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Cooled versus conventional radiofrequency treatment of the genicular nerves for chronic knee pain: 12-month and cost-effectiveness results from the multicenter COCOGEN trial

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ABSTRACT

Background Radiofrequency (RF) treatment of the genicular nerves reduces chronic knee pain in patients with osteoarthritis (OA) or persistent postsurgical pain (PPSP) after total knee arthroplasty (TKA). The objective of this study is to compare long-term outcomes of cooled and conventional RF and perform an economic evaluation.

Methods The COCOGEN trial is a double-blinded, non-inferiority, pilot, randomized controlled trial that compared the effects up to 12 months of cooled and conventional RF in patients with chronic knee pain suffering from OA or PPSP after TKA following a 1:1 randomization rate. Outcomes were knee pain, functionality, quality of life, emotional health, medication use, and adverse events. A trial-based economic evaluation was performed with a 12-month societal perspective. Here, the primary outcome was the incremental costs per quality-adjusted life year (QALY).

Results 41 of the 49 included patients completed the 12-month follow-up. One patient in the PPSP cooled RF group had substantial missing data at 12-month follow-up. The proportion of patients with ≥50% pain reduction at 12 months was 22.2% (4/18) in patients treated with conventional RF versus 22.7% (5/22) in patients treated with cooled RF (p>0.05). There was a statistically significant difference in the mean absolute numerical rating scale at 12 months after cooled RF and conventional RF in patients with PPSP (p=0.02). Differences between other outcomes were not statistically significant. The health economic analysis indicated that cooled RF resulted in lower costs and improved QALYs compared with conventional RF in PPSP but not in OA. There were no serious adverse events.

Conclusions Both RF treatments demonstrated in approximately 22% of patients a ≥50% pain reduction at 12 months. In patients with PPSP, contrary to OA, cooled RF seems to be more effective than conventional RF. Additionally, cooled RF has in patients with PPSP, as opposed to OA, greater effectiveness at lower costs compared with conventional RF.

Trial registration number NCT03865849.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Conventional and cooled radiofrequency (RF) of the genicular nerves reduce therapy-resistant chronic knee pain in patients with osteoarthritis and persistent postsurgical pain; however, long-term effects of this treatment are unknown. Cooled RF is intrinsically more costly than conventional RF, and it is unknown whether a cooled RF treatment is cost-effective compared with conventional treatment.

WHAT THIS STUDY ADDS

⇒ This pilot randomized controlled trial adds long-term clinical and cost-effectiveness results of a comparison between cooled and conventional RF treatment of the genicular nerves to treat chronic knee pain.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A large, powered randomized controlled trial is necessary to prove statistical significance, identify which patients benefit the most, and address uncertainty induced by the small size of this pilot trial.

INTRODUCTION

Osteoarthritis (OA) of the knee is a degenerative disease of the cartilage and subchondral bone which leads to pain, loss of function, and potentially a lower quality of life and financial burden.[1–4] When conservative therapy fails to treat these symptoms, a total knee arthroplasty (TKA) is the last resort. However, not everyone is a suitable candidate for such a procedure because of comorbidities or young age. Patients with comorbidities have a higher perioperative risk, and postoperative revalidation can be difficult. Young patients have worse outcomes with a higher risk of revision.[5] Furthermore, up to 53% of patients develop persistent postsurgical pain (PPSP) after a TKA, forming a second cause of chronic knee pain.[6 7]

Chronic pain has a high impact on a patient's quality of life and is associated with a high

socioeconomic cost.[3 4] Recently, radiofrequency (RF) treatment of the genicular nerves emerged as a minimally invasive treatment for chronic knee pain. By blocking nociceptive pain signals from the knee, through applying a RF current in proximity of the genicular nerves, a patient with knee OA or PPSP after TKA can obtain pain relief and improvement of knee function.[8 9] In addition to the conventional RF treatment, newer modality, cooled RF has been developed to create a bigger lesion size aimed to further improve the success rate and prolong the effect.[10] In a previous publication, both after a conventional and cooled RF treatment of the genicular nerves, a reduction of chronic knee pain in patients with OA and PPSP after TKA up to 6 months was described.[11] While this pilot trial was intrinsically underpowered, cooled RF resulted in a non-significant higher probability of pain reduction compared with conventional RF in the whole study population and in both subgroups (OA and PPSP). In the PPSP group, the discrepancy between the treatment success of cooled RF and conventional RF was higher when compared with the OA group. In another recent trial, cooled RF did not result in significantly higher long-term benefits when compared with conventional RF in patients with OA.[12] Other previous trials also indicate that RF of the genicular nerves leads to improved quality of life in patients with knee OA.[13–15] Whether cooled RF treatment is cost-effective compared with conventional RF in patients with therapy-resistant OA or PPSP is yet unknown.

In this manuscript, we present the 12-month clinical effectiveness results and the cost-effectiveness analysis of cooled versus conventional RF in therapy-resistant chronic knee pain due to OA and PPSP. The analysis is part of the COCOGEN pilot randomized controlled trial, of which the 6-month effectiveness results are published in a separate paper.[11] We hypothesized that at 12 months in both patient groups (OA and PPSP), knee pain after conventional RF treatment is not inferior to cooled RF and that cooled RF is cost-effective compared with conventional RF.

METHODS

Trial design

The COCOGEN trial was a randomized controlled, non-inferiority, pilot trial conducted in three participating centers (Hospital Oost-Limburg, Belgium; Maastricht UMC+, The Netherlands; and Rijnstate, The Netherlands) (online supplemental file 2). Patients were followed up to 12 months after treatment. Ethical approval was granted from the ethical committees of Hospital Oost-Limburg (19/0038U) and Maastricht UMC+ (NL69877.068.19/METC 19–031). The study was registered at ClinicalTrials.gov on 7 March 2019 (NCT03865849). Patients were enrolled between 10 February 2020 and 28 April 2021.

Participants, randomization, and blinding

Adult patients suffering from long-term (>12 months) chronic anterior knee pain due to OA and PPSP after TKA that were unresponsive to conventional treatments (physiotherapy, analgesics, or intra-articular infiltrations) were included in the trial (online supplemental file S1). After stratification per etiology of pain (OA and PPSP), participants were randomized into two treatment groups, the conventional and cooled RF groups, with an allocation ratio of 1:1 and variable block size of 2 or 4 in the online Castor electronic data capture application. In this double-blinded trial, both the patient and the outcome assessor were unaware of the patient's treatment allocation up to 6 months. After a systematic unblinding at 6 months, patients were followed up until 12 months after treatment. Patients were encouraged to continue other conservative care throughout the trial.

Intervention

Participants received RF treatment of the superomedial, superolateral, and inferomedial genicular nerves using a Halyard/Coolief RF generator.[16] No prognostic block prior to the treatment was used. Patients were not sedated, hemodynamically monitored, and positioned in a supine position on a fluoroscopy table with the index knee flexed 10–15°. The RF needle placement was guided by ultrasound, and the final position was controlled using fluoroscopy. The target point was the mentioned genicular nerves at the junction of the shaft and condyle of the femur and tibia. The subcutaneous tissue was anesthetized with 1 mL lidocaine 2% at each entry point before the introduction of the RF needle. After obtaining a sensory threshold (50 Hz) of ≤0.5V and an absent response to motor stimulation (2 Hz) of 1.0 V, 1 mL of lidocaine 2% was injected at each genicular nerve. Each of the three nerves was treated with conventional RF using a 100 mm, 18-gage, straight RF introducer and one 10 mm active tip RF probe set at a temperature of 80°C for 90 s or with cooled RF using a 100 mm long, 17-gage, straight RF introducer and one 4 mm active tip, 18-gage cooled RF probe generating a temperature of 60°C at the tip of the probe for 150 s.

Study endpoints and data collection

Participants were assessed at baseline, 1, 3, 6, and 12 months after the procedure. Data were collected from the medical patient record, questionnaires, and functionality tests in an online patient case report form in the Castor data management tool.

The primary endpoint of the COCOGEN trial was the proportion of patients with ≥50% pain reduction at 3 months. We previously reported that 4 of 23 patients treated with conventional RF (17%) versus 8 of 24 with cooled RF (33%) (p=0.21) reached the primary endpoint at 3 months.[11]

The clinical outcomes at 12-month follow-up were the following: numerical rating scale (NRS), Oxford knee score (OKS), patient's self-reported impression of change measured by the Patient's Global Impression of Change (PGIC), health-related quality of life (HRQoL) expressed in Euroqol 5-dimension 3-level (EQ-5D-3L) questionnaire, mental health measured by the Hospital Anxiety and Depression Scale (HADS) and by the Pain Catastrophizing Scale (PCS), medication use assessed by the Medication Quantification Scale III (MQS III), and adverse events and incidence of a TKA.[17–23] The NRS score at each timepoint was the mean score of the previous 4 days except for the 12-month follow-up. At 12 months, patients were asked to report the NRS in rest and during movement. We reported the mean of these two.

Statistical methods

As COCOGEN is a pilot RCT, the rule of thumb of Julious was used to include 12 patients per treatment group amounting to a total of 48 patients.[24] The rule of thumb ensures enough participants to estimate treatment effects and measures of variance but may not ensure sufficiently high power for null-hypothesis testing. The effectiveness outcomes were analyzed following the per-protocol principle as this is more conservative for testing non-inferiority hypothesis. To test for non-inferiority, the mean NRS difference between groups, including 95% CI, was calculated at 12 months. The lower bound of the 95% CI of the difference was compared with the non-inferiority limit of 0.75 NRS points.[25 26] The analysis of the outcomes was

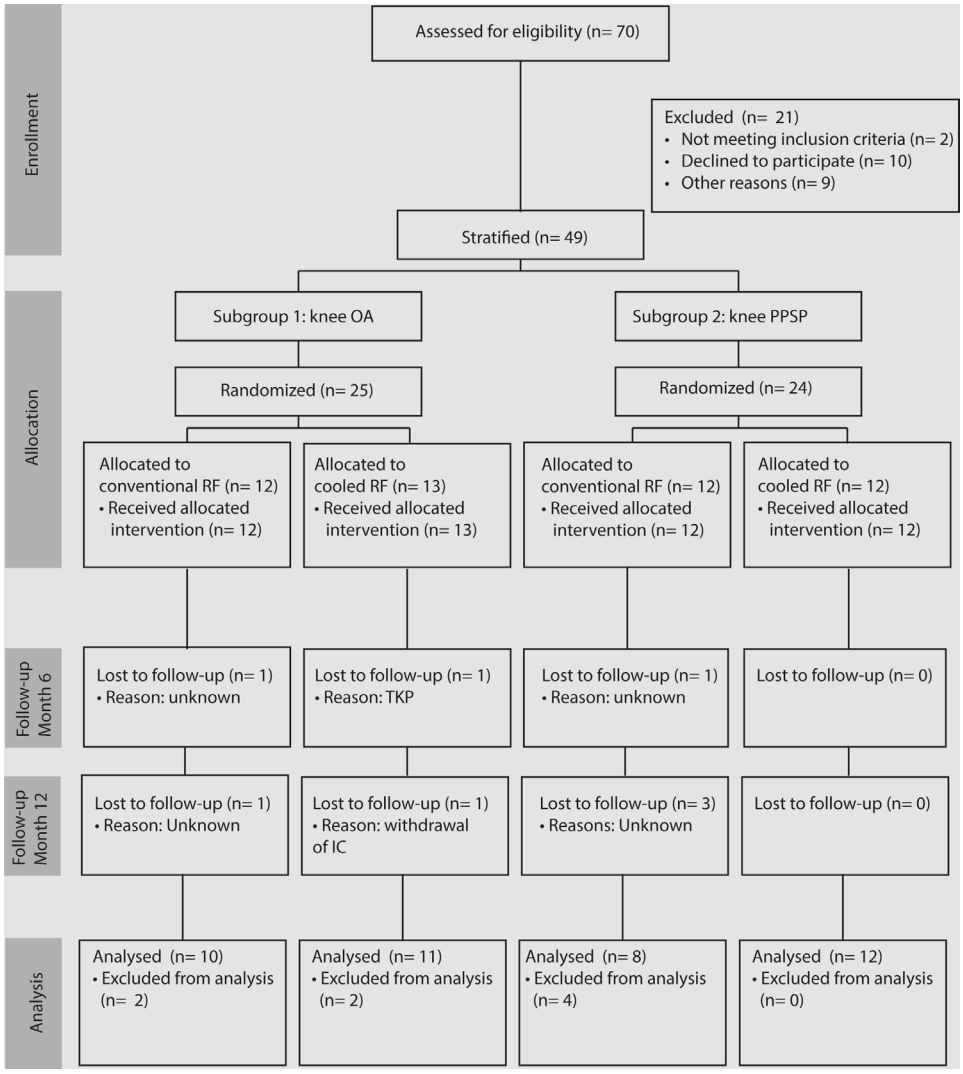

Figure 1 The Consolidated Standards of Reporting Trials flow chart of participants during the trial up to 12 months. IC, informed consent; OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency; TKP, total knee prothesis.

exploratory due to the pilot nature of the trial. The proportion of patients achieving treatment success was calculated as percentage. The difference between groups was computed, including 95% CI, and Pearson's χ^2 test was used for the comparison between the treatment groups. We reported the secondary study parameters as mean or percentage of difference including 95% CI. The mean NRS at 12 months was calculated as the average score of the reported NRS during rest and during movement.

The economic evaluation

The economic evaluation was designed and analyzed to conform with the Dutch guidelines for health economic evaluation (HEE).[27] A cost-effectiveness analysis was performed for patients with OA and PPSP separately. The base case analysis was performed from a societal perspective and a time horizon of 12 months.

Health outcomes

The quality-adjusted life year (QALY) was chosen as the measure of the benefit of the cooled and conventional RF intervention. The QALY is the preferred health outcome in economic evaluations and is a combined measure of HRQoL and survival.[28] HRQoL was measured by the EQ-5D-3L.[29] The EQ-5D-3L is a patient-reported generic measure of HRQoL comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels reflecting the severity of the impact of the patient experiences. The patient's responses were converted to utility scores using the Dutch social tariff.[30] Subsequently, QALYs were calculated using the area under the curve of the time in which a certain health state was multiplied by the utility score of this health state. The EQ-5D was completed electronically at 1, 3, 6, and 12 months after treatment.

Resource use and costs

Resource use was classified into four main categories: RF intervention costs, healthcare resource use, costs to patient and family, and productivity costs. The cost of the RF interventions was calculated as the sum of the cost of a day hospitalization, the costs of the used material, and the cost of the medical personnel. Healthcare resource utilization included healthcare-related visits (eg, general practitioner, physiotherapist, and dietician), visits to other allied professionals (eg, social worker), use of home care (home nursing care and family care), inpatient hospitalizations, and emergency department visits. Patient and family costs included out-of-pocket expenses made by the patient (eg, for

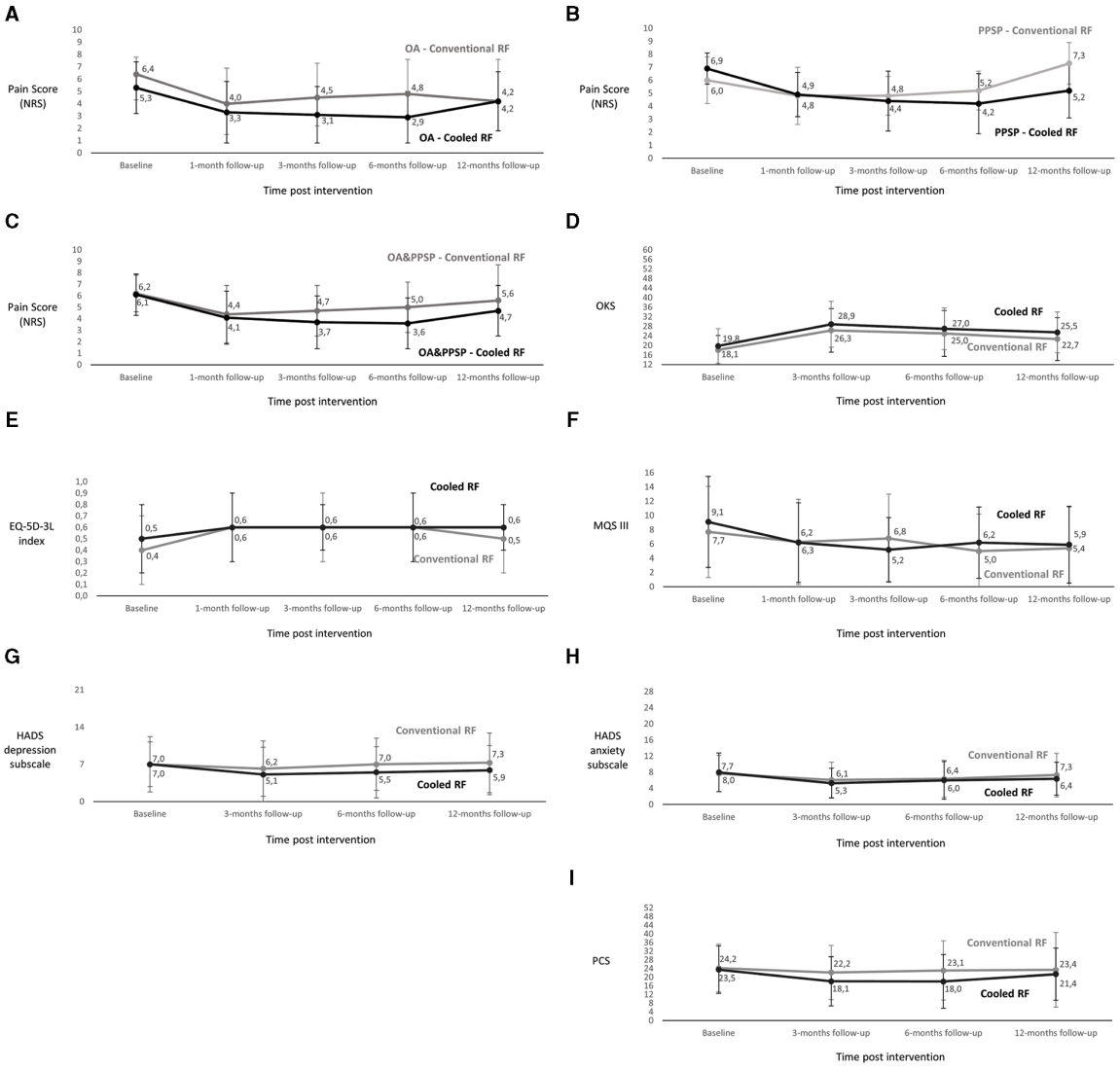

Figure 2 Evolution of the clinical outcomes during the 12-month follow-up of the COCOGEN trial. Vertical lines represent the standard deviation. NRS, numerical rating scale; RF, radiofrequency; OA, osteoarthritis; PPSP, persistent postsurgical pain; OKS, Oxford knee score; EQ-5D-3L, EuroQol 5-dimension 3-level; MQS III, Medication Quantification Scale III; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale.

medication and braces) and informal care costs. Costs due to lost productivity included costs due to short-term and long-term absences from paid and unpaid work.

Data on other healthcare utilization, patient and family costs, and costs due to loss of productivity were collected electronically using an adapted version of the iMTA Medical Consumption Questionnaire (MCQ) and the Productivity Cost Questionnaire (PCQ) at baseline, 3, 6, and 12 months.[31 32] The recall period for the PCQ and MCQ questionnaires was 4 weeks and 3 months, respectively. The iMTA MCQ is a validated generic instrument for measuring resource use and includes questions on healthcare use, for example, consultation with healthcare professionals (medical doctor and general practitioner physiotherapist), interventions, hospitalizations, and informal care and out-of-pocket expenses. The costs of healthcare use were calculated by multiplying the resource use by the price per unit of resource using Dutch reference prices.[27] The unit price in euro for each cost category can be found in online supplemental file S2. The reference year to which all costs have been adjusted for the analysis is 2021. As the follow-up period did not exceed 12 months, no discount rate was applied. Costs of medication use were calculated only based on the information the patients reported in the MCQ questionnaire and not linked to the MQS III score. The iMTA PCQ is designed and validated to assess productivity loss, by quantifying the hours of lost paid and unpaid work. Productivity costs were calculated using the friction cost method.[27]

Statistical analysis of HEE

Missing PCQ data were imputed based on paid work status at previous measurement and earlier/later responses (eg, if a respondent did not have paid work at baseline and the PCQ was missing at 3 months, 0 costs were imputed). Other missing cost and effect data were imputed using multiple imputations using the mice package for R.[33] The imputation model included randomization, age, sex, and cost variables at other time points. Less than 5% of data were missing; hence, 10 imputed datasets were generated.[34 35] Since the MCQ and PCQ were not administered at 9-month follow-up, the mean costs of 6 and 12 months were used to calculate the total 12-month costs for each respondent. Each of the imputed datasets was analyzed separately, and results were pooled using Rubin's rules.

Mean healthcare and societal costs and QALYs for the OA and PPSP subgroups acquired over the 1-year study period were reported using descriptive statistics.[36] The mean differences in costs and effects between cooled and conventional RF were estimated using linear regression models, adjusted for baseline differences and confounders, where appropriate.[37] To address the uncertainty surrounding the differences in costs and effects, non-parametric bootstrapping with 5000 replications was used to estimate their 95%CI.[38] If appropriate, the deterministic incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in mean costs by the difference in mean QALYs between cooled and conventional RF. Non-parametric bootstrapping was used to plot the joint distribution of the difference in costs and QALYs in a cost-effectiveness plane, further exploring uncertainty. Finally, cost-effectiveness acceptability curves show the probability of the cooled RF being cost-effective compared with conventional RF for a range of ceiling ratios for QALY. Ceiling ratios reflect the maximum price health policymakers are willing to pay for an additional QALY. In the Netherlands, the Council for Public Health and Healthcare proposes an informal ceiling ratio between €20.000 and €80.000 per QALY, depending on the burden of disease.[39]

To assess the robustness of results, in addition to the base case analysis of the economic evaluation, additional analyses were performed: (1) an analysis from a healthcare perspective in which costs due to productivity loss and patient and family costs were excluded and (2) an analysis with a short-term perspective (6 months). All analyses were performed in R Studio. The reporting of this economic evaluation follows the Consolidated Health Economic Evaluation Reporting Standards guidelines.[40]

RESULTS

Participants

41 of the 49 included patients reported 12-month outcomes (10 in the OA conventional RF group, 11 in the OA cooled RF group, 8 in the PPSP conventional RF group, and 12 in the PPSP cooled RF group). Figure 1 depicts the Consolidated Standards of Reporting Trials flow chart of participants during the trial up to 12 months. In the OA group, 21 of 25 patients (84%) completed the study, while 20 of 24 patients (83%) of the PPSP group completed the study. One patient in the PPSP cooled RF group had substantial missing data at 12-month follow-up, including the NRS. Between 6 and 12 months, five additional patients dropped out. All randomized patients received the allocated treatment. There were no crossovers between the treatment arms. Baseline patient characteristics were presented in the previous publication.[11]

Effectiveness analysis

The evolution of the clinical outcomes during the 12-month follow-up is presented in figure 2.

Percentage of pain reduction

At 12 months, the percentage of patients that reached ≥50% pain reduction compared with baseline was 22.2% (4/18) after a conventional RF and 22.7% (5/22) after cooled RF (table 1). In both the OA and PPSP populations, the difference in percentage of patients that reached ≥50% pain reduction between cooled and conventional RF was not statistically significant. When using the recommended cut-off of ≥30% pain reduction by the 'Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials' guidelines, only the difference between conventional and cooled RF in the PPSP group was statistically significant (p=0.045). The other differences were not statistically significant.

Numerical rating scale

Whole population: cooled versus conventional RF

The mean pain reduction (ΔNRS) (95% CI) of all patients treated with cooled RF at 12 months compared with baseline was −1.4 (−2.5 to −0.7). This change over time was statistically significant (p=0.018). The mean ΔNRS (95% CI) of all patients treated with conventional RF was −0.8 (−2.3 to 0.7). This change over time was not statistically significant (p=0.29). The mean absolute NRS at 12 months did not differ significantly (p=0.30) between cooled and conventional RF. The non-inferiority comparison between conventional and cooled RF was performed in the whole population due to the limited sample size of this trial. The point estimate difference in NRS was 0.9 at 12 months with 95% CI (−0.8 to 2.6). This includes the non-inferiority margin of 0.75 making it inconclusive at this point (figure 3).

Whole population: PPSP versus OA

The mean NRS of patients with PPSP decreased from 6.4 at baseline to 6.1 at 12 months. In these patients, the mean ΔNRS (95% CI) at 12 months compared with baseline was −0.6 (−1.8 to 0.6). This change over time was not statistically significant (p=0.30). The mean NRS of patients with OA decreased from 5.8 at baseline to 4.2 at 12 months. In these patients, the mean ΔNRS (95% CI) at 12 months compared with baseline was −1.6 (−2.9 to −0.2). This change over time was statistically significant (p=0.024). The mean absolute NRS at 12 months did not differ significantly (p≥0.05) between patients with PPSP and OA.

Table 1 The percentage of patients with ≥30% and ≥50% pain reduction after conventional and cooled RF at 12 months follow-up timepoints in each patient subgroup

	OA			PPSP			Whole group		
	Conv RF, n (%)	Cooled RF, n (%)	P value*†	Conv RF, n (%)	Cooled RF, n (%)	P value*†	Conv RF, n (%)	Cooled RF, n (%)	P value*†
≥50% pain reduction compared with baseline									
6 months	3/11 (27.3)	4/12 (33.3)	1.00	1/11 (9.1)	5/12 (41.7)	0.16	4/22 (18.2)	9/24 (37.5)	0.15
12 months	4/10 (40)	3/11 (27.3)	0.66	0/8 (0)	2/11 (18.2)	0.49	4/18 (22.2)	5/22 (22.7)	1.00
≥30% pain reduction compared with baseline									
6 months	4/11 (36.4)	5/12 (41.7)	1.00	1/11 (9.1)	5/12 (41.7)	0.16	5/22 (22.7)	10/24 (41.7)	0.17
12 months	4/10 (40)	4/11 (36)	1.00	0/8 (0)	5/11 (45)	0.045	4/18 (22.2)	9/22 (40.9)	0.21

*P value compares conventional RF with cooled RF procedure.
†Pearson's χ^2 test used to compare proportions.
OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency.

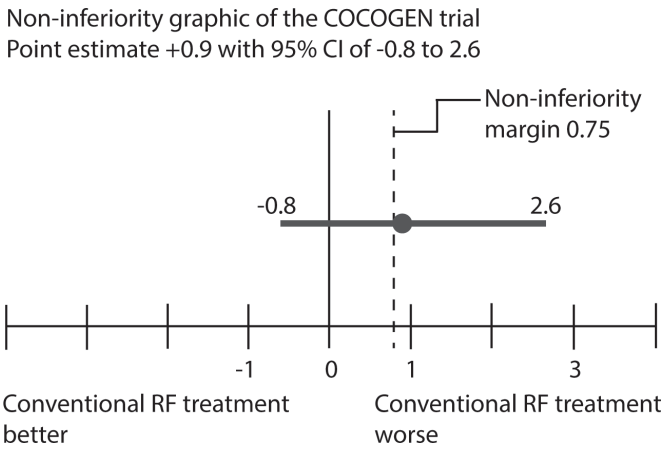

Figure 3 Non-inferiority graphic of the COCOGEN trial.

Patients with PPSP: cooled versus conventional RF

In patients with PPSP treated with cooled RF, the mean ΔNRS (95% CI) at 12 months compared with baseline was −1.7 (−3.2 to −0.3). This change over time was statistically significant (p=0.03). In patients with PPSP treated with conventional RF, the mean ΔNRS (95% CI) at 12 months compared with baseline was 0.9 (−0.9 to 2.7). This change over time was not statistically significant (p=0.27). The mean absolute NRS at 12 months did differ significantly between conventional and cooled RF in patients with PPSP (p=0.02).

Patients with OA: cooled versus conventional RF

In patients with OA treated with cooled RF, the mean ΔNRS (95% CI) at 12 months compared with baseline was −1 (−3 to 0.9). This change over time was not statistically significant (p=0.26). In patients with OA treated with conventional RF, the mean ΔNRS (95% CI) at 12 months compared with baseline was −2.1 (−4.3 to 0). This change over time was statistically significant (p=0.05). The mean absolute NRS at 12 months did not differ significantly between conventional and cooled RF in patients with OA (p=0.41).

Other outcomes

In figure 2, we present the evolution of the other clinical effectiveness outcomes. The mean PGIC, OKS, EQ-5D-3L, HADS depression subscale, HADS anxiety subscale, PCS, and MQS III of the conventional RF and cooled RF group were not statistically significantly different at 12 months of follow-up. Mean scores of the other outcomes in the whole population at 12 months are presented per allocated RF treatment in online supplemental file S3.

Two patients with OA (one in the OA cooled RF group and one in OA conventional) underwent a TKA procedure between 6 and 12 months of follow-up. One additional patient with PPSP treated with conventional RF was treated with corticosteroids and capsaicin patch in the index knee between 6 and 12 months of follow-up. No patient with PPSP underwent a revision or other surgical reintervention of the total knee prothesis.

Safety analysis

There were no adverse events reported that were possibly or definitively related to the procedure at 12 months of follow-up. The infrapatellar hypoesthesia reported after a cooled RF at 6 months did not persist at 12 months.

Health-economic analysis

Participants

23 patients were included and analyzed in the PPSP subgroup and 24 in the OA group. The distribution of included patients in Belgium and the Netherlands was, respectively, 32 and 15. One patient with OA treated with cooled RF and one with PPSP treated with conventional RF were excluded from the analysis as no data were collected on resource use and costs at any of the follow-up moments. We present in online supplemental file S4 the baseline patient characteristics of the analyzed population.

Healthcare use

Costs from a societal perspective for each subgroup at 12 months are outlined in table 2. In PPSP, the two highest contributors to the considerably higher societal costs in the conventional RF group compared with cooled RF were the healthcare costs and the costs to patient and family (ie, out-of-pocket expenses and informal care costs). In the OA group, all three categories (healthcare costs, costs to patient and family, and productivity costs) contributed to the higher total societal costs of the cooled RF group compared with conventional RF.

Cost-utility analysis

In the PPSP group at 12 months after treatment, the difference between the mean QALYs estimated between cooled RF and conventional RF favored cooled RF. At 12 months, the patients with PPSP treated with cooled RF had fewer total costs with a higher gain in QALYs compared with the conventional RF group. Hence, cooled RF is the dominant treatment, and no ICER was calculated. In the OA group at 12 months after treatment, the difference in QALY between the cooled and conventional RF groups favored conventional RF (table 2). At 12 months, the patients with OA who were treated with cooled RF had more total costs with a lower gain in QALYs compared with the conventional RF group. As a result, cooled RF is inferior to conventional RF.

The bootstrapped estimates of incremental costs and QALYs are aggregated in the cost-effectiveness plane and represent uncertainty surrounding the cost and effect differences (figure 4). The majority of the data points in patients with PPSP cover the southeast quadrant indicating that when taking statistical uncertainty into account, cooled RF generates more health gains at lower costs, while most of the data points in the OA population cover the northwest quadrant indicating that cooled RF generally generates poorer health outcomes at higher costs. As a result, in PPSP, cooled RF is highly likely to be cost-effective, while in OA, cooled RF has a very low probability of being cost-effective in comparison with conventional RF at any willingness-to-pay threshold as visualized in the cost-effectiveness acceptability curves (figure 5).

Sensitivity analysis

The cost-utility analysis from the healthcare perspective (ie, excluding productivity costs and costs to patient and family) in the OA population showed that the difference in costs between cooled and conventional RF is substantially lower at 12 months compared with the societal perspective (table 2). Similarly, the cost-saving potential of cooled RF in the PPSP population is lower. However, the final results of the analyses (ie, whether the treatment was likely to be cost-effective) were unchanged.

The results from the 6-month analysis are available in online supplemental file S5 and are congruent to the conclusions reached during the 12-month analysis.

Table 2 Effectiveness outcomes and costs (€) presented per subgroup (OA and PPSP) and per RF modality after multiple imputation, based on 10 imputed datasets

Outcomes	Mean (SE)		Unadjusted mean difference (95% CI)*	Adjusted mean difference (95% CI)*
	Conventional RF	Cooled RF		
Outcomes for the OA group at 12 months after treatment				
QALY	0.604 (0.004)	0.558 (0.002)	−0.046 (−0.227 to 0.134)	−0.040 (−0.187 to 0.106)
Total healthcare-related costs	3405 (64)	4528 (125)	1123 (−2126 to 4372)	371 (−2627 to 3369)
Costs to patient and family	1018 (44)	3391 (85)	2373 (−600 to 5346)	876 (−839 to 2590)
Productivity costs/loss	3881 (0)†	6254 (0)†	2373 (−5266 to 10012)	2494 (−5544 to 10531)
Total societal costs	8303 (60)	14173 (159)	5860 (−3313 to 15052)	145 (−4485 to 14776)
Outcomes for the PPSP group at 12 months after treatment				
QALY	0.516 (0.002)	0.690 (0)	0.174 (0.014 to 0.334)	0.128 (0.008 to 0.247)
Total healthcare-related costs	4313 (216)	2499 (62)	−1814 (−4711 to 1083)	−1961 (−4848 to 925)
Costs to patient and family	2894 (67)	666 (30)	−2228 (−4518 to 62)	−2002 (−4268 to 258)
Productivity loss	3270 (0)†	2286 (0)†	−984 (−4258 to 2290)	−366 (−3680 to 2948)
Total societal costs	10477 (204)	5451 (62)	−5026 (−11022 to 970)	−4376 (−10124 to 1372)

Costs for each category were summed and the mean difference was calculated.
The sample size analyzed per subgroup was as follows: OA conventional RF (n=12), OA cooled RF (n=12), PPSP conventional RF (n=11), PPSP cooled RF (n=12).
*The uncertainty expressed in 95% CI around the mean costs and effects in each subgroup is calculated using non-parametric bootstrap simulations with 5000 replications. Measurements are adjusted for baseline differences in EQ-5D index and costs (healthcare costs, patient and family costs, productivity costs, and total societal costs, respectively).
†These values have a SE of 0 since missing data in productivity costs were imputed separately before the multiple imputation procedure.
OA, osteoarthritis; PPSP, persistent postsurgical pain; QALY, quality-adjusted life year; RF, radiofrequency.

DISCUSSION

The 12-month data of the COCOGEN trial revealed no difference in treatment success (around 22%) between cooled and conventional RF in patients with chronic knee pain when treatment success is defined as pain reduction of ≥50%. In the OA and PPSP group separately, treatment success was not significantly different between the two RF modalities. In patients with OA, treatment success was higher (33.3%) than in the PPSP group (10.5%). Remarkably, in patients with OA, treatment success was higher at 12 months compared with 6 months possibly reflecting an artifact from the small sample size of this trial or a more fluctuating course of pain in patients with OA. In patients with PPSP, treatment success diminished at 12 months in comparison with the 6-month results. When treatment success was defined as ≥30% pain reduction, there was also no significant difference between a conventional RF (22.2%) and a cooled RF (40.9%) in the whole population. In each population separately, the difference was more pronounced in the PPSP group. While there was no significant difference between conventional or cooled RF in patients with OA, this difference was statistically significant in patients with PPSP (0% treatment success after conventional RF, whereas 45% treatment success after cooled RF). Furthermore, only in patients with PPSP, there was a statistically significant reduction of the absolute NRS score after cooled RF (1.7 point

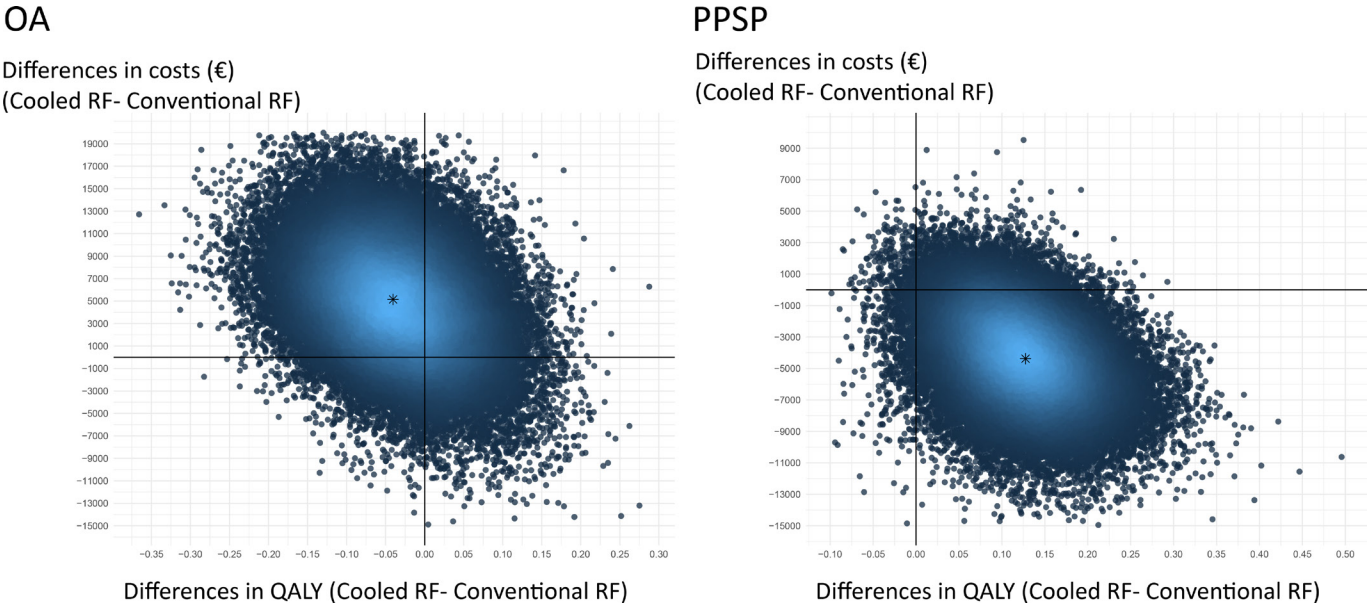

Figure 4 The incremental cost-effectiveness planes for the osteoarthritis and persistent postsurgical pain population representing the cost difference (€) and differences in quality-adjusted life year estimated using EuroQol 5-dimension 3-level between cooled and conventional radiofrequency at the 12-month time point. OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency ablation; QALY, quality-adjusted life year.

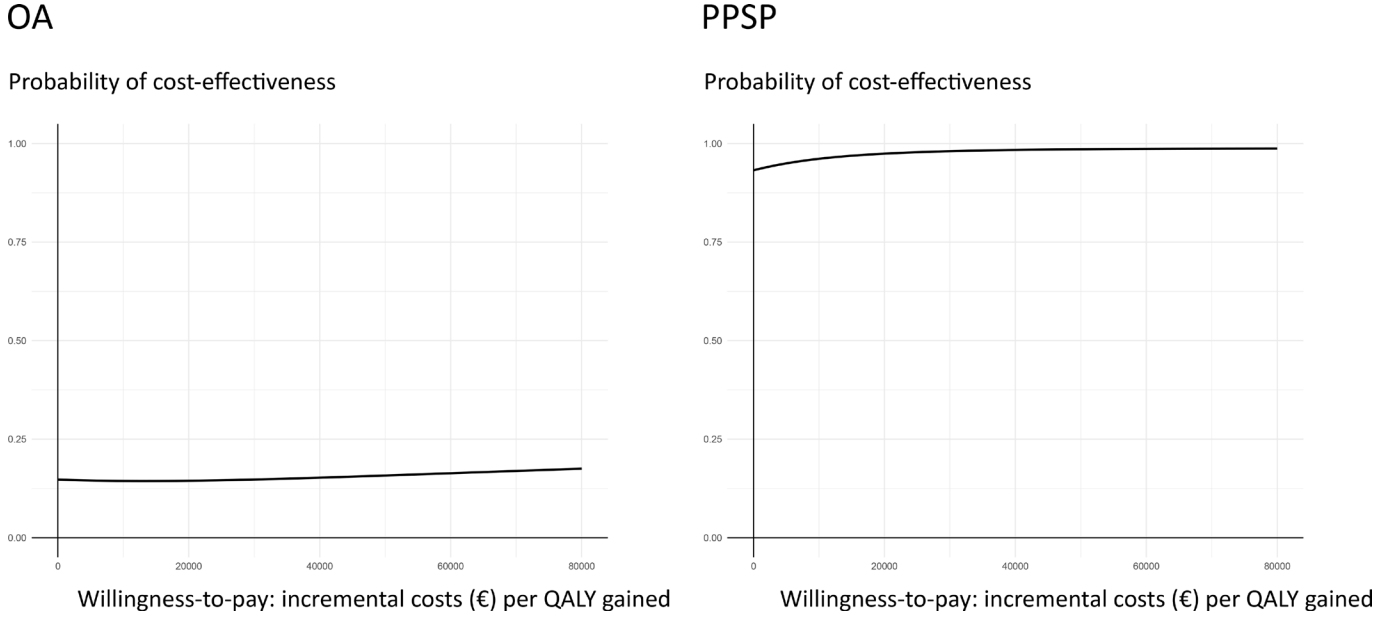

Figure 5 The cost-utility acceptability curve for cooled radiofrequency (RF) compared with conventional RF in the osteoarthritis and persistent postsurgical pain population at 12 months. OA, osteoarthritis; PPSP, persistent postsurgical pain; RF, radiofrequency; QALY, quality-adjusted life year.

decrease), whereas this was not the case after conventional RF (0.9 point increase). A possible explanation could be that in PPSP, patients' anatomy is changed due to the total knee replacement in comparison with patients with OA probably resulting in more anatomical variability. Therefore, cooled RF, which creates a bigger lesion, could be more effective than conventional RF in PPSP. Another possible explanation could be that in the different populations, the etiology of pain is different. In a postoperative state, it seems logical that neuropathic pain dominates over nociceptive pain.[8 41 42] Other alternative strategies to improve treatment success include targeting more than three genicular nerves. At the moment, most studies target three nerves as originally described by Choi *et al*, but the optimal number of nerves to target should be further identified.[16 43 44]

In the cost-effectiveness analysis of the COCOGEN trial, we found that in the PPSP group, cooled RF resulted in a small gain in QALYs at 12 months compared with conventional RF. This was accompanied by a cost-saving potential when cooled RF was performed compared with conventional RF. In the OA group, however, cooled RF resulted in lower QALYs at 12 months and higher costs compared with conventional RF. The high societal costs in the OA group receiving cooled RF may be explained by their poorer health (ie, quality of life) post-treatment, compared with conventional RF, and this may lead to a higher level of care use and productivity loss and thus higher societal costs. Despite the limited number of patients included in this analysis, the findings of this trial indicate that cooled RF is likely to be cost-effective in the PPSP population but not in the OA population at decision-making thresholds used in the Netherlands.

Similar to the findings of other trials in the OA population, the NRS in the COCOGEN trial changed in a statistically significant manner when compared with baseline after cooled RF up to 12 months; however, the effect of cooled RF did not lead to a significant increase in the OKS score.[45 46] Our findings are also in line with the results of the study of Santana *et al* where the effectiveness of the conventional RF seemed to diminish at 12 months resulting in higher NRS scores.[13] Our data reflected a similar evolution after cooled RF, even though these differ from the results from Davis *et al* where treatment effect remained stable up to 12 months.[45]

A single trial by Qudsi-Sinclair *et al* reported long-term data of conventional RF in patients with PPSP patients up to 12 months.[47] The NRS change in the trial by Qudsi-Sinclair and the COCOGEN trial were congruent. The NRS decrease from baseline after conventional RF in the COCOGEN trial and in the trial of Qudsi-Sinclair *et al* is followed by a progressive increase in NRS from 6 to 12 months.

To date, a single economic evaluation has been published on RF of the genicular nerves. Desai *et al* performed a trial-based cost-effectiveness analysis comparing cooled RF with intra-articular steroid injections in patients with OA which strongly favored cooled RF.[15] When compared with Desai *et al*, the OA population in our trial has similar baseline OKS scores and an equivalent EQ-5D index. In contrast to Desai *et al*, however, we found that the improvement in EQ-5D utility after cooled RF was much smaller in OA and that healthcare costs, costs to patient and family, and productivity losses were higher, resulting in a high likelihood that cooled RF is not cost-effective in OA compared with conventional RF. These two trials have several methodological differences: Desai *et al* included healthcare costs only and used a mapping analysis to calculate EQ-5D utility based on the OKS. Generally, the disease-specific OKS is more sensitive to health changes in the OA population than the generic EQ-5D, which may explain the larger QALY gain.

No adverse events developed after both a conventional and a cooled RF at 12 months supporting the long-term safety of both treatments. Secondary outcomes including the quality of life (EQ-5D-3L), emotional health (HADS and PCS), and medication use did not change in a statistically significant manner between cooled and conventional RF up to 12 months.

Currently, there is an increase in research on RF of the genicular nerves and growing evidence that different RF modalities are effective. A comparison of the long-term effects of these interventions in relation to their costs is becoming imperative for the incorporation of this intervention in chronic knee pain decision-making algorithms to guide the optimal allocation of the

available healthcare resources. As mentioned previously, there are a limited number of trials that evaluate 12 months or longer follow-up of patients undergoing RF of the genicular nerves, and there are no prospective trials comparing cooled with conventional RF up to 12 months published until present.[13 45–48]

One of the main strengths of this trial is that it is designed in a pragmatic manner increasing the external validity of the results. Furthermore, this is the first published health economic analysis from a societal perspective comparing cooled and conventional RF in patients with therapy-resistant chronic knee pain. Despite this, no decisive conclusion can be derived based on these results due to the intrinsically small sample size of this pilot trial. This was evident in the effectiveness outcomes and subsequently in the health economic analysis resulting in increased uncertainty surrounding the outcomes. While bootstrap analyses can overcome some statistical uncertainty, results must be interpreted with caution due to the very small number of patients in each subgroup (OA and PPSPS) and the highly skewed nature of cost data. A second limitation of this study was the systematic unblinding after 6 months of follow-up, which may have had an influence on subjective outcome measures taken after unblinding. Third, the COCOGEN study was performed in Belgium and the Netherlands—encompassing two different health systems. There may be some differences in access to first-line and second-line care; however, cost prices are similar in both countries. Moreover, results are presented from both the societal and healthcare perspectives, in line with Dutch and Belgian guidelines, respectively. Fourth, in this trial, we did not include all costs of analgesics. Since we did not see meaningful differences in medication use on the Medication Quantification Scale V.3 score, we do not expect this to have influenced the trial findings. An inclusion of all costs of analgesics is however recommended in a future trial.

The COCOGEN trial was primarily designed as a pilot trial to guide further research. Future studies should be sufficiently powered for between-group comparisons with an inclusion of a sham procedure and a long follow-up to prove the effectiveness of the current technique and should include the collection of resource use and quality of life data to perform a cost-effectiveness analysis. At the moment, the COGENIUS trial (NCT05407610) is being conducted.[49] This is a powered trial that aims to compare conventional and cooled RF with a sham procedure in OA and PPSP with 2 years of follow-up.

CONCLUSIONS

In conclusion, the COCOGEN study showed that RF of the genicular nerves is safe and can result in ≥50% pain reduction in approximately 22% of patients with chronic knee pain at 12 months. In patients with PPSP, contrary to OA, cooled RF seems to be more effective and cost-effective than conventional RF. Larger powered trials with the inclusion of a sham procedure and long follow-up should be conducted to support these findings.

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