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Radiofrequency endometrial ablation for menorrhagia using a mesh electrode[1]

Extract

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The responsibility for the contents of the report lies solely with IQWiG.

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IQWiG thanks the external expert for his collaboration in the project.

Involvement of patients or other persons affected

Patients or other persons affected were consulted as part of the production of the report and two people participated in the interview. IQWiG would like to thank them for commenting on their experience with the disease and its treatment as well as their treatment goals. They were not involved in the actual production of the report.

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Key statement

Research question

The aim of the present investigation is

- to assess the benefit of treatment with radiofrequency endometrial ablation using a mesh electrode versus other treatment methods for endometrial resection or ablation commonly used in German health care (loop resection and/or rollerball ablation as well as balloon ablation)

in patients with menorrhagia and a medical indication for ablative therapy. The focus of the assessment was on patient-relevant outcomes.

Conclusion

Comparison of radiofrequency ablation versus loop resection / rollerball ablation

Two studies were available comparing radiofrequency ablation and loop resection combined with rollerball ablation.

In each case, the data provide a hint of greater benefit with regard to dysmenorrhoea and for less harm with regard to adverse events (AEs) of radiofrequency ablation versus loop resection/rollerball ablation. Less harm in terms of AEs is primarily due to advantages with regard to intraoperative complications.

The data provide no hint of greater benefit or harm for the outcomes of bleeding severity, premenstrual syndrome, activities of daily living, and surgical re-interventions. For bleeding severity, the leading symptom, comparable benefit can be seen for both procedures.

No data were available for other morbidity outcomes, health-related quality of life, and mortality, so that the data provide no hint of greater benefit or harm for any of these outcomes.

Overall, across outcomes, the data provide a hint of greater benefit of radiofrequency ablation versus loop resection combined with rollerball ablation.

Comparison of radiofrequency ablation versus balloon ablation

Four studies were available comparing radiofrequency ablation and balloon ablation.

For bleeding severity, the data provide proof and for premenstrual syndrome, the data provide a hint of greater benefit of radiofrequency ablation versus balloon ablation.

The data provide no hint of greater benefit or harm for the outcomes of dysmenorrhoea/pain, depressive symptoms, anxiety symptoms, state of health, postoperative pain, workdays missed after surgery, surgical re-interventions, AEs, health-related quality of life, and mortality.

No usable data were available for activities of daily living, so again the data provide no hint of greater benefit or harm.

Overall, across outcomes, the data provide an indication of greater benefit of radiofrequency ablation versus balloon ablation.

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CI	confidence interval
COAT	Study to Compare the Effectiveness of Two Different Outpatient Endometrial Ablation Techniques Used for Heavy Periods
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
L / R	loop resection / rollerball ablation
MD	mean difference
NICE	National Institute for Health and Care Excellence (NICE)
OR	odds ratio
PBAC	Pictorial Blood Loss Assessment Chart
PMS	premenstrual syndrome
RCT	randomized controlled trial
RF	radiofrequency ablation
SF	Short Form (health questionnaire)
VAS	Visual Analogue Scale

1 Background

Heavy menstrual bleeding is one of the most common menstrual disorders [1]. In the literature, the terms used are not always consistent [2]. According to the definition in [3], the term menorrhagia refers to prolonged (> 7 to 10 days) and increased menstruation, and the term hypermenorrhoea refers to increased menstruation of normal duration. "Increased" is considered to be a blood loss of > 80 ml [4]. Other definitions focus on subjective feelings, as in the definition of heavy menstrual bleeding by the UK National Institute for Health and Care Excellence (NICE): "Heavy menstrual bleeding (HMB) is defined as excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or material quality of life." (p. 27 [5]). In the following, the term menorrhagia is used for (any) heavy menstrual bleeding.

Possible causes of menorrhagia include fibroids or polyps, but often no cause is known [6]. Prostaglandins appear to play a role in the pathogenesis of menorrhagia [7]. Adenomyosis uteri, a form of endometriosis involving the myometrium, is also often associated with menorrhagia (and dysmenorrhoea) [8].

According to clinical practice guidelines, the first therapeutic option for menorrhagia is drug treatment, in particular hormonal therapy (by means of oral contraceptives or hormonal intrauterine devices) or non-steroidal anti-inflammatory drugs [5,9].

If the bleeding is not sufficiently relieved, if there are contraindications to the available drug therapies, or if these are rejected, surgical intervention may be considered [5,9]. However, surgical procedures are only suitable when there is no (longer) the desire to have children [10]. Uterus-preserving interventions include various procedures for ablation or resection of the endometrium. A distinction is made between first- and second-generation procedures [11,12], with first-generation procedures being performed under hysteroscopic control, while most second-generation procedures are performed without hysteroscopy [11,13]. Monopolar or bipolar loop resection, which is often combined with rollerball ablation, and laser ablation are considered first-generation procedures [13]. Second-generation procedures include, for example, radiofrequency (RF) ablation, (fluid-filled thermal) balloon ablation, microwave ablation, and hydrothermal ablation [13]. The procedures commonly used in Germany are RF ablation, loop resection / rollerball ablation (L / R) and balloon ablation. In addition to uterus-preserving therapies, hysterectomy is a surgical procedure that provides a definitive reduction in bleeding but is more invasive than ablative methods [2]. Hysterectomy may also be considered if previous endometrial ablation has not resulted in a satisfactory reduction in bleeding. In this context, adenomyosis uteri is considered a risk factor for inadequate therapeutic success of endometrial ablation [14].

2 Research question

The aim of the present investigation is

- to assess the benefit of treatment with radiofrequency endometrial ablation using a mesh electrode versus other treatment methods for endometrial resection or ablation commonly used in German health care (loop resection and/or rollerball ablation as well as balloon ablation)

in patients with menorrhagia and a medical indication for ablative therapy. The focus of the assessment was on patient-relevant outcomes.

3 Methods

The target population of the benefit assessment consisted of patients with menorrhagia and a medical indication for ablative therapy. The test intervention was RF ablation of the endometrium using a mesh electrode. The control interventions were loop resection and/or rollerball ablation as well as balloon ablation.

The following patient-relevant outcomes were considered:

- morbidity (e.g., bleeding severity, dysmenorrhoea)
- health-related quality of life
- adverse events (AEs), especially intra- and postoperative complications
- mortality (e.g., as a result of the procedure)

Only randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding study duration.

In parallel with the preparation of the protocol (report plan), a search was conducted for systematic reviews in the MEDLINE (also includes the Cochrane Database of Systematic Reviews) and health technology assessment (HTA) database and on the websites of NICE and the Agency for Healthcare Research and Quality (AHRQ).

It was checked whether there was at least 1 eligible high-quality and up-to-date systematic review whose information retrieval could be used as the basis for the assessment.

If such a high-quality and up-to-date systematic review was available, a supplemental search for studies for the period not covered by the systematic review(s) was performed in a second step. Otherwise, the search for studies was performed without restriction of the search period.

The systematic literature search for studies was performed in the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases.

In addition, the following information sources and search techniques were considered: Study registries, manufacturer inquiries, publicly available documents from regulatory authorities, documents submitted by the Federal Joint Committee (G-BA), screening of reference lists, documents provided from the consultation process, and author inquiries.

The selection of relevant studies was performed independently by 2 individuals. Discrepancies were resolved by discussion between the two. Data were extracted into standardized tables. Across-outcome and outcome-specific risk-of-bias criteria were assessed to evaluate the qualitative certainty of results, and the risk of bias was rated as low or high in each case. The results of the individual studies were described according to outcomes.

For each outcome, results were preferably presented 12 months after the intervention and at the

latest measurement time point. For AEs and pain, results at time points during or shortly after the intervention were also presented, if available.

In addition to the comparison of the results of the individual studies, metaanalyses and sensitivity analyses were performed and effect modifiers examined, provided that the methodological requirements were met.

For each outcome, a conclusion on evidence of (greater) benefit and (greater) harm was made in 4 grades regarding the respective certainty of conclusions: either proof (highest certainty of conclusions), an indication (medium certainty of conclusions), a hint (weakest certainty of conclusions), or none of these 3 situations was present. The latter case occurred when no data were available or the available data did not allow any of the other 3 conclusions. In this case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn.

Finally, an assessment of benefit and harm across outcomes was performed.

4 Results

4.1 Results of information retrieval

One systematic review was assessed as current and of high quality and considered for the purpose of identifying primary studies.

Information retrieval identified 6 RCTs relevant to the research question. No planned or ongoing studies were identified.

Search strategies for bibliographic databases and study registries are provided in the Appendix. The last search took place on 19 March 2021.

Table 1: Study pool for the benefit assessment

Study		**Documents available**		
	Full-text publication (in scientific journals)	**Registry entry / results report from study registries**	**Study report from manufacturer documents (not publicly available)**	**Other documents**
RF ablation versus L / R				
Cooper 2002	Yes [15]	No	No	Yes: instructions of use [16] FDA approval documents [17,18]
Corson 2000	Yes [19,20]	No	No	No
RF ablation versus balloon ablation				
Abbott 2003	Yes [21]	No	No	No
Bongers 2004	Yes [22-25]	No	No	No
COAT	Yes [26,27]	Yes [28] / No	No	No
Penninx 2016	Yes [29]	Yes [30] / No	No	No
FDA: Food and Drug Administration; L / R: loop resection / rollerball ablation; RF: radiofrequency				

4.2 Characteristics of the studies included in the assessment

Of the 6 studies included on RF ablation, 2 (Cooper 2002 [15] and Corson 2000 [19]) included a comparison with loop resection/rollerball ablation, while 4 studies included a comparison with balloon ablation (Abbott 2003 [21], Bongers 2004 [22], Study to Compare the Effectiveness of Two Different Outpatient Endometrial Ablation Techniques Used for Heavy Periods [COAT] [26], and Penninx 2016 [29]). The characteristics of each study are described below separately according to the control intervention.

4.2.1 Comparison of RF ablation versus L / R

Both Cooper 2002 and Corson 2000 compared RF ablation with loop resection combined with rollerball ablation. Both studies were multicentre and conducted in North America. The publication cited in connection with the sample size calculation of Cooper 2002 [31] indicates

that the study, unlike Corson 2000, considered a noninferiority question. In Cooper 2002, 265 patients were randomized, and in Corson 2000, 276 patients were randomized and in each case followed up for up to 36 months after surgery. In both studies, randomization was 2:1; in Corson 2000, randomization switched to 1:1 during the course of the study.

The women included were premenopausal women with menorrhagia without (further) childbearing wish between 25 and 50 years (Cooper 2002) and 30 and 49 years (Corson 2000). For inclusion, patients had to have a Pictorial Blood Loss Assessment Chart (PBAC) score of at least 150 points. In addition, either prior unsuccessful drug therapy was required or the women had a contraindication to drug therapy or they refused drug therapy.

For RF ablation, the NovaSure system was used in Cooper 2002, and the Vesta system was used in Corson 2000. In Cooper 2002, the procedure was performed in both groups without pretreatment of the endometrium and regardless of cycle phase. In contrast, in Corson 2000, patients in both groups were pretreated with low-dose oral contraceptives for 14 days to induce menstrual bleeding, and the procedure was performed 4 to 7 days after the end of pretreatment in each case.

In Corson 2000, RF ablation was performed either in the outpatient practice setting or in the hospital, whereas L / R was always performed in the hospital. In Cooper 2002, specific information on the setting is missing. No postinterventional hospitalization was described in either study, so it can be assumed that the interventions were performed in an outpatient setting in each case.

4.2.2 Comparison of RF ablation versus balloon ablation

Four studies (Abbott 2003, Bongers 2004, COAT, and Penninx 2016) compared RF ablation with balloon ablation. Abbott 2003 and COAT were conducted in the United Kingdom, and Bongers 2004 and Penninx 2016 (the only multicentre study among these 4 studies) were conducted in the Netherlands. All 4 studies investigated a superiority question. In 2 studies (Abbott 2003 and Bongers 2004), subjects were randomized 2:1, and in the other 2 studies (COAT and Penninx 2016), subjects were randomized 1:1. The number of patients randomized in each study ranged from 57 to 126, and the duration of follow-up was 1 year (Abbott 2003 and Penninx 2016), 5 years (COAT), and 10 years (Bongers 2004).

The women included were premenopausal women without (further) childbearing wish who suffered from menorrhagia with a PBAC score ≥ 150 points (Bongers 2004, Penninx 2016) or > 150 points (Abbott 2003) or women in whom the extent of menstrual bleeding affected their quality of life (COAT). COAT included women aged 25 years and older; the other studies did not define an age range. In addition, COAT included only those women who had previously received unsuccessful drug therapy; the other 3 studies did not describe such a criterion.

All 4 studies used the NovaSure medical device for RF ablation. In 2 studies (Abbott 2003 and Bongers 2004), RF ablation was performed without pretreatment of the endometrium, whereas in the control group, curettage was performed immediately before balloon ablation. In Penninx

2016, ablation was performed without pretreatment of the endometrium in both groups. In COAT, there is no information in this regard. In Bongers 2004, the procedures in both groups were performed regardless of the day of the menstrual cycle. In Penninx 2016, surgery for both groups was scheduled to take place between day 3 and day 8 of the menstrual cycle. Data on this issue were missing in Abbott 2003 and COAT. In 2 studies (COAT and Penninx 2016), patients were treated in an outpatient practice setting; in the other 2 studies (Abbott 2003 and Bongers 2004), patients were treated in an outpatient setting in a hospital.

In Bongers 2004, a technical defect in the device occurred during the course of the study during RF ablation, which, according to the authors, resulted in reduced treatment time for some patients. The defect was noticed after the treatment of 44 patients (in both groups in total), and the study group could not determine how many patients were treated with the defective device. The number of cases was then increased by 44 patients. In addition, 2 separate analyses were performed for all outcomes, 1 including all patients and 1 restricting the analyses to patients randomized after the defect was detected and the generator replaced. For this report, the analyses including all patients were used.

4.3 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from all 6 studies. Table 2 shows the overview of available data on patient-relevant outcomes from the included studies.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes																
	Morbidity															Hr QoL	Mor-tality
	Bleeding severity																
	Amenorrhoea	Reduction in bleeding	Passing of blood clots	Menstrual duration	Dysmenorrhoea/pain	PMS	Depressive symptoms	Anxiety symptoms	Sexual function	Activity of daily living	Health state	Postoperative pain	Workdays missed after surgery	Surgical re-interventions	AEs	Health-related quality of life	Mortality
RF ablation vs. L / R																	
Cooper 2002	●	●[a]	–	–	●	●	–	–	–	●[b]	–	–	–	●	●	x[c]	–
Corson 2000	●	●[a]	–	–	○	–	–	–	–	○[d]	–	–	–	●	●	x	–
RF ablation vs. balloon ablation																	
Abbott 2003	●	●[a]	–	●	●	●	–	–	○[e]	–	●[f]	●	–	●	●	●[c]	–
Bongers 2004	●	●[a]	●	●	●	–	●[g]	●[h]	–	–	–	–	–	●	●	●[i]	●
COAT	●	●[j]	–	–	●	○	–	○	○[e]	○[d]	●[f, k]	○	●	●	●	●[l]	–
Penninx 2016	●	–	●	●	●	–	–	–	–	–	–	●	–	●	●	●[l]	–

●: Data were reported and were usable.
○: Data were reported but were not usable for the benefit assessment.
x: Data were not reported despite planned data collection.
-: No data were reported (no further information) / The outcome was not recorded.
a. Recorded with the PBAC
b. Recorded with the Menstrual Impact Questionnaire
c. Recorded with the SF-12
d. Time to return to normal activity recorded
e. Recorded with the Sexual Activity Questionnaire
f. Recorded with the EQ-5D VAS
g. Recorded with the Self-rating Depression Scale
h. Recorded with the State-Trait Anxiety Inventory
i. Recorded with the SF-36
j. Recorded with the VAS
k. Recorded with the Menorrhagia Outcome Questionnaire
l. Recorded with the Multi-Attribute Utility Assessment Tool

AE: adverse event; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HrQoL: health-related quality of life; L / R: loop resection / rollerball ablation; PBAC: Pictorial Blood Loss Assessment Chart; PMS: premenstrual syndrome; RF: radiofrequency; SF-12: Short Form-12 health questionnaire SF-36: Short Form-36 health questionnaire; VAS: visual analogue scale vs.: versus

In the two studies comparing RF ablation with L / R (Cooper 2002 and Corson 2000), the collection of health-related quality of life data was planned, but no results reported. In addition, the reported outcomes on pain and return to normal activity in Corson 2000 were not usable due to inadequate reporting.

In Abbott 2003, the description of the analysis of sexual function data was inadequate. In COAT, more than 30% of the randomized patients' data were missing for the outcomes of sexual function and premenstrual syndrome (PMS) at all time points and for the outcomes of amenorrhoea, reduction in bleeding, dysmenorrhoea, state of health, and health-related quality of life at 6 months and 1 year, making these data unusable. In addition, for anxiety symptoms and postoperative pain in this study, the method of outcome assessment was not adequate because the assessment of the extent of symptoms was made by the person performing the surgery. In addition, in this study, the outcome "return to normal activity" was not usable due to inadequate outcome description.

4.4 Assessment of the risk of bias of results

4.4.1 Comparison of RF ablation versus L / R

The risk of bias was rated as high across outcomes for both studies (Cooper 2002 and Corson 2000). In both studies, this was due to unclear concealment of group allocation. In Corson 2000, the generation of the randomization sequence was also unclear, and the study showed signs of selective reporting. In Cooper 2002, it was unclear whether selective reporting was present. In addition, patients and treating staff were unblinded in both studies (and outcomes were solely subjective outcomes).

The outcome-specific risk of bias of all outcomes presented was also considered high due to the high risk of bias across outcomes. Therefore, no further outcome-specific assessment of the risk of bias was performed.

4.4.2 Comparison of ablation versus balloon ablation

The risk of bias was rated as low across outcomes for 1 study (Bongers 2004) and as high for the remaining 3 studies (Abbott 2003, COAT, and Penninx 2016). The rating as high for Abbott 2003 and COAT was due to the fact that it was unclear whether group allocation had been concealed and whether reporting was selective. In COAT, it was also unclear whether patients were blinded. In Penninx 2016, the fact that it was unclear how the randomization sequence had been generated and whether reporting was selective caused a high risk of bias across outcomes. For these 3 studies, the outcome-specific risk of bias was also considered high due to the already high risk of bias across outcomes. Therefore, no further outcome-specific assessment of the risk of bias was performed.

For Bongers 2004, an outcome-specific assessment of the risk of bias was carried out.

In the outcome-specific assessment of Bongers 2004, 2 aspects in particular were regarded as potentially creating bias, each of which only affected specific outcomes and time points. These were, first, the lack of clarity about whether, at 10 years, the outcome assessors continued to be blinded. In this case, the outcome assessors were the patients themselves and the persons who conducted the telephone interview and extracted the data from patient records. This aspect resulted in a high outcome-specific risk of bias at 10 years for each of the outcomes of

amenorrhoea, passing of blood clots, dysmenorrhoea, and surgical re-interventions (hysterectomies and re-ablations).

Second, the intention-to-treat (ITT) principle was not considered adequately implemented for the following outcomes or time points, as in each case more than 10% of randomized patients were not included: amenorrhoea at 10 years, passing of blood clots and dysmenorrhoea (each at 5 and 10 years), depressive symptoms and health-related quality of life (all time points presented), surgical re-interventions (hysterectomies and re-ablations), and AEs at 10 years. For other outcomes or time points, the ITT principle was not considered to be adequately implemented as the reference value of the analysis was unclear: This concerned menstrual duration and surgical re-interventions (hysterectomies and re-ablations) at 5 years.

For the results on AEs, a potential bias-creating factor was that AEs in the non-immediate postoperative period were probably incompletely recorded or reported. Additionally, for intraoperative AEs, the outcome assessors (i.e., the surgeons) were not blinded.

A low risk of bias was seen in the results of the following outcomes or time points in Bongers 2004: amenorrhoea at 1 year and 5 years, reduction in bleeding (reported at 1 time point only), passing of blood clots, menstrual duration, dysmenorrhoea, and surgical re-interventions at 1 year, and mortality (reported at 1 time point only).

4.5 Results on patient-relevant outcomes

4.5.1 Comparison of RF ablation versus L / R

4.5.1.1 Results on bleeding severity

In order to illustrate bleeding severity in its different dimensions, results of different related outcomes were used to characterize the umbrella outcome. The results then resulted in a joint conclusion on benefit for the outcome of bleeding severity.

For the comparison of RF ablation versus L / R, data on bleeding severity were available from both studies (Cooper 2002 and Corson 2000), with a moderate qualitative certainty of results. The following data were used: results on amenorrhoea at 1 year (both studies) and 3 years (Cooper 2002), reduction of bleeding at 1 year to ≤ 75 points (Cooper 2002) or < 75 points (Corson 2000) in the PBAC score, elimination or reduction of bleeding to light or normal menstruation at 3 years (Cooper 2002), and mean PBAC score at 1 year (both studies).

With regard to the amenorrhoea rate, there was no statistically significant effect in either the pooled effect estimate at 1 year (odds ratio [OR] 1.03; 95% confidence interval [CI] [0.70; 1.52]; p = 0.876) or the outcome at 3 years in 1 study (OR 1.40; 95% CI [0.77; 2.57]; p = 0.307).

In the responder analysis with a PBAC score ≤ 75 or < 75 points as a response criterion at 1 year (OR 1.51; 95% CI [0.90; 2.53]; p = 0.120), there was no statistically significant effect of the pooled effect estimate. Likewise, there was no statistically significant effect with regard to

elimination of bleeding or reduction to light or normal menstrual bleeding at 3 years in 1 study (OR 2.13; 95% CI [0.59; 7.61]; p = 0.307).

Regarding the mean PBAC score at 1 year, there was a statistically significant effect of the pooled effect estimate in favour of RF ablation (mean difference [MD] -9.40; 95% CI [-18.02; -0.78]; p = 0.033). There was a standardized effect (Hedges' g) of -0.20; the 95% CI for this effect [-0.39; -0.02] exceeded the irrelevance threshold of -0.2. Therefore, there is a possibility that this effect is in an irrelevant range.

Therefore, with regard to bleeding severity, overall the data provide no hint of greater benefit or harm of RF ablation versus L / R.

4.5.1.2 Results on dysmenorrhoea / pain

For the comparison of RF ablation versus L / R, data on dysmenorrhoea were available from 1 study (Cooper 2002), with a moderate qualitative certainty of results. Results were available on the proportion of patients with dysmenorrhoea at 1 and 3 years. Usable data on other types of pain were not available.

At 1 year, there was a statistically significant effect in favour of RF ablation (OR 0.51; 95% CI [0.28; 0.92]; p = 0.025), but not at 3 years (OR 0.54; 95% CI [0.27; 1.07]; p = 0.082).

Therefore, with regard to dysmenorrhoea, overall the data provide a hint of greater benefit of RF ablation versus L / R.

4.5.1.3 Results on premenstrual syndrome

For the comparison of RF ablation versus L / R, data on PMS were available from 1 study (Cooper 2002), with a moderate qualitative certainty of results. Results were available on the proportion of patients with PMS at 1 and 3 years.

There was no statistically significant effect at either 1 year (OR 1.04; 95% CI [0.60; 1.83]; p = 0.893) or 3 years (OR 0.75; 95% CI [0.42; 1.37]; p = 0.407).

Therefore, with regard to PMS, the data provide no hint of greater benefit or harm of RF ablation versus L / R.

4.5.1.4 Results on depressive symptoms

No data were collected on this outcome.

4.5.1.5 Results on anxiety symptoms

No data were collected on this outcome.

4.5.1.6 Results on activities of daily living

For the comparison of RF ablation versus L / R, usable data on activities of daily living were available from 1 study (Cooper 2002), with a moderate qualitative certainty of results. Data were collected using the Menstrual Impact Questionnaire. Usable results were available at 1 year.

There was no statistically significant effect for any of the 8 items of the Menstrual Impact Questionnaire (see Table 23 of the full report).

Therefore, with regard to activities of daily living, the data provide no hint of greater benefit or harm of RF ablation versus L / R.

4.5.1.7 Results on state of health

No data were collected on this outcome.

4.5.1.8 Results on postoperative pain

No data were collected on this outcome.

4.5.1.9 Results on workdays missed after surgery

No data were collected on this outcome.

4.5.1.10 Results on surgical re-interventions

For the comparison of RF ablation versus L / R, data with a moderate qualitative certainty of results were provided for the specific surgical re-interventions of hysterectomy and re-ablation, but not for surgical re-interventions overall. Results were available from both studies on hysterectomies at 1 and 3 years and on re-ablations at 1 year (Cooper 2002 and Corson 2000).

There was no statistically significant pooled effect for hysterectomies at 1 year (OR 0.71; 95% CI [0.24; 2.07]; p = 0.525) or 3 years (OR 0.85; 95% CI [0.39; 1.87]; p = 0.685) or for re-ablations at 1 year (OR 1.84; 95% CI [0.29; 11.79]; p = 0.520).

Therefore, based on the results on hysterectomies and re-ablations, the data provide no hint of greater benefit or harm of RF ablation versus L / R with regard to surgical re-interventions.

4.5.1.11 Results on adverse events

For the comparison of RF ablation versus L / R, data on AEs were available from both studies (Cooper 2002 and Corson 2000), with a moderate qualitative certainty of results.

In Cooper 2002, AEs were reported separately for 4 different periods (intraoperative, <24 hours postoperatively, >24 hours to 2 weeks postoperatively, >2 weeks to 1 year postoperatively). It was not possible to determine whether and how many patients experienced AEs in more than one time window. Therefore, an overall rate of patients with AEs (i.e., across all 4 time periods) could not be calculated.

In Corson 2000, it was unclear whether AEs were systematically recorded and fully reported. Only intraoperative AEs were reported, as well as other events designated as treatment complications, without specifying the reference period.

In addition, AEs reported in both studies included non-patient-relevant events and those with questionable patient relevance.

Therefore, a metaanalytic summary of the results of both studies was only meaningful for intraoperative AEs.

There was a statistically significant pooled effect for intraoperative AEs (OR 0.22; 95% CI [0.06; 0.83]; p = 0.026), providing an indication of an effect in favour of RF ablation.

The 3 intraoperative AEs under RF ablation (in 3 patients) were 1 bradycardia of questionable patient relevance (Cooper 2002) and 2 events judged not to be patient relevant (1 slippage of the electrode balloon into the caesarean scar and 1 muscle fasciculation, Corson 2000). This compares with a total of 10 events (in 10 patients) in the control groups of both studies, including 1 event of unclear patient relevance. The 10 events were 4 uterine perforations, 4 cervical tears, 1 cervical stenosis, and 1 fluid overload. Fluid overload refers to the excessive absorption of irrigation fluid into the bloodstream, which can lead to electrolyte imbalances with potentially life-threatening neurologic complications [32]. In the affected patient, it was stated that no complications resulted from fluid overload. However, because information on symptoms was lacking, it is unclear for this event whether it can be considered directly patient-relevant. Therefore, if only the patient-relevant events (0 versus 9) were considered, the advantage of RF ablation versus L / R would be even more pronounced.

At later time points, AEs were reported only in small numbers in the two studies. In Cooper 2002, there were 6 (3.4%) and 4 patients (4.4%) with AEs in each of the intervention and control groups in the period < 24 hours postoperatively (excluding the intraoperative period). In the period > 24 hours to 2 weeks postoperatively, 4 (2.3%) and 6 (6.7%) patients were reported with an AE, and in the period > 2 weeks to 1 year, 19 (10.9%) and 15 patients (16.7%). In Corson 2000, 4 postoperative events each were reported in the two control groups (without specifying the concrete period and without specifying the number of patients with an event). Recognizably serious or life-threatening events were not among them.

Due to the uncertainty as to whether individual patients had several AEs at different time points and what the overall rate of patients with AEs would be, overall the data provide only a hint of less harm of RF ablation versus L / R with regard to AEs overall.

4.5.1.12 Results on health-related quality of life

The recording of this outcome was planned in both studies, but no results were reported.

4.5.1.13 Results on mortality

No data were collected on this outcome.

4.5.2 Comparison of RF ablation versus balloon ablation

4.5.2.1 Results on bleeding severity

In order to illustrate bleeding severity with its different dimensions, results of different related outcomes were used to characterize the umbrella outcome. The results then resulted in a joint conclusion on benefit for the outcome of bleeding severity.

For the comparison of RF ablation versus balloon ablation, data on bleeding severity were available from all 4 studies in this comparison. Results on amenorrhoea, reduction in bleeding, passing of blood clots, and menstrual duration were used.

Amenorrhoea

Data with a high qualitative certainty of results were provided for the proportion of patients with amenorrhoea by 1 study at 1, 5 and 10 years (Bongers 2004); further 10-year data were available from 3 further studies, in each case with a moderate qualitative certainty of results. Results at the 3-month (COAT), 1-year (Abbott 2003, Bongers 2004, and Penninx 2016), 5-year (Bongers 2004 and COAT), and 10-year (Bongers 2004) time points were used.

Data at 1 year (Abbott 2003, Bongers 2004, and Penninx 2016) were metaanalytically pooled together with the data at 3 months (COAT). Inclusion of the 3-month data seemed appropriate, under the assumption that a treatment effect achieved after a few months in terms of bleeding severity usually does not change markedly.

In Bongers 2004, which provided data with a high qualitative certainty of results for the time points mentioned below, there was a statistically significant effect (OR 9.25; 95% CI [2.64; 32.36], $p < 0.001$) in favour of RF ablation at 1 year. The pooled effect at 1 year was also statistically significant (OR 4.25; 95% CI [1.63; 11.07]; $p = 0.017$). There were no statistically significant effects for the later time points, neither in Bongers 2004 at 5 years (OR 2.09; 95% CI [0.93; 4.69]; $p = 0.077$) nor in the pooled effect at 5 years from 2 studies (OR 1.65; 95% CI [0.87; 3.10]; $p = 0.123$). The same applied to the 10-year time point from Bongers 2004 (OR 1.37; 95% CI [0.57; 3.29]; $p = 0.571$).

The results at the later time points do not question the advantage at 1 year because, given the average age of the patients at baseline (between 41.8 and 43.8 years in the Bongers 2004 and COAT studies), it was expected that menopause had already begun in some of the women after 5 and 10 years.

Therefore, with regard to amenorrhoea, the data provide proof of an effect in favour of RF ablation versus balloon ablation.

Reduction in bleeding

With regard to the median PBAC score, 1-year data were available from Bongers 2004 and Abbott 2003 with a high and moderate qualitative certainty of results respectively. In Bongers 2004, however, numerical data on the PBAC score were missing, and the data could not be read with sufficient precision from the graph presented. In addition, with regard to the proportion of patients with subjective improvement in menorrhagia (much or a little better vs. the same or worse), data were available from 1 study (COAT) at 3 months, with a moderate qualitative certainty of results.

A metaanalytic summary of data on reduction in bleeding was not possible due to differences in operationalizations between COAT and Abbott 2013 or the lack of numerical data (Bongers 2004).

The graphical representation of Bongers 2004 suggested a numerical advantage of RF ablation versus balloon ablation, and the p-value was reported as 0.02.

In Abbott 2003, the median PBAC score in each of the intervention and control groups was only 3 (range 0-1720) and 21 (range 0-157) points at 1 year.

The proportion of patients with subjective improvement in menorrhagia was not statistically significantly different in COAT at 3 months (OR 1.55; 95% CI [0.24; 9.85]; p = 0.750).

Primarily based on the results of Bongers 2004, the data therefore provide an indication of an effect in favour of RF ablation versus balloon ablation for a reduction in bleeding, with a high certainty of results.

Passing of blood clots

Regarding the proportion of patients with passing of blood clots at 1 year, 1 study (Bongers 2004) provided data with a high and another study (Penninx 2016) provided data with a moderate qualitative certainty of results. Bongers 2004 also provided data with a moderate qualitative certainty of results at 5 and 10 years.

In Bongers 2004, there was a statistically significant effect in favour of RF ablation at 1 year (OR 0.15; 95% CI [0.03; 0.79], p = 0.012). The pooled effect from both studies at the same time point was also statistically significant in favour of RF ablation (OR 0.39; 95% CI [0.16; 0.92]; p = 0.031).

Results at 5 years from Bongers 2004 also showed a statistically significant effect in favour of RF ablation (OR 0.2; 95% CI [0.06; 0.62]; p = 0.003), whereas at 10 years, the effect was not significant (OR 0.65; 95% CI [0.14; 3.13]; p = 0.645). The results at the latter time point do not call into question the advantage at 1 and 5 years because, given the average age of the patients at baseline (42.6 and 43.1 years in Bongers 2004), it was expected that menopause had already started in some of the women after 10 years.

Therefore, with regard to the passing of blood clots, the data provide proof of an effect in favour of RF ablation versus balloon ablation.

Menstrual duration

Regarding menstrual duration in days at 1 year, 1 study (Bongers 2004) provided data with a high and 2 other studies provided data with a moderate qualitative certainty of results (Abbott 2003 and Penninx 2016). In addition, 1 study provided data with a moderate qualitative certainty of results at 5 years (Bongers 2004). Women with amenorrhoea were included in the calculation of menstrual duration in Bongers 2004 (duration = 0 days), but not in Abbott 2003. In Penninx 2016, it was unclear whether women with amenorrhoea were included in the analysis or not.

Because of the inclusion of women with amenorrhoea in the menstrual duration data and a different proportion of women with a menstrual duration of 0 days between the two groups, conversion of the data available in Bongers 2004 (median, minimum, and maximum) to mean difference, standard deviation, and p-value was not meaningful.

Because of the different operationalizations with regard to the consideration of patients with amenorrhoea, a metaanalytical summary of the results was not meaningful.

All 3 studies showed statistically significant effects in favour of RF ablation and therefore clearly unidirectional effects: Bongers 2004 showed a statistically significant shorter menstrual duration after RF ablation versus balloon ablation at both 1 and 5 years (difference between medians for both time points -3; 95% CI [-1; -6]; $p < 0.05$). Abbott 2003 and Penninx 2016 also demonstrated a statistically significant shorter menstrual duration after RF ablation at 1 year (Abbott 2003: MD -1.38; 95% CI [-2.13; -0.62]; $p < 0.001$; Penninx 2016: MD -1.8; 95% CI [-2.63; -0.57]; $p = 0.003$).

Therefore, with regard to menstrual duration, the data provide proof of an effect in favour of RF ablation versus balloon ablation.

Conclusion on benefit with regard to bleeding severity

Therefore, with regard to bleeding severity, overall the data provide proof of greater benefit of RF ablation versus balloon ablation.

4.5.2.2 Results on dysmenorrhoea/pain

For the comparison of RF ablation versus balloon ablation, data on dysmenorrhoea were available from all 4 studies in this comparison and additional data on pain during sexual intercourse were available from 1 study (Abbott 2003)

Dysmenorrhoea

With regard to dysmenorrhoea, 1 study (Bongers 2004) provided data with a high qualitative certainty of results at 1 year; 2 further studies (Abbott 2003 and Penninx 2016) provided data

with a moderate qualitative certainty of results. Furthermore, 1 study (COAT) provided usable data at 3 months and 1 study (Bongers 2004) provided usable data at 5 and 10 years, in each case with a moderate qualitative certainty of results.

In 1 study (Abbott 2003), the severity of dysmenorrhoea was assessed using a visual analogue scale (VAS, range 0-100), whereas in the other 3 studies (Bongers 2004, COAT, Penninx 2016), dysmenorrhoea was assessed using categories. In Bongers 2004, the categories strong and moderate were recorded, but it was not clear from the data whether the results referred to women with the response strong or with the responses strong and moderate dysmenorrhoea. In Penninx 2016, the proportion of patients with dysmenorrhoea was counted without differentiating by symptom severity. In COAT, outcomes were reported as the proportion of patients with improvement in dysmenorrhoea (much or somewhat better versus the same or worse).

A metaanalytic summary of the results of Bongers 2004 and Penninx 2016 on dysmenorrhoea after 1 year was performed. The results of COAT and Abbott 2003 were considered separately because of the different operationalizations.

For Bongers 2004, there was no statistically significant effect at 1 year (OR 0.48; 95% CI [0.15; 1.59]; p = 0.262), with a high certainty of results. Likewise, no statistically significant difference were shown for the pooled effect on the rate of patients with dysmenorrhoea (OR 0.50; 95% CI [0.23; 1.10]; p = 0.084) and the improvement of dysmenorrhoea symptoms in 1 study (COAT) at 3 months (OR 1.05; 95% CI [0.31; 3.47]; p > 0.999). Only the results on the severity of dysmenorrhoea measured by VAS from 1 study (Abbott 2003) at 1 year showed a statistically significant effect in favour of RF ablation (p = 0.008; no information on effect estimate and CI).

Pain during sexual intercourse

Data on pain during sexual intercourse at 1 year were available from 1 study (Abbott 2003), with a moderate qualitative certainty of results.

Pain during intercourse was assessed using a VAS (score range 0-100).

Results at 1 year showed no statistically significant effect (p = 0.23; no information on effect estimate and CI).

Conclusion on benefit with regard to dysmenorrhoea/pain

Therefore, with regard to dysmenorrhoea/pain, overall the data provide no hint of greater benefit or harm of RF ablation versus balloon ablation.

4.5.2.3 Results on premenstrual syndrome

For the comparison of RF ablation versus balloon ablation, data on PMS were available from 1 study (Abbott 2003), with a moderate qualitative certainty of results. In the study, PMS severity was measured using a VAS (range 0-100). Results at 1 year were used.

There was a statistically significant decrease in PMS symptoms with RF ablation versus balloon ablation after 1 year: The median in the intervention and control groups was 0 and 32 (range 0-100, p = 0.007).

Therefore, with regard to PMS, the data provide a hint of greater benefit of RF ablation versus balloon ablation.

4.5.2.4 Results on depressive symptoms

For the comparison of RF ablation versus balloon ablation, data on depressive symptoms assessed by the Self-rating Depression Scale (SDS) were available from 1 study (Bongers 2004), with a moderate qualitative certainty of results and. Results at 6 months were used. There was no statistically significant effect at 6 months (p = 0.67, no information on effect estimate and CI).

Therefore, with regard to depressive symptoms, the data provide no hint of greater benefit or harm of RF ablation versus balloon ablation.

4.5.2.5 Results on anxiety symptoms

For the comparison of RF ablation versus balloon ablation, data on anxiety symptoms assessed by the State-Trait Anxiety Inventory (STAI) were available from 1 study (Bongers 2004), with a high qualitative certainty of results. Results at 2 weeks were used. There was no statistically significant effect at 2 weeks (p = 0.39, no information on effect estimate and CI).

Therefore, with regard to anxiety symptoms, the data provide no hint of greater benefit or harm of RF ablation versus balloon ablation.

4.5.2.6 Results on activities of daily living

No usable data were available for this outcome.

4.5.2.7 Results on state of health

For the comparison of RF ablation versus balloon ablation, data on state of health were available from 2 studies (Abbott 2003 and COAT), with a moderate qualitative certainty of results. Data were collected using the Menorrhagia Outcomes Questionnaire (scores standardized to a mean of 50, higher scores indicate worse outcome: COAT) and the VAS of the European Quality of Life Questionnaire - 5 Dimensions (EQ-5D, score range 0-100: Abbott 2003 and COAT). Results at 3 months (COAT) and 1 year (Abbott 2003) were used. No metaanalytic summary of the EQ-5D VAS results was performed, as it was questionable whether the results of the different measurement time points were sufficiently comparable. A statistically significant effect was shown neither in the Menorrhagia Outcomes Questionnaire at 1 year in COAT (MD -0.4; 95% CI [-3.4; 2.3]; p = 0.8) nor in the EQ-5D VAS at 3 months in COAT (MD -1.9; 95% CI [-11.4; 7.6]; p = 0.7) nor at 1 year in Abbott 2003 (MD -2.1; 95% CI [-5.9; 10.3]; no p-value given, not statistically significant).

Therefore, with regard to state of health, the data provide no hint of greater benefit or harm of RF ablation versus balloon ablation.

4.5.2.8 Results on postoperative pain

For the comparison of RF ablation versus balloon ablation, data on postoperative pain were available from 2 studies (Abbott 2003 and Penninx 2016), with a moderate qualitative certainty of results. In both studies, pain severity was measured using a VAS (range 0-100 and 0-10). Results were available at 1, 4, 12, and 24 hours postoperatively (Penninx 2016) and 4 hours postoperatively (Abbott 2003).

A metaanalytic summary of the results at 4 hours was not possible, as no measures of dispersion were given in Abbott 2003 and could not be derived.

Penninx 2016 showed no statistically significant effect at any of the 4 measurement time points (see Table 48 of the full report). In Abbott 2003, however, there was a statistically significant effect in favour of RF ablation 4 hours postoperatively (median in intervention and control groups: 48 and 78, no measures of dispersion given; $p = 0.01$).

Therefore, regarding postoperative pain, the data provide no hint of greater benefit or harm of RF ablation versus balloon ablation due to the heterogeneous results.

4.5.2.9 Results on workdays missed after surgery

For the comparison of RF ablation versus balloon ablation, data on workdays missed after surgery were available from 1 study (COAT), with a moderate qualitative certainty of results.

There was no statistically significant effect (MD 0.2; 95% CI [-5.9; 6.2]; $p > 0.99$).

Therefore, with regard to workdays missed after surgery, the data provide no hint of greater benefit or harm of RF ablation versus balloon ablation.

4.5.2.10 Results on surgical interventions

For the comparison of RF ablation versus balloon ablation, data on the specific surgical re-interventions of hysterectomy and re-ablation were available from all 4 studies in this comparison. No data were available for surgical re-interventions overall. Results for hysterectomies and re-ablations at 1 year, 5 years and 10 years were used.

Hysterectomies

Regarding the proportion of patients with hysterectomy at 1 year, 1 study provided data with a high qualitative certainty of results (Bongers 2004), while 2 other studies provided data with a moderate qualitative certainty of results (Abbott 2003 and Penninx 2016). Furthermore, data were available from 2 studies (Bongers 2004 and COAT) at 5 years and from 1 study at 10 years (Bongers 2004), in each case with a moderate qualitative certainty of results.

In the study with a high qualitative certainty of results (Bongers 2004), the effect at 1 year was not statistically significant (OR 0.49; 95% CI [0.12; 2.08], p = 0.406). The pooled effects for hysterectomy rates at the 1-year (OR 0.69; 95% CI [0.16; 2.91]; p = 0.381) and 5-year (OR 0.75; 95% CI [0.29; 1.94]; p = 0.549) time points were also not statistically significant. Results at 10 years from 1 study also showed no statistically significant effect (OR 1.02; 95% CI [0.32; 3.24]; p > 0.999).

Re-ablations

For the proportion of patients with a re-ablation, data were available from all 4 studies at 1 year (Abbott 2003 and Penninx 2016), 5 years (Bongers 2004 and COAT), and 10 years (Bongers 2004), in each case with a moderate qualitative certainty of results.

For the results at 1 year, no metaanalytic summary was performed, as only 1 event occurred in 1 study and a summary would not have been informative.

Neither the pooled effect at 5 years (OR 0.29; 95% CI [0.04; 2.19]; p = 0.232) nor the effect at the individual study level at 10 years (OR 1.01; 95% CI [0.09; 11.59]; p > 0.999) was statistically significant.

Conclusion on benefit with regard to surgical interventions

Therefore, based on the results on hysterectomies and re-ablations, overall the data provide no hint of greater benefit or harm of RF ablation versus balloon ablation with regard to surgical re-interventions.

4.5.2.11 Results on adverse events

All 4 studies provided data on AEs with a moderate qualitative certainty of results.

In Abbott 2003 it was reported that no serious intraoperative complications occurred. Data on whether there were any additional nonserious intraoperative complications are lacking. Therefore, it is unclear whether AEs were fully recorded and reported. It was also reported that by the end of the 1-year observation period, endometritis was suspected in 2 / 37 (5%) patients in the intervention group and 2 / 18 (11%) in the control group and those affected were treated with oral antibiotics. According to the publication, one patient in the intervention group had severe pain 4 months after the procedure, caused by haematometra. For one patient in the control group, it was reported that she became pregnant 8 months after the intervention and suffered an incomplete miscarriage.

In Bongers 2004 it was reported that no complications occurred during treatment. Further data on AEs are found only at the 10-year follow-up: 1 / 69 (1%) patients evaluated in the intervention group underwent hysterectomy due to cervical stenosis causing haematometra and cycle-related pain. No AEs were reported among the 35 patients in the control group evaluated at this time. In addition, among the reasons for hysterectomies were other events that could be counted as AEs (see Table 51 of the full report). Data on other AEs that did not occur during

treatment or that did not lead to a hysterectomy are missing. That such other AEs did not occur at all is unlikely, given the long observation period of 10 years. Incomplete recording or reporting of AEs in the non-immediate postoperative period is therefore likely to have occurred

In COAT it was reported that 2 patients in each of the intervention and control groups (out of 42 and 39 patients in the intervention and control groups) had postoperative complications. These were 1 patient in the intervention group with severe pain radiating to the leg, 1 patient each from the two groups who were hospitalized for 1 night for postoperative pain control, and 1 patient in the control group with vasovagal reaction. Serious intraoperative complications did not occur according to data in the publications. In the period up to 3 months, endometritis was also reported in 2 / 42 patients (5%) of the intervention group and 5 / 39 patients (13%) of the control group. It is therefore unclear whether the data on AEs in the non-immediate postoperative period up to 3 months are complete. Data on AEs occurring later are missing. It is unlikely that these did not occur at all, given the long observation period of 5 years. An incomplete recording or reporting of AEs in the period beyond 3 months is therefore likely.

In Penninx 2016 it was only reported that no complications had occurred. Whether this statement refers to a specific period or to the entire duration of follow-up of 1 year was not specified. Therefore, it is unclear whether AEs were fully recorded and reported.

On the basis of the data available, the data provide no hint of greater or less harm of RF ablation versus balloon ablation for the outcome of AEs.

4.5.2.12 Results on health-related quality of life

For the comparison of RF ablation versus balloon ablation, data on health-related quality of life were available from all 4 studies, with a moderate qualitative certainty of results. The following data were used: results of the Multi-attribute Utility Assessment Tool (score range 0-100, higher scores mean higher quality of life) at 3 months and 1 year (COAT and Penninx 2016), the Physical and Mental Component Scores of the Short Form (SF)-12 health questionnaire at 1 year (Abbott 2003), and the single items of the SF-36 health questionnaire at 6 months and 5 years (Bongers 2004).

A metaanalytic summary was not useful due to the different measurement time points (for the Multi-attribute Utility Assessment Tool) or the different types of evaluation (for the SF-12 and SF-36).

There were no statistically significant effects in either the Multi-attribute Utility Assessment Tool at 3 months (difference in change from baseline 4.8; 95% CI [-8.0; 17.6]; p = 0.5) and 1 year (not statistically significant, without further data) or in the 8 items of the SF-36 questionnaire at 6 months and 5 years (see Table 56 of the full report). Only the Mental Component Score (MD -8.1; 95% CI [-15.7; -0.34]; p = 0.04) showed a statistically significant effect at 1 year, but not the Physical Component Score (MD -1.8; 95% CI [-7.3; 3.6]; not statistically significant, no p-value given).

Therefore, with regard to health-related quality of life, overall the data provide no hint of greater benefit or harm of RF ablation versus balloon ablation.

4.5.2.13 Results on mortality

For the comparison of RF ablation versus balloon ablation, data on mortality were available at 10 years from 1 study (Bongers 2004), with a high qualitative certainty of results.

In that study, recording of mortality was not planned, but 2 deaths were reported among patients who dropped out of the study. The 2 deaths were not reported until the 10-year time point, so it is assumed that they occurred between 5 and 10 years after surgery.

There was no statistically significant effect with regard to mortality at 10 years (p = 0.405, effect estimate and CI not informative).

Therefore, with regard to mortality, the data provide no hint of greater benefit or harm of RF ablation versus balloon ablation.

4.6 Summarized evaluation of results

Evidence map

The following Table 3 shows the evidence map with regard to patient-relevant outcomes.

Table 3: Evidence map with regard to patient-relevant outcomes

Morbidity											HrQoL	Mortality
Bleeding severity	Dysmenorrhoea / pain	PMS	Depressive symptoms	Anxiety symptoms	Activities of daily living	State of health	Postoperative pain	Workdays missed after surgery	Surgical re-interventions	AEs	Health-related quality of life	Mortality
RF ablation vs. L / R												
⇔	⇗	⇔	–	–	⇔	–	–	–	⇔	⇗	–	–
RF ablation vs. balloon ablation												
⇑⇑	⇔	⇗	⇔	⇔	–	⇔	⇑⇓	⇔	(⇔)	⇔	⇔	(⇔)

⇑⇑: proof of greater benefit or less harm of RF ablation versus control intervention.
⇗: hint of greater benefit or less harm of RF ablation versus control intervention.
⇔: no hint, indication or proof, homogeneous result.
(⇔): no hint, indication or proof, homogeneous result; the 95% confidence interval for the relative effect is so imprecise that neither a halving nor doubling of the effect can be excluded.
⇑⇓: no hint, indication or proof, heterogeneous result.
-: no (usable) data reported.

AE: adverse event; HrQoL: health-related quality of life; PMS: premenstrual syndrome; vs.: versus

Assessment of the extent of unpublished data

Abstracts of one previously unpublished study [33-35] were identified. The study, conducted in China, compared an unspecified RF ablation with L / R. However, the relevance to the present question could not be conclusively clarified on the basis of the available data. The knowledge of this study remains without impact on the overall conclusion due to the questionable relevance of the test intervention.

Weighing of benefit and harm

Comparison RF ablation versus L / R

Regarding bleeding severity, the leading symptom, the data provide no hint of greater or less benefit of RF ablation versus L / R. However, both ablation methods suggest a comparable benefit in the overall view, based on the effects of the outcomes used and their precision.

In each case, the data provide a hint of greater benefit with regard to dysmenorrhoea or less harm with regard to AEs of RF ablation versus L / R.

The hint of less harm in terms of AEs is primarily based on the advantages with regard to intraoperative complications. Cooper 2002, which can be assumed to have full reporting of AEs, showed few later events (in intervention and control groups in 10.9% and 16.7% of patients in the period >2 weeks to 1 year), including no identifiably serious events. The fact that the AE data are only available separately for 4 different time windows, while the overall rate of patients with AEs remains unknown, therefore does not significantly affect the weighing of benefit and harm.

In surgical re-interventions, the data provide no hint of greater or less benefit of RF ablation versus L / R. It cannot be estimated with sufficient certainty whether RF ablation has a comparable benefit to L / R. However, hysterectomies and re-ablations were performed comparatively infrequently in both groups up to 3 years after surgery. Therefore, the uncertainty as to whether RF ablation has a higher re-intervention rate than L / R carries little weight in the overall weighing of benefit and harm.

The fact that no data on mortality are available does not affect the weighing of benefit and harm because, due to the comparatively low invasiveness of the test and control intervention, deaths are to be expected only in exceptional cases.

The results of the other reported outcomes do not contribute any additional information to the overall weighing of benefit and harm.

Overall, across outcomes, the data provide a hint of greater benefit of RF ablation versus L / R.

Comparison RF ablation versus balloon ablation

For bleeding severity as the leading symptom, the data provide proof of greater benefit of RF ablation versus balloon ablation; for PMS, the data provide a hint of greater benefit.

For surgical re-interventions, the data provide no hint of greater or less benefit of RF ablation

versus balloon ablation. In this comparison too, it is not possible to assess with sufficient certainty whether RF ablation has a comparable benefit with regard to surgical re-interventions. Overall, comparatively few hysterectomies and even fewer re-ablations were performed in both groups up to 10 years after surgery. Therefore, the uncertainty as to whether RF ablation has a higher re-intervention rate than balloon ablation carries little weight in the overall weighing of benefit and harm.

(Serious) AEs were reported in all 4 studies. Neither RF ablation nor balloon ablation revealed AEs of relevant frequency or severity, so the data provide no hint of greater or less harm. However, in 2 studies (Abbott 2003 and Penninx 2016), it is unclear whether AEs were fully recorded or reported. In the other 2 studies (Bongers 2004 and COAT), incomplete recording or reporting of AEs in the non-immediate postoperative period is likely. Therefore, a comparative assessment of harm from RF ablation versus balloon ablation is difficult.

The results of the other outcomes reported do not contribute any additional information to the overall weighing of benefit and harm. This also applies to the results on mortality, because in 1 study (Bongers 2004), only 2 deaths occurred, which, moreover, were reported more than 5 years after the procedure, with no apparent causal relationship.

Overall, across outcomes, the data provide an indication of greater benefit of RF ablation versus balloon ablation.

5 Conclusion

Comparison of radiofrequency ablation versus loop resection / rollerball ablation

Two studies were available comparing radiofrequency ablation and loop resection combined with rollerball ablation.

In each case, the data provide a hint of greater benefit with regard to dysmenorrhoea and for less harm with regard to AEs of radiofrequency ablation versus loop resection/rollerball ablation. Less harm in terms of AEs is primarily due to advantages with regard to intraoperative complications.

The data provide no hint of greater benefit or harm for the outcomes of bleeding severity, premenstrual syndrome, activities of daily living, and surgical re-interventions. For bleeding severity, the leading symptom, comparable benefit can be seen for both procedures.

No data were available for other morbidity outcomes, health-related quality of life, and mortality, so that the data provide no hint of greater benefit or harm for any of these outcomes.

Overall, across outcomes, the data provide a hint of greater benefit of radiofrequency ablation versus loop resection combined with rollerball ablation.

Comparison of radiofrequency ablation versus balloon ablation

Four studies were available comparing radiofrequency ablation and balloon ablation.

For bleeding severity, the data provide proof and for premenstrual syndrome, the data provide a hint of greater benefit of radiofrequency ablation versus balloon ablation.

The data provide no hint of greater benefit or harm for the outcomes of dysmenorrhoea/pain, depressive symptoms, anxiety symptoms, state of health, postoperative pain, workdays missed after surgery, surgical re-interventions, AEs, health-related quality of life, and mortality.

No usable data were available for activities of daily living, so again the data provide no hint of greater benefit or harm.

Overall, across outcomes, the data provide an indication of greater benefit of radiofrequency ablation versus balloon ablation.

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Please see full final report for full reference list.

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The full report (German version) is published under
https://www.iqwig.de/en/projects/n20-06.html

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

1. ***PubMed***

Search interface: NLM

The following filters were adopted:

- Systematic review: Wong [36] – High specificity strategy

#	Searches
#1	Search: menorrhagia OR hypermenorrhea OR menometrorrhagia OR dysmenorrhoea OR heavy periods OR abnormal periods OR heavy menstrua* OR Heavy menstrual bleed* OR abnormal menstrual bleed* OR heavy menses OR abnormal menses OR dysfunctional uterine bleed* OR abnormal uterine bleed* OR uterine dysfunction* OR heavy bleed* Sort by: Publication Date
#2	Search: ablation Sort by: Publication Date
#3	Search: endometrial ablation OR radiofrequency ablation Sort by: Publication Date
#4	Search: #2 OR #3 Sort by: Publication Date
#5	Search: "The Cochrane database of systematic reviews"[Journal] OR search[tiab] OR MEDLINE[tiab] OR systematic review[tiab] OR "meta-analysis"[pt:noexp] Sort by: Publication Date
#6	Search: #1 AND #4 AND #5 Sort by: Publication Date
#7	Search: (#6 AND 2005:2020[DP])

2. Health Technology Assessment Database

Search interface: INAHTA

#	Searches
1	menorrhagia OR hypermenorrhea OR menometrorrhagia OR dysmenorrhoea OR heavy periods OR abnormal periods OR heavy menstrua* OR Heavy menstrual bleed* OR abnormal menstrual bleed* OR heavy menses OR abnormal menses OR dysfunctional uterine bleed* OR abnormal uterine bleed* OR uterine dysfunction* OR heavy bleed*
2	endometrial ablation OR radiofrequency ablation OR ablation
3	#2 AND #1
4	#2 AND #1 (2005-2020)

Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to March Week 2 2021
- Ovid MEDLINE(R) Daily Update March 18, 2021

The following filters were adopted:

- RCT: Lefebvre [37] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	**Searches**
1	exp Uterine Hemorrhage/
2	menorrhagia.ti,ab.
3	((uterine or menstrual) adj1 bleeding*).ti,ab.
4	or/1-3
5	exp Ablation Techniques/
6	ablation*.ti,ab.
7	or/5-6
8	and/4,7
9	randomized controlled trial.pt.
10	controlled clinical trial.pt.
11	(randomized or placebo or randomly or trial or groups).ab.
12	drug therapy.fs.
13	or/9-12
14	13 not (exp animals/ not humans.sh.)
15	and/8,14
16	15 not (comment or editorial).pt.
17	16 and (english or german).lg.
18	17 and 20180501:3000.(dt).
19	remove duplicates from 18

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to March 18, 2021
- Ovid MEDLINE(R) Epub Ahead of Print March 18, 2021

#	**Searches**
1	menorrhagia.ti,ab.
2	((uterine or menstrual) adj1 bleeding*).ti,ab.
3	or/1-2
4	ablation*.ti,ab.
5	and/3-4
6	trial.ti.
7	(clinical trial* or random* or placebo).ti,ab.
8	or/6-7
9	and/5,8
10	9 not (comment or editorial).pt.
11	10 and (english or german).lg.
12	11 and 20180501:3000.(dt).
13	remove duplicates from 12

2. Embase

Search interface: Ovid

- Embase 1974 to 2021 March 18

The following filters were adopted:

- RCT: Wong [36] – Strategy minimizing difference between sensitivity and specificity

#	**Searches**
1	exp menstruation disorder/
2	menorrhagia.ti,ab.
3	((uterine or menstrual) adj1 bleeding*).ti,ab.
4	or/1-3
5	endometrium ablation/
6	ablation*.ti,ab.
7	or/5-6
8	and/4,7
9	(random* or double-blind*).tw.
10	placebo*.mp.
11	or/9-10
12	and/8,11
13	12 not medline.cr.
14	13 not (exp animal/ not exp human/)
15	14 not (Conference Abstract or Conference Review or Editorial).pt.
16	15 and (english or german).lg.
17	16 and 20180501:3000.(dc).
18	remove duplicates from 17

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 3 of 12, March 2021

#	Searches
#1	[mh "Uterine Hemorrhage"]
#2	menorrhagia:ti,ab
#3	((uterine or menstrual) NEAR/1 bleeding*):ti,ab
#4	#1 or #2 or #3
#5	[mh "Ablation Techniques"]
#6	ablation*:ti,ab
#7	#5 or #6
#8	#4 and #7
#9	#8 with Cochrane Library publication date from May 2018 to present, in Trials
#10	#9 not (*clinicaltrials*gov* OR *who*trialsearch* OR *clinicaltrialsregister*eu* OR *anzctr*org*au* OR *trialregister*nl* OR *irct*ir* OR *isrctn*org* OR *controlled*trials*com* OR *drks*de*):so
#11	#10 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))

A.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
(menorrhagia OR menstrual bleeding OR uterine bleeding) AND ablation AND AREA [First posted on or after 05/01/2018]

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch
- Type of search: Standard Search

Search strategy
menorrhagia AND ablation OR bleeding AND ablation