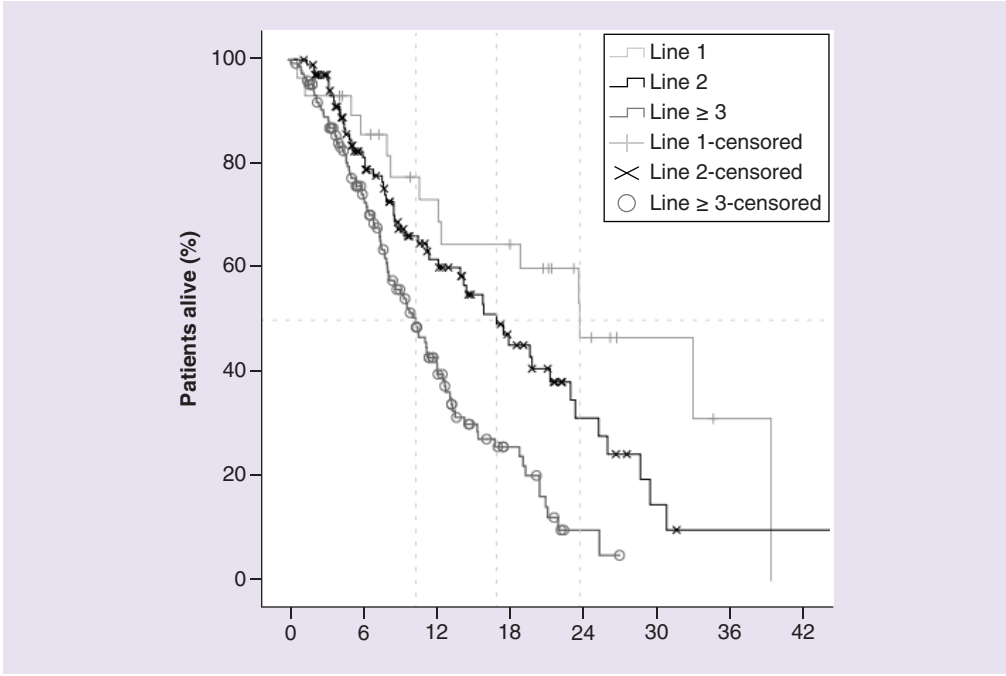

Figure 3. Kaplan-Meier curve showing overall survival (months) from start of radium-223.
Dotted lines indicate median overall survival for different lines.

Table 5. Univariable and multivariable Cox-proportional hazard analysis for overall survival.

Characteristics	Univariable analysis of original data (n = 285)				Multivariable analysis of pooled data after imputation (n = 285)		
	n/N‡	HR	95% CI	p-value	HR	95% CI	p-value
Age (years	161/285	1.009	0.989–1.030	0.378	1.006	0.981–1.031	0.653
Charlson score:							
– 6	100/182	REF	–	–	REF	–	–
– 7–8	46/84	0.978	0.690–1.388	0.903	0.965	0.644–1.447	0.864
– >9	15/19	1.972	1.140–3.411	0.015†	1.702	0.904–3.203	0.100
ECOG PS:							
– 0	26/56	REF	–	–	REF	–	–
– 1	70/135	1.285	0.818–2.020	0.276	1.004	0.610–1.651	0.998
– ≥2	29/37	3.949	2.300–6.778	<0.001†	2.206	1.070–4.548	0.032†
Lymph node involvement Yes vs no	116/211	1.198	0.798–1.797	0.384	0.972	0.591–1.601	0.910
Visceral disease Yes vs no	121/220	2.522	1.226–5.190	0.012†	1.440	0.641–4.232	0.490
Time castration to mCRPC (mo)	161/285	0.996	0.989–1.002	0.207	0.996	0.988–1.003	0.232
Hb (mmol/l)	145/256	0.616	0.522–0.727	<0.001†	0.796	0.655–0.967	0.022†
ALP (U/l)	136/246	1.001	1.001–1.002	<0.001†	1.001	1.000–1.001	0.028†
LDH (U/l)	114/191	1.003	1.002–1.004	<0.001†	1.002	1.000–1.003	0.016†
PSA (μg/l)	138/248	1.000	1.000–1.000	0.009†	1.000	1.000–1.000	0.463
Prior treatment:							
– Line 1	14/29	REF	–	–	REF	–	–
– Line 2	52/106	1.744	0.957–3.181	0.070	1.823	0.945–3.517	0.073
– Line ≥3	55/150	3.293	1.821–5.956	<0.001†	3.267	1.689–6.317	<0.001†

†Significant at $p < 0.05$;
‡Number of patients with event (i.e., death) of total included in univariate analysis.
CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; Hb: Hemoglobin; HR: Hazard ratio; mCRPC: Metastatic castration-resistant prostate cancer; REF: Reference category.

in earlier treatment lines has to be interpreted with caution due to the cumulative effect of subsequent treatments after Ra-223 and the small number of patients with Ra-223 in line 1 (n = 29). Differences in OS between different positions of Ra-223 in the treatment sequence can partially be explained by the fact that patient and disease characteristics in higher treatment lines reflect a more advanced disease stage. In mCRPC, cancer biology becomes more aggressive due to the progressive nature of the disease and resistance to previous systemic treatments with also an increase in the incidence of visceral metastases [9,17]. In our cohort, this is reflected by worse prognostic factors at the start of Ra-223 in patients treated with Ra-223 in line ≥3, especially lower Hb and higher PSA. Worse ECOG and higher ALP were also associated with worse OS. Complete assessment of known prognostic factors is necessary before the start of Ra-223 especially in patients who had two or more previous systemic treatment lines [7].

In our cohort, 51% of patients completed all 6 injections of Ra-223 which is similar to previous large unselected cohorts (51% to 63%) [18–21], but lower than in the pivotal Phase III ALSYMPCA trial (63%) [3]. The main reason for early discontinuation was progressive disease recorded as PSA, radiological and/or clinical progression, which were the only factors for disease progression included in our study protocol. Progression assessment was not protocol mandated and performed based on the views and opinions of treating physicians. Ra-223 could be discontinued earlier than necessary for example based on incomplete progression assessment or flare in PSA or pain not related to progression. We found a negative association with treatment completion for higher LDH and lower Hb, which was consistently found in retrospective studies [18,20,22,23]. More hospital admissions and blood transfusions occurred in patients with one to five Ra-223 injections, which were likely a sign of disease progression since Ra-223 has a low myelotoxic profile with no differences in rate of hematologic complications (i.e., anemia and blood transfusion) compared with placebo in ALSYMCPA [24,25]. Treatment completion could have a positive effect on OS as reported by previous studies [18,26,27]. However, results on the effect of treatment completion and OS have to be interpreted with caution due to the effect of immortal time bias.

43% experienced at least one SSE after first Ra-223 injection, mostly radiation therapy to the bone in agreement with ALSYMPCA [6]. Although our cohort was more frequently pre-treated with other LPDs, this did not seem to affect the occurrence of clinically relevant SSEs after first Ra-223 injection. Bone metastases and loss of bone mineral density due to ADT cause significant risk of SSEs in mCRPC-patients [28]. In our population only four patients (2%) experienced a clinically apparent pathologic fracture, which is comparable to the findings from the ALSYMPCA trial (5%) [6]. We found that most physicians combine Ra-223 treatment with bone health agents, especially in higher treatment lines. The reasons not to initiate bone health agents were unclear, but could include contra-indications as hypocalcemia or renal insufficiency or an estimated low risk of SSE by clinicians. Post-hoc analyses have shown that the combination of bone health agents could have potential extra benefit on SSE and OS [29].

We observed similar biochemical response rates in our real-world population (4% with ≥50% PSA decline and 58% with ≥30% ALP decline) as in ALSYMPCA. Changes in PSA levels indicate a response on androgen-receptor level, because PSA expression is regulated by the androgen-receptor axis. However, Ra-223 does not target the androgen-receptor axis, but the tumor growth in bones and tumor-induced osteoblastic bone growth. This may be one of the reasons for low PSA responses during Ra-223 (6 to 15%) [18,19,23] and frequent ALP responses (33 to 47%) [3,23,30]. It is suggested that decline in ALP, but also LDH, is associated with longer survival, but biomarker changes have not been proven to be surrogates for survival [12]. Especially in Ra-223 which has little effect on PSA, evaluation of treatment response and the decision for treatment discontinuation should be based on a combination of changes in biochemical markers as ALP and LDH and changes in other response measurements, such radiologic assessment and clinical condition [10–12,17,30].

Our study was performed in the era without the registration of docetaxel and abiraterone acetate plus prednisone for metastatic hormone-sensitive prostate cancer and without the current EMA restriction for Ra-223 (i.e., restriction of Ra-223 after two prior systemic treatments for mCRPC or in patients ineligible for other systemic treatments). These changes will probably have an effect on the clinical practice of Ra-223 treatment in the Netherlands. While in this cohort Ra-223 was mainly started after no or one prior LPD (47%), it seems inevitable that in the future more patients will be treated with more than one LPD before Ra-223. However, patients progressing after two previous treatment lines are more likely to have developed visceral metastases, missing the window of opportunity for Ra-223. Moreover, it is likely that the efficacy of Ra-223 is lower in later treatment lines due to more advanced disease phase [31].

In our study, we showed that hematologic events are more prevalent and OS is shorter when Ra-223 is initiated in line ≥3. Moreover, there is a short window of opportunity for Ra-223 due to the occurrence of visceral metastases

in later disease stage [9]. By restricting the use of Ra-223 in later treatment lines, the window of opportunity may be passed causing loss of a treatment option in mCRPC.

The first limitation of our study was the high number of missing values, which is inherent to the retrospective design. Missing values on baseline characteristics reflect incomplete evaluation of patients or lack of structured reporting in daily practice. Our evaluation of optimal patient selection can therefore be incomplete. This underlines the need for better documentation at the start of a new systemic treatment. However, imputation of missing baseline data could offer a solution for multivariable analysis but residual confounding could still be present in multivariable analysis.

The second limitation was the fact that this study was not able to capture all data on treatment decisions. Other factors than the known patient and disease characteristics as for example availability of Ra-223 in the hospital may play a role in the patient selection for Ra-223 and the choice of specific sequences. These unknown factors may also affect outcomes such as treatment completion and early discontinuation. Moreover, ALP progression as a reason of Ra-223 discontinuation was not registered in our protocol. Due to the lack of protocol mandated progression assessment, progression-free survival could not be evaluated. This limitation indicates the need of prospective research in a large population to provide better guidance on the optimal patient selection and timing of Ra-223.

Conclusion

Our study suggests that in the Netherlands Ra-223 was mainly prescribed at the second and third line after prior docetaxel and/or androgen-receptor targeting therapies in the years 2014–2018. Later timing of Ra-223 did not affect treatment completion or occurrence of SSE, but adverse events were more frequent and OS was significantly shorter in patients treated with Ra-223 in line ≥3 compared with earlier treatment lines. Poorer survival was only partially explained by worse baseline characteristics at the start of Ra-223. Further prospective research is necessary to investigate optimal timing and monitoring of Ra-223 in the treatment landscape with multiple treatment options, especially in light of the registration of LPDs for metastatic hormone sensitive prostate cancer and current restrictions provided in the EMA guidance.

Summary points

- Timing of radium-223 (Ra-223) in metastatic castration resistant prostate cancer (mCRPC) remains challenging due to alternative options and short window of opportunity.
- We have investigated the use and outcomes of Ra-223 in the real-world CAPRI registry including 3,616 CRPC patients from 20 Dutch hospitals.
- In 2014–2018 Ra-223 was mainly started in line 2 or line 3 after chemotherapy or new androgen-receptor targeting agents in the Netherlands.
- Half of the patients completed all Ra-223 injections which was not related to line of treatment.
- Thirty-four percent of patients experienced a symptomatic skeletal event (i.e. radiation therapy, surgery to the bone, pathologic fracture or spinal cord compression) during follow-up without differences between line of treatment.
- Anemia and thrombocytopenia ≥grade 2 were more common in patients with Ra-223 in line 3 or higher.
- We found that overall survival is also affected by later timing of Ra-223, which could be partially explained by worse patient characteristics.
- Although results have to be validated in prospective trials, these results warrant careful consideration of treatment after two prior treatments with a necessity of complete assessment of known prognostic factors.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Legal entity responsible for the abstract

Institute for Medical Technology Assessment, Erasmus University Rotterdam. Winald Gerritsen and Carin Uyl-de Groot had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Clinical trial identification

The CAPRI study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

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