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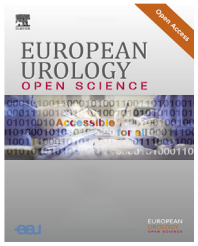

European Association of Urology

Prostate Cancer

Reducing Biopsies and Magnetic Resonance Imaging Scans During the Diagnostic Pathway of Prostate Cancer: Applying the Rotterdam Prostate Cancer Risk Calculator to the PRECISION Trial Data

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Abstract

Background: Risk stratification in the diagnostic pathway of prostate cancer (PCa) can be used to reduce biopsies and magnetic resonance imaging (MRI) scans, while maintaining the detection of clinically significant PCa (csPCa). The use of highly discriminating and well-calibrated models will generate better clinical outcomes if context-dependent thresholds are used.
Objective: To retrospectively assess the effect of the upfront use of the Rotterdam Prostate Cancer Risk Calculator (RPCRC) developed in a screening cohort and the RPCRC-MRI developed in a clinical cohort while exploring the need to adapt thresholds in biopsy-naïve men in the PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not?) trial.
Design, setting, and participants: In the transrectal ultrasonography arm, we evaluated 188 men; in the MRI arm, we evaluated 206 (for the reduction of MRI scans) and 137 (for the reduction of targeted biopsies) men.

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Outcome measurements and statistical analysis: Performance was assessed by discrimination, calibration, and clinical utility.
Results and limitations: The performance of the RPCRC was good. However, intercept adjustment was warranted. Net benefit was observed from a recalibrated probability of 32% for any PCa and 10% for csPCa. After recalibration and applying a threshold of 20% for any PCa or 10% for csPCa, 28% of all biopsies could have been reduced, missing five cases of csPCa. The uncalibrated RPCRC could reduce 35% of all MRI scans, with a threshold of 20% for any PCa or 4% for csPCa. In the MRI arm, performance was good without stressing recalibration. Net benefit was observed from a probability of 22% for any PCa and 7% for csPCa. With a threshold of 20% for any PCa or 4% for csPCa, 9% of all targeted biopsies could be reduced, missing one grade group 2 PCa.
Conclusions: The performance of the RPCRC and RPCRC-MRI in men included in the PRECISION trial was good, but recalibration and adaptation of the risk threshold of the RPCRC are indicated to reach optimal performance.
Patient summary: In this report, we show that risk stratification with the Rotterdam Prostate Cancer Risk Calculator has added value in reducing harm, but adjustment to reflect the characteristics of the patient cohort is indicated.

1. Introduction

In the diagnostic pathway of prostate cancer (PCa), pathological confirmation is required, and it is strongly advised to perform a prostate biopsy in men who are at an elevated risk of having clinically significant PCa (csPCa), which can be burdensome for many men. The Rotterdam Prostate Cancer Risk Calculator (RPCRC) quantifies the probability of detecting PCa and csPCa at prostate biopsy using the information of several clinical parameters (ie, prostate-specific antigen [PSA], presence of abnormal digital rectal examination [DRE], suspicious lesion on transrectal ultrasound, and prostate volume) and recommends prostate biopsy if the individual risk is >20% for any PCa and/or >4% for csPCa. It has been shown in a population-based biopsy-naïve cohort that with this so-called multivariable risk-based approach as compared with a "biopsy all men with PSA $\geq$3.0 ng/ml," the RPCRC could reduce 33% of all prostate biopsies, while missing 14% of all PCa and 7% of all csPCa cases [1].

As an alternative or an adjunct to this multivariable risk-based strategy, imaging can also be used as a risk stratification tool. Imaging alone for risk stratification in men deemed suitable for biopsy was tested in the PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not?) trial, where biopsy-naïve men with a clinical suspicion of PCa were randomized to either a magnetic resonance imaging (MRI) arm or a transrectal ultrasonography (TRUS) arm [2]. In the MRI arm, all men were scanned and only those with positive MRI (ie, Prostate Imaging Reporting and Data System [PI-RADS] $\geq$3) received targeted prostate biopsy, while all men in the TRUS arm received systematic prostate biopsy. The data showed that 28% of all prostate biopsies could be avoided using MRI as a triage test, which suggests that not all MRI scans were necessary. This concept has been tested by using the RPCRC as an upfront risk stratification tool, which led to a reduction of 51% of all MRI scans for men with a prior negative biopsy [3]. In addition to the possibility of risk stratifying before MRI, the RPCRC has recently been updated to include the PI-RADS score and age as well as the usual clinical parameters in the new RPCRC-MRI [4] calculator. Since the PRECISION trial data showed that 21% of all positive scans were not related to a PCa diagnosis, this prediction tool could be of aid in decisions to avoid biopsy after MRI.

The aim of this study is to retrospectively assess the ability of upfront risk stratification using the RPCRC and the RPCRC-MRI to reduce systematic prostate biopsies, MRI scans, and targeted prostate biopsies for biopsy-naïve men. In addition, we will investigate whether the currently recommended risk thresholds of 20% for any PCa or 4% for csPCa need adaptation to reflect contemporary clinical practice to reach optimal performance [5].

2. Patients and methods

The PRECISION trial study characteristics have been described previously [2]. In short, 500 men with a clinical suspicion of PCa without a prior negative biopsy and a maximum PSA level of 20 ng/ml were randomized to either the MRI arm or the TRUS arm. In the MRI arm, only men with positive MRI (defined as PI-RADS $\geq$3) received targeted prostate biopsies (a maximum of three lesions were sampled with a maximum of four biopsies per lesion), while men with negative MRI were not biopsied. In the TRUS arm, all men received ten to 12 systematic biopsy cores. Since an abnormal DRE is a strong clinical indicator to pursue to prostate biopsy, in the current study, we included only men with elevated PSA and negative DRE findings recorded.

2.1. Statistical analyses

The probability of any PCa and csPCa was calculated using the RPCRC and the RPCRC-MRI, utilizing the required clinical information [1,4,6]. Discrimination of the model was assessed by the area under the receiver-operating characteristic curve. Calibration was assessed visually by calibration curves, and quantified by the calibration slope and

calibration in the large. The net benefit of the model at a range of risk thresholds was evaluated by a decision curve analysis (DCA). To account for the difference in setting (ie, the RPCRC is developed in a population-based screening setting, while the PRECISION trial represents a contemporary clinical setting), we recalibrated the model based on the calibration in the large. All statistical analyses were performed using R version 3.5.1.

3. Results

3.1. Can we reduce systematic biopsies in men with elevated PSA and normal DRE?

In the TRUS arm of the PRECISION trial, 42 of the 248 randomized men had a PSA value of <3.0 ng/ml or abnormal DRE and 18 men were not biopsied, leaving 188 men for evaluation. Missing information of three men was once imputed by predicting mean matching. In clinical practice, there is a preselection for referral compared with a population-based screening setting (ie, all men with PSA ≥3.0 ng/ml are referred for prostate biopsy), as indicated by the higher PSA density in the PRECISION trial (Table 1).

The performance of the original (ie, uncalibrated, population based) and the intercept-adjusted RPCRC is presented in Figure 1, and shows a good calibration curve with a slope of 0.68 (95% confidence interval [CI] 0.35–1.05) for any PCa and 0.87 (95% CI 0.51–1.27) for csPCa and shows a calibration in the large of 1.11 (95% CI 0.80–1.43) for any PCa and 1.39 (95% CI 1.01–1.76) for csPCa. Note that the calibration slope does not change after recalibration, and after recalibration the calibration in the large is zero. The calibration curve stresses the importance of recalibration. After intercept adjustment, especially the calibration curve for csPCa shows excellent calibration. The discrimination is 0.67 (95% CI 0.59–0.75) for any PCa and 0.73 (95% CI 0.63–0.81) for csPCa. The DCA is presented in Figure 2 and shows for the intercept-adjusted RPCRC an increase in net benefit (ie, the model based approach compared to biopsy all men) from a probability of 32% for any PCa and 10% for csPCa and limited net benefit of the original RPCRC as compared with biopsying all men.

The recalibrated RPCRC, applying a risk based cutoff for biopsy of 20% for any PCa or 4% for csPCa, could have reduced 5% (nine cases) of the 188 prostate biopsies, missing 6% (five cases) of all PCa and 5% (two cases) of all csPCa. An increased risk-based cutoff of 20% for any PCa or 10% for csPCa could have reduced 28% (52 cases) of all prostate biopsies, missing 18% (16 cases, +11 additional cases) of all PCa and 12% (five cases, +three additional cases) of all csPCa (characteristics of missed csPCa: PSA range 4.2–6.9, PSA density 0.06–0.10, 2 × grade group [GG]2, 2 × GG3, 1 × GG4 disease; see Supplementary Table 1 for a comparison of sensitivity, specificity, negative predictive value, and positive predictive value).

3.2. Can we reduce MRI and targeted biopsies in men with elevated PSA and normal DRE?

In the MRI arm of the PRECISION trial, 39 of the 252 randomized men had PSA below 3.0 ng/ml or an abnormal DRE, and seven men did not undergo MRI (leaving 206 men to evaluate the reduction on MRIs). Of these men, 141 (66%) had PI-RADS ≥3, of whom 137 (97%) underwent targeted prostate biopsy and 84 were diagnosed with PCa (61%), of whom 70 were defined to have csPCa (51% of all men biopsied and 83% of all PCa detected; see Table 1 for patient characteristics).

The uncalibrated RPCRC with a threshold of 20% for any PCa or 4% for csPCa can reduce 35% (72 cases) of all MRI scans, of which 28% (40 cases) of all cases with positive MRI would have been undetected, missing 20% (17 cases) of all PCa and 16% (11 cases) of all csPCa cases. Applying the recalibrated RPCRC (based on the prevalence of the TRUS arm) and a cutoff of 20% for any PCa and 10% for csPCa would have avoided 13% (27 cases) of all MRI scans, of which 12% (17 cases) of all positive MRI cases would have

Table 1 – Comparison of patient characteristics from the PRECISION trial and the development cohorts of the RPCRC and RPCRC-MRI

	PRECISION TRUS arm (n = 188)	PRECISION MRI arm Reduction MRI (n = 206)	PRECISION MRI arm Reduction targeted prostate biopsies (n = 137)	RPCRC development cohort initial biopsy (n = 3616)	RPCRC-MRI development cohort initial biopsy (n = 504)
Age					
Median (IQR)	65 (60–69)	64 (59–69)	65 (60–70)	66 (61–70)	65 (59–70)
PSA					
Median (IQR)	6.5 (5.2–8.5)	6.8 (5.2–9.3)	7.5 (5.4 – 9.9)	4.3 (3.1–6.4)	6.5 (5.0–9.4)
Prostate volume					
Median (IQR)	45 (35–60)	47 (35–65)	45 (35 – 61)	41 (32–55)	45 (33–63)
Unknown	3 (2%)	–	–	–	–
PSA density					
Median (IQR)	0.14 (0.10–0.20)	0.14 (0.10–0.21)	0.16 (0.11 – 0.23)	0.10 (0.06–0.15)	0.14 (0.10–0.23)
PI-RADS score					
≤2	–	65 (32%)	–	–	105 (21)
3	–	49 (24%)	47 (34%)	–	99 (20)
4	–	54 (26%)	54 (39%)	–	163 (32)
5	–	38 (18%)	36 (26%)	–	137 (27)
PCa					
Any PCa	88 (47%)	Only men with positive MRI were biopsied	84 (61%)	885 (25%)	294 (58%)
csPCa (GG ≥2)	42 (22%)	Only men with positive MRI were biopsied	70 (51%)	313 (9%)	213 (42%)

csPCa = clinically significant PCa; GG = grade group; IQR = interquartile range; MRI = magnetic resonance imaging; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PRECISION = Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not; PSA = prostate-specific antigen; RPCRC = Rotterdam Prostate Cancer Risk Calculator; TRUS = transrectal ultrasonography.

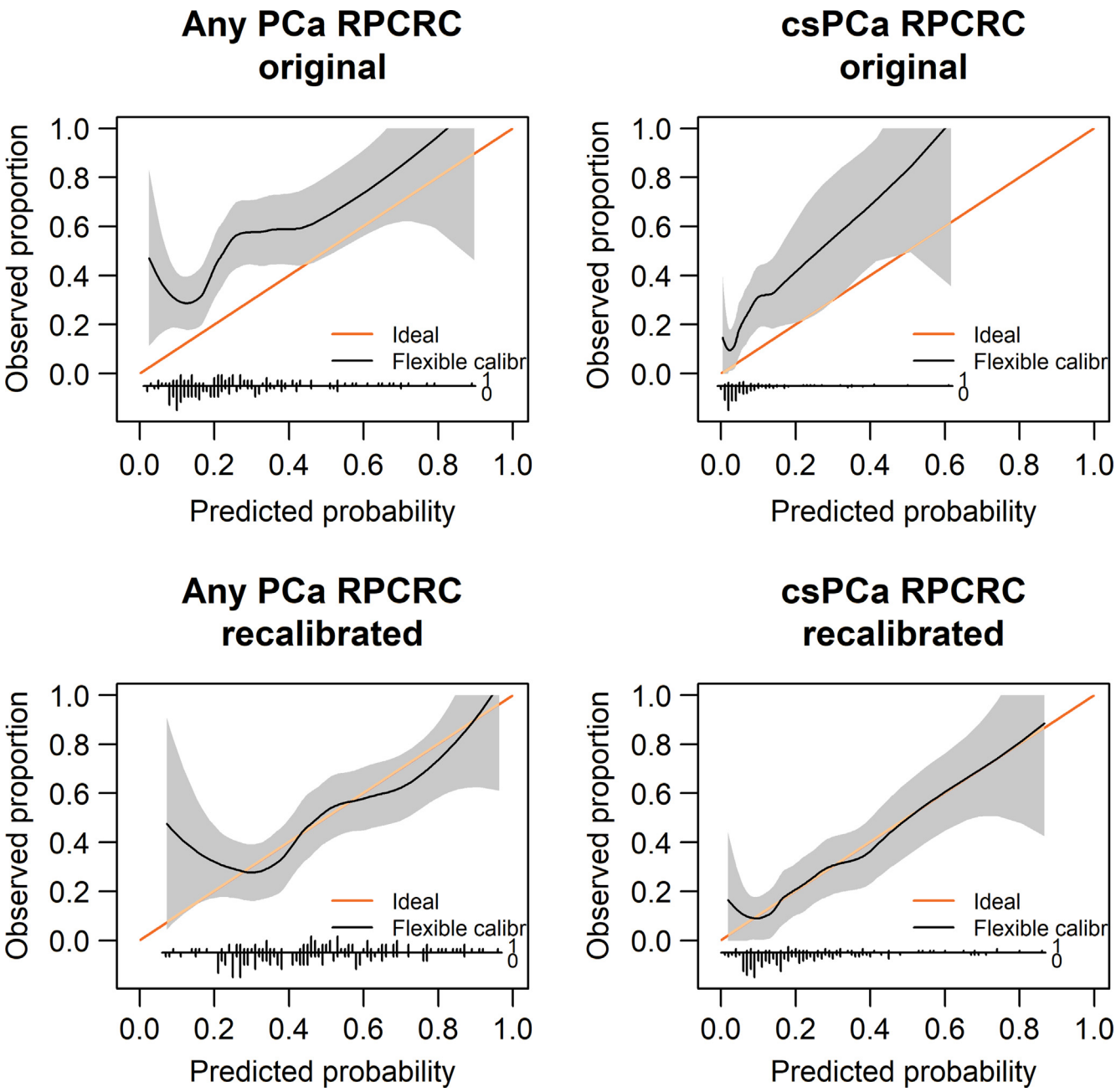

Fig. 1 – Calibration curves of the RPCRC in the TRUS arm. csPCa = clinically significant PCa; PCa = prostate cancer; RPCRC = Rotterdam Prostate Cancer Risk Calculator; TRUS = transrectal ultrasonography.

been undetected, missing 8% (seven cases) of all PCa and 7% (five cases) of all csPCa (3 × PI-RADS 4, 2 × PI-RADS 5).

The performance of the RPCRC-MRI (ie, only for men with positive MRI) is presented in Figure 3 and shows an almost perfect calibration with a slope of 0.99 (95% CI 0.64–1.39) for any PCa and 1.63 (95% CI 1.14–2.21) for csPCa, and a calibration in the large of 0.30 (–0.10 to 0.70) for any PCa and 0.59 (95% CI 0.21–0.97) for csPCa, which does not support the need for recalibration. The discrimination is 0.80 (95% CI 0.73–0.87) for any PCa and 0.86 (95% CI 0.79–0.92) for csPCa. The DCA is presented in Figure 4 and shows for the RPCRC-MRI an increase in net benefit from a probability of 22% for any PCa and 7% for csPCa compared with biopsy all with positive MRI. For men with positive MRI, the RPCRC-MRI with a threshold of 20% for any PCa or 4% for csPCa could reduce 9% (12 cases, all PI-RADS score 3) of all targeted biopsies, missing one GG2 PCa (1% of all csPCa; see Supplementary Table 1 for accuracy metrics).

4. Discussion

In this study, we assessed the ability of the RPCRC (in the TRUS arm for the reduction of systematic biopsies and the

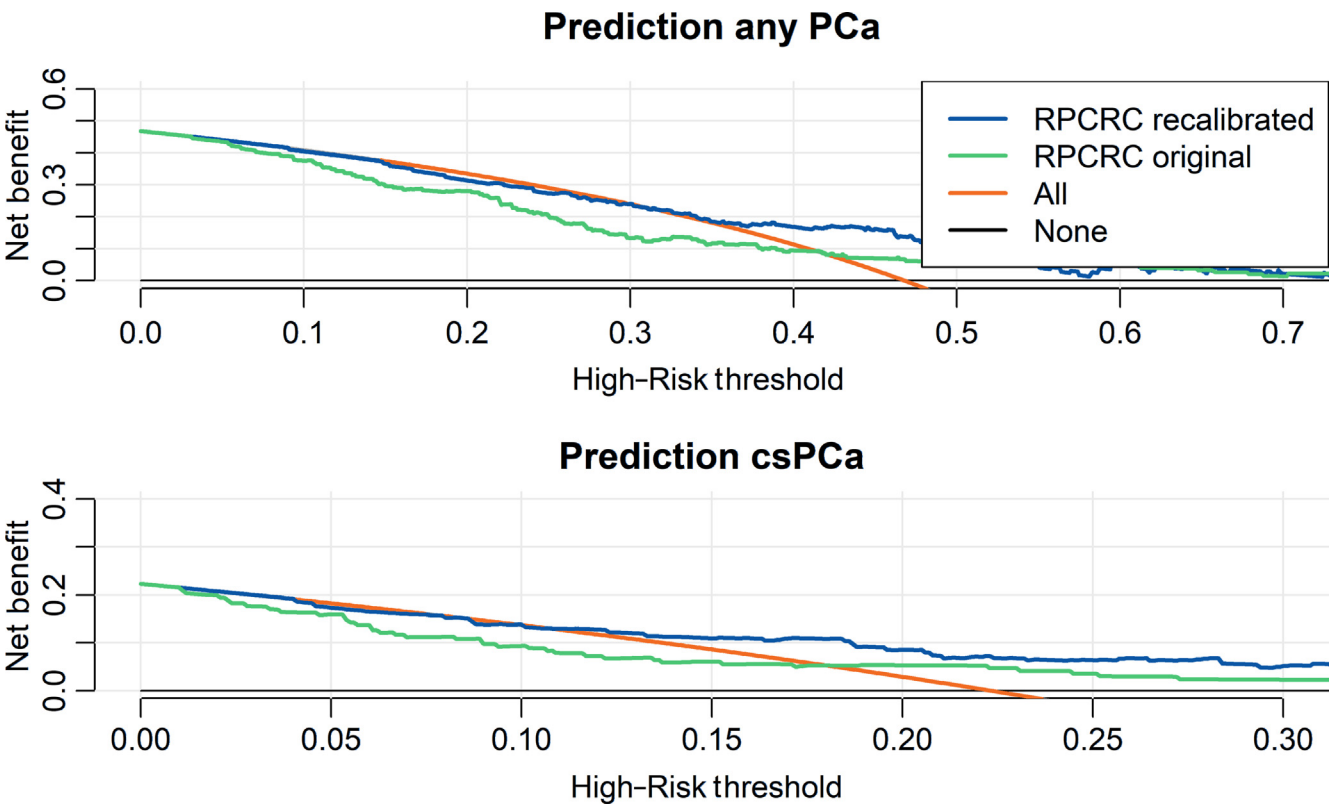

Fig. 2 – Decision curve analysis for the recalibrated and original (unadjusted) RPCRC. csPCa = clinically significant PCa; PCa = prostate cancer; RPCRC = Rotterdam Prostate Cancer Risk Calculator.

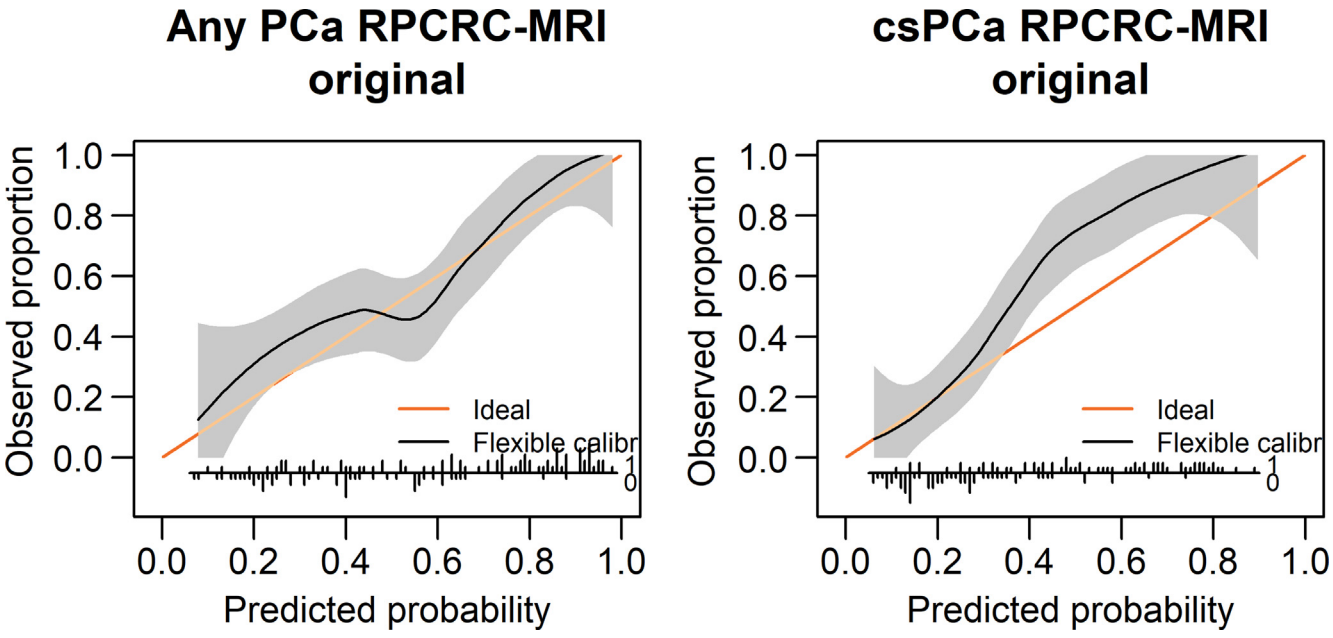

Fig. 3 – Calibration of the RPCRC-MRI. csPCa = clinically significant PCa; MRI = magnetic resonance imaging; PCa = prostate cancer; RPCRC = Rotterdam Prostate Cancer Risk Calculator.

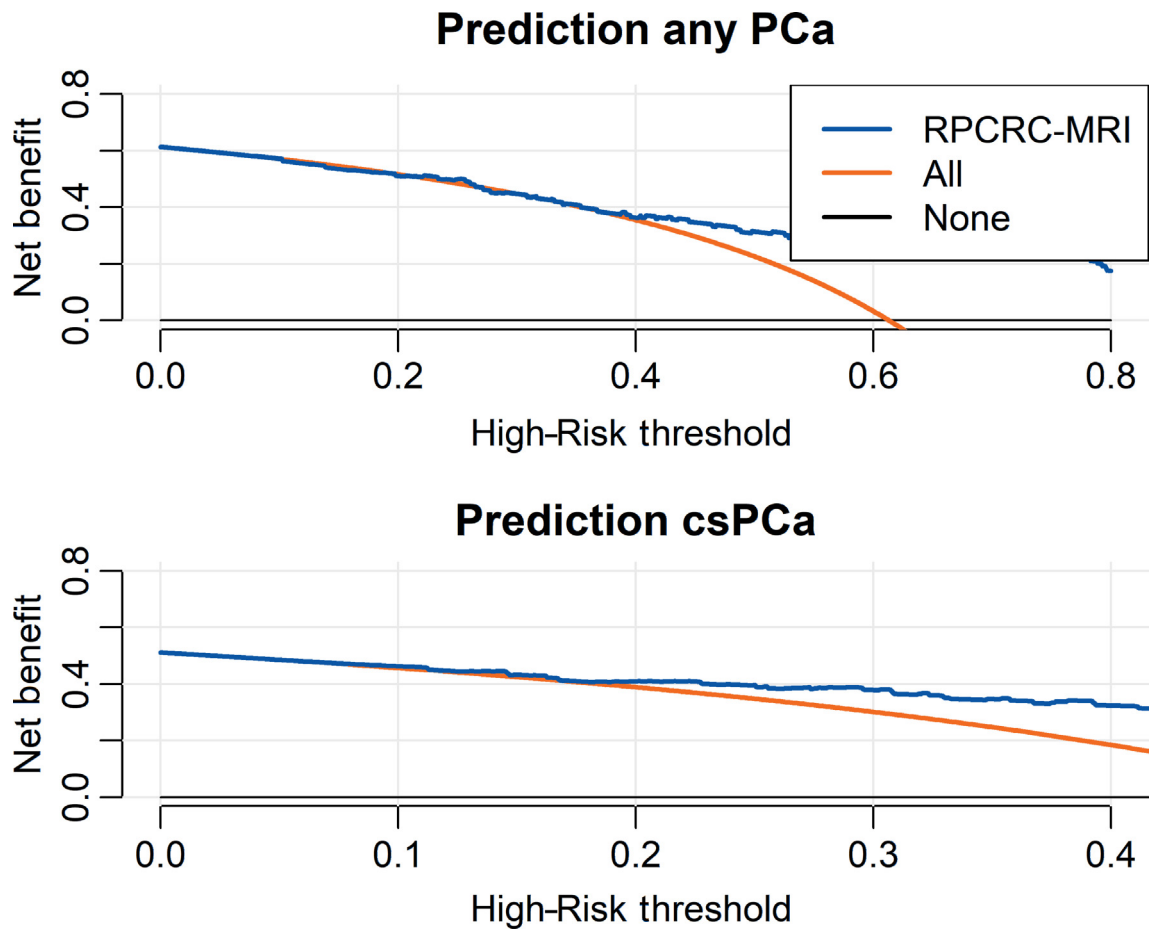

Fig. 4 – Decision curve analysis for the RPCRC-MRI. csPCa = clinically significant PCa; MRI = magnetic resonance imaging; PCa = prostate cancer; RPCRC = Rotterdam Prostate Cancer Risk Calculator.

MRI arm for the reduction of MRI scans) and the RPCRC-MRI (only in the MRI arm) to reduce the numbers of prostate biopsies and MRI scans in a contemporary clinical cohort for biopsy-naïve men. We found that the overall performance of the RPCRC and RPCRC-MRI was good, but recalibration was warranted for the RPCRC. In addition, we concluded that only recalibration of the RPCRC does not suffice to reach optimal performance. With an adapted threshold of at least 20% for any PCa or 10% for csPCa, the recalibrated RPCRC could reduce 28% of all biopsies, missing five cases of all csPCa. A similar rate of missed csPCa was reported by a recent study including a Dutch contemporary clinical cohort, which applied the RPCRC before MRI for biopsy-naïve men. They found that 37% of all MRI scans could be avoided, missing only two out of the 51 cases of csPCa after targeted prostate biopsies with similar clinical characteristics [7]. Another Dutch contemporary cohort showed that calibration of the RPCRC was excellent, while the current data show that recalibration is indicated [8]. This is unexpected since the prevalence of both any PCa and csPCa is comparable. An explanation for this finding could be a preselection before referral and not in the difference in case mix. To elaborate on the latter, the distribution of probabilities below 10% for any PCa is lower in the current study than in the study of Gayet et al [8], although this is not true for csPCa. It can also be observed that the rate of abnormal DRE is almost twice as high in the previously mentioned Dutch studies than in the PRECISION trial. However, since we only included men with a normal DRE, this is not likely to explain the discrepancy.

The RPCRC is developed using data of a population-based screening cohort, while the RPCRC-MRI is developed based on a contemporary clinical cohort, a difference that influences a priori probability of detecting (cs)PCa. To account for the difference in a priori risk, the intercept of the model can be adjusted [9,10]. In this study, we observed that recalibration was warranted for the RPCRC, while this was not true for the more contemporary RPCRC-MRI. However, after adjusting the intercept, it became obvious that, due to this increased a priori risk, the previously defined risk thresholds for the RPCRC needed to be adjusted as well, as was reflected by the DCA. To elaborate, with the current recommended threshold of 20% for any PCa or 4% for csPCa, the RPCRC could have reduced 5% of all prostate biopsies. However, an updated threshold of 20% for any PCa or 10% for csPCa could have reduced 28% of all prostate biopsies, missing five cases (compared with two cases with the standard threshold) of csPCa. On the contrary, the RPCRC-MRI is

developed in a contemporary setting and did not need recalibration. With the currently recommended threshold of 20% for any PCa or 4% for csPCa, the use of the RPCRC-MRI in this high-risk contemporary cohort could still reduce 9% of all targeted prostate biopsies, missing only one GG2 disease. In summary, with model recalibration (to reflect the higher a priori risk in a contemporary clinical cohort in a model developed in a screening cohort), adaptation of the risk threshold should not be overlooked to reach optimal performance [5].

The role of MRI as a triage test is still debated [11–14]. Several multicenter studies concluded that MRI can safely be used to reduce the number of biopsies in case of negative MRI, which reported a similar proportion of missed csPCa cases as in the current study [15–17]. The Cochrane review of Drost et al [18,19] demonstrated that 9% of men with negative MRI actually have csPCa. This percentage applied to the current data translates into six men who had undetected csPCa, which is almost equal to the five cases of csPCa that we would miss in the TRUS arm with risk stratification. Follow-up data of the PRECISION trial are not yet available, so it remains unclear how much csPCa is potentially missed and whether this has implications for the effect of treatment.

A strength of this study is the high-quality data of the PRECISION trial, representing 25 centers from 11 countries with an independent data monitoring committee and central pathological and radiological quality control. In addition, the cohort represents contemporary clinical practice since the data were collected from 2016 through 2017. Another strength of this study is that we used a well-validated risk stratification tool [8,20–23], in which we provide insight into the application of a validated tool in a contemporary setting.

A limitation of the current study is that we could not evaluate whether it would have been possible to identify patients with negative MRI who were likely to benefit from further clinical examination based on clinical variables such as a high PSA density with negative MRI. Risk stratification is mostly used to identify patients who are not likely to benefit from further clinical examination, but it can also be used to select patients with a negative triage test for further examination. Another limitation is that our results apply only to a specific population (ie, patients within the PRECISION trial with a negative DRE). However, this patient population represents a contemporary clinical cohort, so we believe that our results are generalizable to other clinical cohorts. Another limitation is that the RPCRC3 is developed for a population-based screening cohort. However, we show that with an intercept adjustment, this risk calculator can be applied to a contemporary clinical cohort.

Our results can support a new population-based screening trial. The most recent population-based screening trial in Sweden, the Stockholm3 (STHLM3) trial [24], showed that 62% of the randomized men with elevated PSA who underwent MRI had negative MRI [25]. The Göteborg PCa screening 2 trial showed that 75% of the randomized men with elevated PSA had negative MRI and 38% of all targeted prostate biopsies were not related to a diagnosis of PCa [26]. With upfront risk stratification using PSA and other clinical variables, it would have been possible to reduce the numbers of MRI scans and prostate biopsies in case of positive MRI, as is suggested by a new contemporary algorithm for early detection to stimulate early detection of PCa [27,28].

5. Conclusions

In conclusion, we investigated whether we could reduce the numbers of systematic prostate biopsy procedures, MRI scans, and targeted prostate biopsies in a contemporary clinical cohort. We found that, with good performance of the RPCRC and RPCRC-MRI, recalibration and an increase in the threshold of the RPCRC were necessary to reach optimal performance. After recalibration, 28% of all TRUS-guided systematic biopsies could be avoided, applying a risk-based cutoff of 20% for any PCa or 10% for csPCa. In addition, the use of the RPCRC could also have led to a reduction of 35% of all MRI scans. Subsequently, in men with positive MRI, the use of the RPCRC-MRI could reduce 9% of all targeted prostate biopsies. Our results confirm that when using risk stratification tools, albeit biomarkers, nomograms, or imaging modalities, clinicians should be aware of the a priori risk of their patient cohort to realize the full benefit of this powerful approach in daily clinical practice.

***Author contributions*:** Sebastiaan Remmers had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Roobol, Remmers.
Acquisition of data: Kasivisvanathan, Moore.
Analysis and interpretation of data: Remmers, Kasivisvanathan, Verbeek, Moore, Roobol.
Drafting of the manuscript: Remmers.
Critical revision of the manuscript for important intellectual content: Remmers, Kasivisvanathan, Verbeek, Moore, Roobol.
Statistical analysis: Remmers.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2021.11.002.

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