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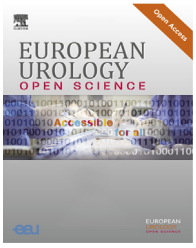

European Association of Urology

Sexual Medicine

Treatment with Autologous Adipose-derived Regenerative Cells for Peyronie's Disease in Men: The Straight @head Pilot Study

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Abstract

Background and objective: We evaluated the effectiveness of injecting autologous adipose-derived regenerative cells (ADRCs) into plaque in men with chronic Peyronie's disease (PD).

Methods: This pilot safety study recruited 22 Danish men with chronic PD from an outpatient clinic. Patients received one bolus of ADRCs injected into plaque, with follow-ups at 1, 3, 6, and 12 mo. The primary endpoint was a reduction in penile curvature. Secondary endpoints were serious adverse events in relation to treatment, and patient-reported results for improvements, distress, and unhappiness related to PD.

Key findings and limitations: There was no significant difference in curvature after treatment. However, the participants reported subjective improvements, less distress, and a decrease in unhappiness. No severe adverse events were observed during 12-mo follow-up.

Conclusions and clinical implications: Injections of ADRCs into PD plaque appear to be safe but had no significant measurable effect on penile curvature. Half of the participants reported a subjective improvement.

Patient summary: We studied the safety and effectiveness of injections of patient-derived regenerative cells for chronic Peyronie's disease. While the curvature of the penis did not significantly improve, the treatment was safe and some men reported a decrease in their distress and an improvement in penile shape.

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1. Introduction

Peyronie's disease (PD) has a significant impact on men's lives, with a prevalence ranging from 3.2% to 8.9% in studies [1]. PD results from fibrous plaque formation in the tunica albuginea due to disorganized collagen and elastin deposition [2]. PD progresses through two phases: an acute phase, with symptoms such as pain and debilitating curvature, and a chronic phase, in which curvature becomes permanent, affecting quality of life [1,3,4]. Despite various treatments, surgery remains the gold standard in the chronic phase [5].

Stem cells, particularly from adipose tissue, are widely used in tissue engineering because they can self-replicate, differentiate, and promote angiogenesis [6]. They can be either freshly isolated as adipose-derived regenerative cells (ADRCs), also known as stromal vascular-fraction cells (SVFs), or culture-expanded as adipose-derived stem cells (ASCs). ADRCs, which are easily accessible, have been studied in scar regenerative surgery [7,8], erectile dysfunction [9], and lymphedema [10]. They act primarily through paracrine pathways in responding to cytokine signaling [11]. Since PD plaques are fibrous tissue resulting from excessive collagen in the extracellular matrix, interest in stem cell treatment for PD is growing [12–20].

Studies by Castiglione et al demonstrated the positive effects of ASCs in rat models of acute PD [12] and chronic PD [13]. Subsequent research by the same group on the effects of ADRCs on erectile dysfunction in models of acute [20] and chronic PD [16] showed prevention and reversal of fibrosis. Other studies supported the ASC findings, showing a significant reduction in tunica albuginea fibrosis, with an enhanced benefit when ADCs expressed human IFNA2B [14,15]. However, human trials on stem cell therapy for PD are limited. In 2015, Levy et al [21] injected placental matrix–derived mesenchymal stem cells into five PD patients, which reduced plaque and curvature. In 2016, Lander et al [22] found that ADRCs combined with extracorporeal shockwave therapy (ESWT) in 11 men with chronic PD led to symptom improvements with minimal side effects. A 2023 survey highlighted the widespread use of off-label stem cell therapy for PD in the USA, with many clinics reporting high success rates [23].

The aim of our study was to determine whether ADRC injections can reduce penile curvature by 17° or more in comparison to baseline and to assess the safety of ADRC injection into plaque in men with chronic PD.

2. Patients and methods

2.1. Approvals

Written informed consent was obtained from all participants. The study was approved by the Danish Health and Medicines Agency (EudraCT number 2020-004297-22), the National Committee on Health Research Ethics (74705), and the Danish Data Protection Agency (1/21757). It was registered on ClinicalTrials.gov as NCT04771442 and adhered to the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice (GCP) guidelines, monitored by the GCP unit at Odense University Hospital.

2.2. Study design

Straight @head (S@h) was a prospective, open-label, single-arm, phase 1 study evaluating the safety and efficacy of a single ADRC injection into plaque in men with chronic PD. Screening began in July 2022, with treatments carried out between September 2022 and January 2023. Patients were recruited from the urology departments at the University Hospital of South West Jutland and Odense University Hospital, Denmark.

2.3. Patients

Of 39 men screened, 22 were enrolled; exclusions were for insufficient subcutaneous fat, lack of palpable plaque, or refusal of alprostadil injection. The previously published study protocol provides the detailed inclusion and exclusion criteria [24].

Detailed medical histories were obtained, and participants completed the Danish Peyronie's Disease Questionnaire (DK-PDQ) [25], the Sexual Health Inventory for Men (SHIM) [26], and the Erection Hardness Scale. A historical control group from the IMPRESS I and II trials was used for comparisons [27,28].

2.4. Outcome measures

Curvature was assessed using investigator-produced photographs taken after intracavernous injection of alprostadil or aviptadil/phentolamine in a redosing fashion, with sexual self-stimulation if needed. A urologist who was blinded to whether the photos were before or after treatment measured penile curvature using a goniometer, with verification lines added to the images (Supplementary Figs. 1 and 2).

2.5. Follow-up

Follow-up visits at 1, 3, 6, and 12 mo included recording of adverse events and penile examinations to assess PD plaque, penile length, and pharmacologically induced erections at 1 and 12 mo.

A single investigator (M.H.W.) conducted all inclusion and control visits. Data were managed using Research Electronic Data Capture (REDCap) tools [29,30] hosted at Odense Patient Explorative Network (www.sdu.dk/ki/open).

2.6. Adipose tissue collection

Liposuction was conducted under general anesthesia at the Department of Plastic Surgery, Odense University Hospital. Water jet–assisted liposuction (Body-jet, Human Med AG, Schwerin, Germany) was used to aspirate 200–250 ml of abdominal fat. A penile block with 20 ml of Marcain 5 mg/ml was administered after surgery.

2.7. Adipose tissue preparation

The labeled lipoaspirate (Supplementary Fig. 3) was transported to the Department of Biochemistry, where ADRCs

were isolated using a Celution 800/IV system (Cytori Therapeutics, San Diego, CA, USA, see Appendix 4) in a volume of 5 ml. Within 3 h, 2.5 ml of the ADRC product was injected into the patient's plaque. A tourniquet was applied at the base of the penis under penile block. The tourniquet was removed after 30 min.

Total viable nucleated cells recovered and the percentage viability were measured using a NucleocounterNC-100 system (ChemoMetec, Lillerød, Denmark). Cellular components were analyzed via flow cytometry on a BD LSRII system using FlowJo v10 software for a panel of cell-surface markers (CD31, CD34, CD73, and CD90).

2.8. Postoperative care

Patients were advised to use abdominal bandages for 4 wk and to perform penile exercises for at least 6 wk, and up to 3 mo if possible (Supplementary material).

2.9. Statistical analyses

On the basis of results from IMPRESS I and II [27,28], a curvature reduction of 17° was the target effect, with at least 15 participants required for 90% power (β) and a significance level (α) of 5%. Continuous variables were analyzed using paired t tests. Paired dichotomous variables were compared using McNemar's test. Statistical significance was set at $p < 0.05$.

The following is a summary of the study according to the DOSES framework [31]:

- Donor: autologous.
- Origin of tissue: adipose.
- Separation from other cell types/preparation method: minimal manipulation techniques (centrifugation, collagenase).
- Exhibited cell characteristics associated with behavior: cell markers CD31, CD34, CD73, and CD90.
- Site of delivery: intraplaque injection.

3. Results

3.1. Patient characteristics

Twenty-two men were included, with a mean age of 58.6 yr (range 44–74). Half of the patients ($n = 11$, 50%) had undergone previous PD treatment more than 6 mo before enrollment, with the majority having received ESWT ($n = 9$, 81%). Some participants had tried multiple alternatives. All men completed 12 mo of follow-up (Table 1).

3.2. PD characteristics

Mean penile deformation before treatment was 55.0° dorsally and 30.1° laterally. Eighteen (81.8%) of the men had experienced shortening of their penis during the course of their PD (Table 2).

3.3. Primary outcome

After ADRC injection into PD plaque, mean reductions in both dorsal (−6.2°) and lateral (−8.5°) curvature were observed, although the changes were not statistically

Table 1 – Characteristics of the study population at baseline, adverse events, patient-reported angle of curvature after treatment, and ADRC characteristics

Parameter	Result
Patients (*n*)	22
Mean body mass index, kg/m^2 (standard deviation)	27 (2.3)
Medical history of erectile dysfunction, *n* (%)	4 (18.2)
Penile trauma, *n* (%)	4 (18.2)
Patients with a partner, *n* (%)	21 (95)
Mean time together with partner, yr (standard deviation)	28.0 (14.2)
Comorbidity, *n* (%)	
Depuytren disease	6 (27.2)
Hypertension	3 (13.6)
Diabetes mellitus, type 2	2 (9)
Previous treatment, *n* (%)	
Extracorporeal shockwave therapy	9 (81)
Collagenase injections	2 (18)
Penile traction therapy	2 (18)
Surgery	1 (9)
Smoking status, *n* (%)	
Active smoker	2 (9)
Former smoker	7 (32)
Never smoked	13 (59)
First symptom of PD, *n* (%)	
Pain	8 (36.4)
Palpable lump	6 (27.3)
Bend	7 (31.8)
Other	1 (4.5)
PD duration, *n* (%)	
≥0.5 to <1 yr	1 (4.5)
≥1 to <1.5 yr	1 (4.5)
≥1.5 to <2 yr	4 (18,2)
≥2 to <2.5 yr	6 (27,3)
≥2.5 to <3 yr	1 (4.5)
≥3 to <3.5 yr	1 (4.5)
≥3.5 to <4 yr	1 (4.5)
≥4 yr	7 (32)
Plaque with no calcification, *n* (%)	18 (81.8)
Curvature deviation (%)	
Dorsal curvature	9 (40.9)
Dorsolateral curvature	8 (36.4)
Either only right or left curvature	4 (18.2)
Ventral curvature	1 (4.5)
Adverse events, *n* (%)	
Sore abdomen	
<3 d	10 (45)
<7 d	2 (9)
<14 d	2 (9)
Penile bruising	4 (18)
Uneven abdomen	4 (18)
Bruising of the abdomen	3 (14)
Itchy abdomen	2 (9)
Sensory disturbances in the abdomen	2 (9)
Fungal infection at the glans	1 (4.5)
Prolonged effect of penile block postoperatively (~20 h)	1 (4.5)
Contact with the general physician, *n* (%)	0
Calls or visits to the hospital, *n* (%)	0
How was the angle of curvature after ADRC treatment, (subjective) *n* (%)?	
Better	11 (50)
Worse	0
Unchanged	11 (50)
ADRC characteristics	
Mean drained fat tissue, ml (standard deviation)	214,5 (10.6)
Mean ARDC yield, cells/g fat tissue (standard deviation)	1.2×10^5 (7.6×10^4)
Mean cell size, μm (standard deviation)	11.3 (0.4)
Mean viability, % (standard deviation)	87.3 (2.2)
Mean number of ADRCs injected, million cells (standard deviation) [range]	20.4 (7.9) (11.3–33.5)
Mean aggregation, % (standard deviation)	12.1 (3.6)
Mean CD34 positivity, % (standard deviation)	54 (6.6)
Mean CD90 positivity, % (standard deviation)	87 (5.5)
Mean CD73 positivity, % (standard deviation)	53.8 (7.9)
Mean CD31 positivity, % (standard deviation)	32.4 (8.4)

ADRCs = adipose tissue–derived regenerative cells; PD = Peyronie's disease

Table 2 – Curvature parameters for the 22 patients at baseline and after intervention

	Baseline	12 mo	MD (95% CI)	MPIC (%)	*p* value
Penile deformity, *n* (%)					–
Dorsal curvature					
0					
<30°	1 (4.5)	1 (4.5)			
30°–60°	15 (68.2)	18 (81.8)			
> 60°	6 (27.3)	3 (13.6)			
Lateral curvature					
0	4 (18.2)	5 (22.7)			
<30°	11 (50.0)	10 (45.5)			
30°–60°	3 (13.6)	5 (22.7)			
> 60°	4 (18.2)	2 (9)			
Primary curvature					0.014
30°–60°	13 (59)	19 (86.4)			
>60°	9 (41)	3 (13.6)			
Flaccid penis length (cm)					0.67
Mean (SD)	13.0 (1.7)	12.7 (1.4)			
Range	10.0-17.0	10.5-15.5			
Mean number of plaques (SD)	1.8 (0.39)	1.2 (0.42)			0.67
Mean plaque size, mm^3 (SD) [a]	538 (512)	251 (285)			0.02
Mean curvature, ° (range)					
Dorsal curvature	55.0 (27–93)	48.8 (16–82)	−6.2 (−0.4 to 12.9)	7.0	0.07
Lateral curvature	30.1 (0–88)	21.6 (0–108)	−8.5 (−1.9 to 19.0)	–	0.10
Primary curvature	59.7 (34–93)	47.4 (2–82)	−12.3 (−5.5 to −20.4)	16.8	0.0037

CI = confidence interval; MD = mean difference; MPIC = mean percentage improvement in curvature; SD = standard deviation; SHIM = Sexual Health Inventory for Men.
[a] On ultrasound.

significant (Table 2). Six participants (27%) experienced a reduction of 17° or more (range 21°–56°) in one or both directions.

Table 3 – Patient-reported scores for PD symptoms

Parameter	Patients, *n* (%)		*p* value
	Baseline	12 mo	
Penile curvature (*n* = 21)			
Moderate	9	7	
Severe	12	8	
Combined moderate and severe	21 (100)	15 (71)	0.014
Change in penile shape (*n* = 22)			
Moderate	6	5	
Severe	14	9	
Combined moderate and severe	20 (90)	14 (64)	0.014
Decrease in penile rigidity (*n* = 22)			
Moderate	3	3	
Severe	5	2	
Combined moderate and severe	8 (36)	5 (23)	0.083
Pain on erection (*n* = 22)			
Moderate	2	1	
Severe	1	1	
Combined moderate and severe	3 (14)	2 (9)	0.317
Presence of plaque/lesion (*n* = 22)			
Moderate	3	7	
Severe	4	6	
Combined moderate and severe	7 (32)	13 (59)	0.014
Penile shortening (*n* = 22)			
Moderate	6	5	
Severe	9	8	
Combined moderate and severe	15 (68)	13 (59)	0.157
Distress over PD (*n* = 21)			
Moderate	8	4	
Severe	12	9	
Combined moderate and severe	20 (95)	13 (62)	0.008
Feeling unhappy (*n* = 22)			
Moderate	11	7	
Severe	5	4	
Combined moderate and severe	16 (75)	11 (50)	0.025

PD = Peyronie's disease.

3.4. Secondary outcome

No serious adverse events were observed (Table 1). All participants were given a schedule for noting adverse reactions for the first 2 wk. Two adverse events were classified as Clavien-Dindo grade I: a prolonged effect of penile bupivacaine injection lasting 20 h, and a fungal infection on the glans penis that developed 3 wk after surgery in a man with diabetes. All adverse events had resolved by final follow-up. Other secondary outcome results are presented in Table 2.

3.5. Subjective satisfaction

There were significant reductions in mean patient scores for distress over PD ($p = 0.008$), change in penile curvature and shape ($p = 0.014$), and feeling unhappy ($p = 0.025$). Data were obtained from only 21 patients, as one patient did not respond (Table 3).

The participants reported favorable postoperative outcomes, such as softer plaque ($n = 8$, 36%), an improvement in blood flow and erection quality ($n = 7$, 32%), and positive feedback from their partner ($n = 7$, 32%).

3.6. DK-PDQ and SHIM results

The mean score for psychological and physical symptoms significantly decreased from 13 points at baseline to 8.3 points at 12-mo follow-up ($p = 0.001$). Decreases in scores for the other two DK-PDQ domains were not statistically significant, and there were no significant changes in SHIM scores (Table 4).

3.7. ADRC characteristics

The mean amount of adipose tissue harvested was 214 ml (standard deviation 10.6). All patients were discharged from

Table 4 – DK-PDQ and SHIM scores reported by the Straight @head cohort (*n* = 22) at baseline and 12 mo

	Baseline	12 mo	Mean difference	*p* value
Sexually active within the past 3 mo, *n* (%)	17 (77)	15 (68)		0.157
Mean DK-PDQ domain scores (SD)				
Psychological and Physical Symptoms	13 (4.8)	8.3 (7.0)	−4.7	0.001
Penile Pain	4.7 (6.0)	4.6 (6.9)	−0.1	0.731
PD Symptom Bother	8 (3.5)	6.2 (4.8)	−1.8	0.589
Mean SHIM score (SD)	20.1 (4.2)	21.6 (6.4)	+1.5	0.794

DK-PDQ = Danish Peyronie's Disease Questionnaire; PD = Peyronie's disease; SD = standard deviation; SHIM = Sexual Health Inventory for Men.

Table 5 – Changes from baseline to 12 mo in the Straight @head cohort versus the placebo group in IMPRESS I & II

Parameter	Straight @head cohort	IMPRESS I & II placebo group
Subjects (*n*)	22	284
Change in domain scores (points)		
Psychological and Physical Symptoms (scale 0–24)	−4.7	−1.3
Penile Pain (scale 0–30)	−0.1	−4.3
PD Symptom Bother (scale 0–16)	−1.8	−1.8
Change in curvature (°)	−12.3	−9.3
Change in curvature (%)	16.8	18.2
Change in penile length (cm)	−0.3	+0.2

PD = Peyronie's disease.

the hospital on the same day as tissue harvesting. Table 1 lists results for the ADRC characteristics.

3.8. Comparison to the control group in IMPRESS I and II

IMPRESS I and II [27,28] were two extensive multi-institutional, double-blind, randomized, placebo-controlled phase 3 studies on intralesional administration of collagenase from *Clostridium histolyticum* in 832 individuals versus placebo in 281 participants. The placebo injection consisted of a buffer solution containing sucrose. Since S@h was a phase 1 study and lacked a placebo group for comparison, we opted to use the placebo groups from the IMPRESS studies as a control.

The S@h and IMPRESS groups had comparable mean age and PD bother symptoms at baseline. However, the mean PDQ pain score was higher in IMPRESS and the placebo group experienced a reduction in curvature of 18.2% (−9.3° ± 13.6°). Analysis of primary curvature in S@h revealed a mean percentage improvement of 16.8%, equivalent to a reduction of −12.3°. The prevalence of curvature exceeding 60° was 22.4% in the placebo group, in contrast to the much higher rate of 41% in the S@h cohort.

Regarding secondary efficacy measures, the placebo group experienced a significant reduction in pain score, but change of only −1.3 points for the PDQ Psychological and Physical Symptoms domain. Conversely, the decrease was considerable in the S@h cohort, at 4.3 points (Table 5).

4. Discussion

We evaluated the safety and efficacy of ADRC injection into plaque in men with chronic PD. Although there was no significant reduction in penile curvature, the study results confirm the safety of this treatment, and there were significant improvements in plaque size and subjective perception of penile curvature and distress. There was a statistically significant reduction in primary curvature. To the best of our knowledge, there have been no comprehensive reports on the effects of ADRC injection in men with PD.

We reported both lateral and dorsal curvature measurements for each patient, as we believe that this approach provides a more accurate representation of the overall impact of the deformity. We did not prioritize one curvature direction over the other, as focusing on just one plane would be unrepresentative. Notably, 27% of the study participants had curvature exceeding 30° in both the lateral and dorsal planes. Reports for IMPRESS I and II [27,28] do not clarify the criteria for determining the degree of primary curvature and it is unclear whether the investigator or the participant made the decision. For instance, would dorsal curvature of 66° cause more distress than lateral curvature of 58°, as observed in one of our participants?

We are aware that reporting curvature from two angles does not fully capture the extent of the deformity; we also observed significant variability in curvature measurement, even when using the same tool. Ziegelmann et al [32] estimated that variations can range from 10° to 20° when determining the maximum curvature, and this estimate falls within the effect range reported for many treatments, including the present study.

4.1. Comparison to other studies

Only one clinical study on ADRC has been conducted, in which ADRC treatment was combined with ESWT [22]. Although patients reported subjective improvements, the lack of detailed documentation limits the ability to make comparisons. The authors did not report the effect on the degree of curvature degree, results for PDQ subsections 2

and 3, objective findings, or the characteristics of the ADRCs used. The lack of detailed results precludes any comparison to our findings. However, it is noteworthy that the authors did not report any serious adverse events related to the liposuction procedure or plaque injection.

In our study, the effects on curvature were comparable to those observed in the placebo groups from IMPRESS I and II [28]. Despite statistically significant reductions in scores for the Psychological and Physical Symptoms domain of the DK-PDQ, the impact of ADRC injection on curvature in our study was less pronounced than the impact of sucrose injections in IMPRESS I and II.

In the IMPRESS studies, the placebo group initially had higher pain levels, making any reduction in pain more noticeable. By contrast, S@h participants had low pain levels at baseline, which did not change significantly (only 0.1 points). Furthermore, the degree of curvature was lower at baseline in IMPRESS, so although the absolute change in curvature was more significant in our study, this did not translate to a higher mean percentage change.

Unfortunately, beyond the PDQ, subjective improvements or soft outcome values for the placebo group in IMPRESS I and II are not mentioned, in contrast to the detailed subjective improvements recorded in S@h, making comparisons challenging.

4.2. ADRC characteristics

Our results indicated higher percentages of specific surface markers than in some studies [9,33], probably because of better fat quality and a lower level of blood contamination, resulting in a higher yield of viable cells. This is consistent with studies showing high levels of CD90 and CD73 in SVFs, which was attributed to the gentle suctioning process [6].

Some 50% of our cohort reported a subjective improvement in curvature, raising questions about the reasons for this perception. Possible explanations include a desire to see an improvement after the liposuction procedure, reporting positive outcomes to please the researcher, and a sense of control and engagement from actively participating in treatment. The absence of a placebo group makes it difficult to attribute these changes solely to the treatment. Psychological benefits were noted despite minor curvature improvements, suggesting that psychological wellbeing is an important factor [32]. However, it is uncertain if these changes are clinically meaningful, although they may translate into improved psychological wellbeing and self-esteem, potentially enhancing patients' overall satisfaction with their treatment. A quality-of-life questionnaire could provide better insights into the clinical significance of and overall satisfaction with this treatment approach.

4.3. Clinical implications and future directions

This study enhances our understanding of stem cell therapy for PD and emphasizes the need for further research to refine treatment protocols. Future studies should optimize cell dosage and delivery methods, explore long-term effects, and evaluate multifocal approaches for targeting of PD plaque. Combinations of ADRCs with treatments such as penile traction, anti-inflammatory drugs, and antioxidants should also be investigated. Standardization of outcome measures is essential for multicenter randomized trials to validate stem cell therapy as a standard treatment. In addition, future studies should use patient-reported outcome measures and longer-term follow-up to assess whether improvements are sustained and meaningful in daily life and relationships. Determination of the minimally significant difference for these outcomes will help in evaluating their relevance to patients.

4.4. Strengths and limitations

Our study has some limitations, including the fact that participants were neither randomized nor blinded, leading to the absence of a placebo group. The small sample size raises the potential for a type II error; however, the study robustness was enhanced by including 22 participants, which was greater than the minimum of 15 required for statistical significance.

The Peyronie's Disease Questionnaire was culturally adapted for Denmark [25] but the DK-PDQ has not been validated. The SHIM questionnaire, which has not been validated for men with PD [26], could introduce bias, as PD itself can result in sexual inactivity.

Although subjective, ultrasound measurements revealed a significant reduction in plaque size. Despite being measured by the same investigator, there was a steep learning curve, and a lack of correlation between the degree of curvature and plaque size has been reported [34].

5. Conclusion

This clinical trial, grounded in animal research and building on a prior clinical study, is the first well-conducted investigation into the effects and safety of ADRC treatment in patients with chronic PD. Although the reductions in penile curvature were not statistically significant, there were notable improvements in secondary outcomes, such as plaque size and subjective distress measures. The treatment was safe, but further research is necessary to determine the potential of ADRCs in PD treatment, probably in combination with nonsurgical approaches.

Author contributions: Majken H. Wiborg 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: Wiborg, Lund.
Acquisition of data: Wiborg, Harken Jensen.
Analysis and interpretation of data: Wiborg, Krøijer.
Drafting of the manuscript: Wiborg.
Critical revision of the manuscript for important intellectual content: Wiborg, Lund, Laursen, Harken Jensen, Sørensen, Chakari.
Statistical analysis: Krøijer.
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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2024.12.005.

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