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## GENERAL DISCUSSION

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The overall aim of this thesis was to investigate (1) the diagnostic accuracy of patient history and physical examination for chronic low back pain (CLBP) originating from the facet joints, (2) effectiveness and cost-effectiveness of radiofrequency (RF) denervation for CLBP and (3) the generalizability of these results. This was done by (1) performing a systematic literature review about diagnosing pain originating from the facet joints in patients with CLBP (*chapter 2*); (2) performing a systematic literature review on the effectiveness of RF denervation for patients with CLBP (*chapter 3*); designing (*chapter 4*) and performing three randomised controlled trials (RCTs) on the effectiveness and cost-effectiveness of RF denervation for patients with CLBP originating from the facet joints (*chapter 5*), sacroiliac (SI) joints (*chapter 6*) or a combination of the facet joints, SI-joints and/or discs (*chapter 7*); and (3) assessing the generalizability of these results by comparing the course of LBP symptoms in RCTs to the course of LBP symptoms in observational cohorts (*chapter 8*).

In this chapter, the main findings will be summarised and discussed per part of this thesis, and strengths and limitations of these studies will be addressed. Furthermore, the findings will be compared with current literature and implications for further research and practice will be presented.

### Main findings

*Part 1: What is known about the diagnostic accuracy of patient history and/or physical examination in diagnosing CLBP originating from the facet joints?*

In *chapter 2*, the diagnostic accuracy of patient history and/or physical examination in comparison with diagnostic blocks to identify facet joint pain in patients with CLBP was investigated. Based on this systematic diagnostic review, no firm conclusions could be drawn due to a wide variation in index test and reference standard combinations, clinical heterogeneity, and an overall high risk of bias of the included studies.

*Part 2: What is the effectiveness and cost-effectiveness of RF denervation for CLBP originating from the facet joints, SI-joints, discs or a combination of those structures?*

In *chapter 3*, the effectiveness of RF denervation for the treatment of patients with CLBP was assessed by a systematic literature review. Overall, moderate quality evidence suggested that facet joint RF denervation has a greater effect on pain compared to placebo

over the short term. Low-quality evidence indicated that facet joint RF denervation is more effective than placebo for functional status on the short term. Evidence of low to very low quality showed that facet joint RF denervation is more effective for pain than steroid injections. RF denervation used for disc pain showed conflicting results. When RF denervation is used for SI-joint pain, low-quality evidence showed no differences between placebo and RF denervation in effects on pain and functional status over the short term, and one study showed a small effect on both pain reduction and improved functional status over the intermediate term in favour of the RF denervation. Overall, we found no high-quality evidence to support the notion that RF denervation provides pain relief or improves functional status for patients with CLBP.

*Chapter 4* presented the design of four RCTs and an observational study. Those studies were part of a larger collective initiative to evaluate minimal interventional treatments (MinT) in addition to a standardised exercise programme compared to a standardised exercise programme alone: the MinT study. The study in which participants with disc problems were assessed was prematurely terminated, as no participants with isolated disc problems were diagnosed after five months. The results of the other three RCTs are described in *chapter 5 through 7*.

*Chapter 5* showed that there were no between-group differences for pain and functional status when RF denervation was added to a standardised exercise programme compared to a standardised exercise programme alone in patients with CLBP originating from the facet joints, at any follow-up moment during a year. Only statistically significant very short-term (until six weeks) effects on global perceived recovery (GPE) were found in favour of the RF denervation group. Our findings suggested that facet joint RF denervation is neither more effective nor cost-effective when added to a standardised exercise programme.

*Chapter 6* showed that RF denervation added to a standardised exercise programme compared to a standardised exercise programme alone resulted in a statistically significant difference in pain reduction, functional status, and GPE in the short term (until three months) in favour of the RF denervation group for patients with chronic SI-joint pain. However, no long-term differences in effects were found, nor can RF denervation in addition to a standardised exercise programme be considered cost-effective.

*Chapter 7* showed statistically significant results for RF denervation added to a standardised exercise programme compared to a standardised exercise programme alone three months after the start of the intervention for pain when used for patients with CLBP originating from the facet joints, SI-joints and/or discs. At the 12 months follow up assessment a statistically significant difference was found in functional status in favour of the control group. The economic evaluation showed that RF denervation in addition to a standardised exercise programme was not cost-effective compared to a standardised exercise programme alone.

*Part 3: Is the course of LBP symptoms in RCTs comparable to the course of LBP symptoms in observational studies?*

*Chapter 8* showed a largely similar course of LBP symptoms over a period of three months in patients with CLBP originating from the facet joints and SI-joints in a randomised study group compared to patients in an observational study group. Results from the RCTs seem to be generalizable to a similar patient population in clinical practice, and only small differences were shown when comparing RCT results to results in an observational study group with a slightly different population.

### **Methodological considerations**

This thesis contributes to the field of evidence-based treatments for patients with CLBP potentially originating from the facet joints, SI-joints or discs. Different types of study designs were used in this thesis: systematic literature reviews, RCTs, economic evaluations, and an observational study. The main findings of these studies as summarised in the previous paragraph should be placed into perspective of some of the main methodological considerations.

#### *Study design*

In *chapter 4 through 7*, the performed RCTs had a non-blinded study design in combination with patient reported outcomes. This might be a potential limitation that could have influenced the results. Evidence suggests that treatment effects may be exaggerated for subjective outcomes, if patients and outcome assessors are not blinded.<sup>1</sup> This would most likely have led to an overestimation of the treatment effect on the short term. Hence, the small short-term effects identified in two of the trials might be a consequence of this lack of blinding.

Furthermore, the trials presented in *chapter 4 through 7* were performed in 16 pain centres and over 100 physiotherapy practices in The Netherlands. The advantages of multicentre trials are numerous, e.g. quicker recruitment of the number of patients and a representative sample of patients at the pain clinic.<sup>2</sup> However, interventions that are performed in multicentre trials might show more variation than in a single centre study. This variation in RF denervation techniques can mediate the treatment effects. In our pragmatic trials variation is important as this variation resembles clinical practice more closely, thereby increases the generalizability of the results.

Another reason for the choice of a pragmatic study design in *chapter 4 through 7* was the possibility to perform an economic evaluation. While reading and interpreting an economic evaluation, it is important to bear in mind that:

- Self-reported cost questionnaires are prone to recall bias. We tried to limit this by minimising the recall period to three months.<sup>3</sup>
- The generalizability of an economic evaluation to other countries may be limited by differences in healthcare and/or social security systems and the results of the economic evaluations of these trials are only representative for the Dutch setting.<sup>4</sup>
- The perspective of the economic evaluation should be taken into account while interpreting the results. In our trials, a societal perspective was chosen to measure the costs and effects. Gold et al.<sup>21</sup> assert that *'when a CEA is conducted from the societal perspective, the analyst considers everyone affected by the intervention and counts all significant health outcomes and costs that flow from it, regardless of who experiences the outcomes or costs'*. By setting one standard perspective, the comparability of different CEA's will be increased. In The Netherlands, the standard perspective for economic evaluations that are funded by governmental research programs is the societal perspective. Therefore our economic evaluations are performed from a societal perspective.

*Chapter 8* showed that the course of LBP symptoms of patients who received RF denervation in a RCT was rather comparable to the course of LBP symptoms of patients who received RF denervation in an observational study. Therefore, we concluded that within-group trial results give a rather good indication of the course in more or less the same patients, in an observational setting. Within evidence-based medicine RCTs are viewed as the 'gold standard' for evaluating effectiveness of interventions, although other

research designs may add to the existing knowledge. Non-randomised and observational studies are particularly prone to selection bias, bias by comorbidities and confounding by indication.<sup>5</sup> On the other hand, the generalizability of RCT results is often questioned in clinical practice because of strict in- and exclusion criteria of the participants in RCTs. But, as stated above, our study showed a more or less similar course of LBP symptoms in an observational study as compared to the within-group course of the participants in a RCT, even if the participants in the observational study did not have similar inclusion criteria as the patients in the RCT. This supports the generalizability of the RCT results.

### *Study population*

There is no widely agreed gold standard for diagnosing CLBP originating from the facet joints, SI-joints or discs. This implies a number of limitations in research of diagnosis and treatment for CLBP.

In *chapter 2*, the diagnostic block was considered the reference standard to which the diagnostic accuracy of patient history and physical examination was compared. The lack of a gold standard represents a flaw in the test accuracy study design, since the index test can never be deemed to perform better than the reference standard, and its value may therefore be underestimated.<sup>6,7</sup> However, despite the lack of validity and the chance of false-positive tests, these diagnostic blocks are currently the best tests available to diagnose pain from the facet joints, SI-joints and discs.<sup>8-11</sup>

In *chapter 5 through 7*, the patients included in the RCTs were diagnosed with CLBP originating from the facet joints or SI-joints by a positive diagnostic block. In both trials, 50% pain improvement after a single medial branch block was used as diagnostic criterion. Controversy about the ideal cut-off value in terms of selecting patients for RF denervation, and the use of single or double diagnostic blocks exists. Pain reduction of 50% or more as definitive diagnosis is mostly used in previous performed RCTs and in standard practice, but there is discussion about which threshold should be used for a positive block in clinical practice.<sup>6,8,12</sup> Performing multiple blocks parallel will decrease the false-positive rate, but will increase the number of false-negative blocks.<sup>13</sup> One trial performed in the United States, supports the notion that double-block tests are not effective or cost-effective for diagnosing CLBP originating from the facet joints.<sup>14</sup> But controversy about the optimal number of diagnostic blocks for diagnosing CLBP from the SI-joint remains.<sup>15,16</sup>

In *chapter 4*, the design of four RCTs was presented. After an inclusion period of five months, no patients were included in the trial investigating the cost-effectiveness of RF denervation for CLBP originating from the isolated discs. For that reason, this trial was prematurely terminated. We can only guess for reasons for the lack of patients with isolated disc problems at the participating pain clinics. The most obvious reason is that isolated disc problems are not diagnosed in the Dutch pain clinics. Furthermore, the diagnosis and treatment of the discs is more invasive than procedures for the facet joints and SI-joints. Based on the risks, the discs are treated after the facet joints and SI-joints, when patients still report pain. The trial in which CLBP originating from multiple sources was investigated; one-third of the LBP patients were diagnosed with pain originating from the discs, but no disc procedures were performed.

In *chapter 4 through 7*, patients were excluded from participation in the trials if they were treated with RF denervation in the past six months. Patients, who had a successful RF denervation in the past, might have a better response to a subsequent RF denervation. However, support for repeating RF denervation is based on evidence from small, uncontrolled studies.<sup>17,18</sup> Moreover, in the observational study, in which participants resemble the general pain population at the pain clinic, we did not find clinically relevant differences compared to the RCT results.

#### *Trial intervention*

Three pragmatic trials were performed to investigate the effectiveness and cost-effectiveness of RF denervation in patients with CLBP originating from the facet joints, SI-joints or discs. We have chosen for this pragmatic design, because this is considered the best design for an economic evaluation and the effectiveness of RF denervation in a routine clinical care setting could be evaluated. However, a few considerations should be mentioned.

Firstly, the standardised exercise programme was chosen as an active control. All participants received a standardised exercise programme based on the guideline on LBP of the Royal Dutch Society for Physiotherapy.<sup>19</sup> Because the recommendations in this guideline are described in rather general terms, the specific treatment, although based on this guideline, can vary between physiotherapists. Therefore, a more standardised treatment protocol was developed in cooperation with experienced physiotherapists.

Participating physiotherapists were instructed to provide this programme and it might be possible that the physiotherapists in our trial performed better than the general physiotherapist. The generalizability of the results might be limited by the level of standardisation of the protocol and the education of the physiotherapists which was linked to this protocol. But as the same protocol was used in both groups we do not expect that this had an important impact on our between-group differences. Furthermore, patients in the observational study received an exercise programme from physiotherapists that were not specifically instructed, and these patients showed similar outcomes as the RCT patients.

Secondly, both the intervention group and the control group in our trials decreased in pain intensity. However, because we did not include a group that did not receive any intervention, it is unknown if this result is accomplished by the exercise programme or reflects the natural course of LBP. But, because the population consisted of patients with long-lasting CLBP, the latter is not likely.

Thirdly, it is unclear if the difference in decrease in pain intensity between the groups of the RCTs was clinically relevant. Prior to performing the trials, a minimally clinically important difference (MCID) of two points for pain intensity was set. This difference between the groups was not achieved during the complete follow-up for none of the RCTs, and thereby it should be concluded that RF denervation does not have added value to a standardised exercise programme. However, this MCID is consensus based and there is no generally accepted definition of a MCID for interventions in patients with CLBP.

Fourthly, in the trial in which we investigated the effect of RF denervation for CLBP originating from the SI-joints, we assessed different treatment modalities (Palisade technique (performed in 73% of the participants), Cooled RF (22%), and Simplicity III (5%)) in the intervention group. The treatment choice was based on the preference of the pain specialist. This heterogeneity in treatment might have averaged the effect of each treatment modality. Although the groups were too small for a subgroup analysis we do not expect much difference in outcomes per treatment modality based on comparison of the mean differences. Moreover, as stated above, the variation in RF denervation techniques in our pragmatic trials resembles clinical practice, thereby increasing the generalizability of the results.

## Reflections

Due to clinical heterogeneity no firm conclusions could be drawn about the diagnostic accuracy of patient history and/or physical examination compared to a diagnostic facet joint block (*chapter 2*). A disadvantage of many diagnostic studies is that they are often based on post hoc analyses in observational cohort studies or RCTs, and not designed as a true diagnostic accuracy study. This has disadvantages in the design and interpretation of the studies. The importance of diagnostic accuracy studies should be stressed, because one of the main limitations in research in the field of LBP is limited abilities for diagnosing LBP. For example, facet joint RF denervation is a treatment specifically designed for CLBP originating from the facet joints, so including patients with other causes of CLBP might 'dilute' a treatment effect.

Most previous studies, in which the effectiveness of RF denervation was evaluated, were placebo controlled studies. The systematic literature review in *chapter 3* showed no high-quality evidence to support the notion that RF denervation provides pain relief or improves functional status for patients with CLBP. A systematic review by Henschke et al. from 2010 concluded that only low quality to very low quality evidence could support the use of RF denervation procedures for CLBP over placebo and other treatments.<sup>20</sup> The only beneficial treatment effect reported by these review authors was found in facet joint RF denervation. Henschke et al.<sup>20</sup> showed the same small results for injection therapy, as did the systematic review of Staal et al.,<sup>21</sup> that concluded that evidence was insufficient to support use of injection therapy for sub-acute LBP and CLBP. These findings were consistent with the results in *chapter 3* suggesting that RF denervation is more effective than steroid injections and placebo for facet joint pain; however, the evidence was of low quality. Also, Poetscher et al.<sup>22</sup> concluded in a systematic review that facet joint RF denervation was more effective than placebo for pain control and functional improvement three months after the intervention and was possibly more effective than steroid injections for pain control. These results are supported by evidence of low to moderate quality. A review performed in 2014, also examining RF denervation for CLBP,<sup>23</sup> showed similar results as the review in *chapter 3* and also recommended that future studies should examine the clinical significance of the achieved pain reduction and the long-term efficacy of RF denervation. We added to this recommendation that these studies should be high-quality RCTs with larger sample sizes and study protocols of these studies should be registered. All previously published reviews stated that adverse effects were not sufficiently reported.

### Implications for research

- There is a strong need for good quality and accurately reported prospective diagnostic accuracy studies. These studies should especially focus diagnostic accuracy of existing, commonly used tests. Knowing the specific underlying pathology of LBP can improve treatment effects.
- Heterogeneity in the patient population of clinical trials can result in an average treatment effect that may mask a wide range of individual responses to any specific treatment.<sup>24</sup> Our trials showed small treatment effects, which mirrors the effects of many interventions in the LBP field. Studies that investigate the mechanism of treatment effects in subgroups of patients have the potential to improve understanding of the condition.<sup>19,25</sup> Future research should focus on identifying subgroups of patients with CLBP that might benefit from RF denervation. High quality studies with the aim to find prognostic variable for treatment success are needed.
- It is widely accepted that CLBP is a biopsychosocial condition. Psychosocial predictors only explain a small portion of the prognosis of LBP. The previous mentioned diagnostic and prognostic studies should investigate the full biopsychosocial spectrum of LBP. Current research seems to have forgotten the 'bio' in biopsychosocial. As psychosocial factors explain only a small portion of the diagnosis and prognosis of LBP, biological factors should be included in future research. Factors from the full biopsychosocial spectrum seem most likely to identify clinically important subgroups.<sup>26</sup>
- Many studies only report statistically significant differences but do not relate these outcomes to predefined clinical meaningful improvements. Due to the lack of a clear definition of clinical relevance, it is important to perform new studies evaluating the smallest worthwhile effects of interventions for patients with CLBP in different settings.<sup>27,28</sup>
- Furthermore, it is important that future studies include multiple outcome measures (like medication use, healthcare utilization, and costs) to augment pain and function data.<sup>29</sup>
- The results of an economic evaluation are difficult to interpret and hard to compare between countries. *Chapter 5 through 7* describe the first trials to show that RF denervation for patients with CLBP in the Netherlands is not cost-effective. Of interest is if these results are internationally transferrable. Well-powered RCTs with

an economic evaluation and proper follow-up to evaluate the added value of RF denervation to usual care in other countries in which RF denervation is a common treatment are suggested.

The management of patients with LBP has been positively influenced by the rise in high quality clinical trials, systematic reviews and practical guidelines in the recent decades.<sup>30-37</sup> Still, there is scope for improvement for future RCTs in the field of CLBP: 1) the study protocol should be published and registered to avoid selective reporting; 2) the implementation of the STARD guidelines for the reporting of diagnostic studies, STROBE guidelines for observational studies and CONSORT guidelines for RCTs should be improved to increase the readability and ability to review the current literature.<sup>38-41</sup>

### Implications for practice

- In shared decision making, patients should be well informed about the effects of RF denervation for SI-joint and combination problems that only last for (on average) six weeks, but have no long term effects compared to an exercise programme alone. The frequent and indiscriminate use of RF denervation should be reconsidered, preferably in a research setting, and efforts should be made to find a comprehensive alternative treatment for patients with CLBP who did not benefit from conservative care. Furthermore, patients should be informed about the potential benefits, harms and costs, and that conservative treatment could also provide an improvement in the long term without the need for RF denervation.
- Pain physicians should consider facet joint RF denervation only in a research setting, in which effort should be made to find subgroups of patients who might benefit from RF denervation.
- Based on a recently performed review from Kamper et al,<sup>42</sup> multidisciplinary rehabilitation, including all aspects of the bio-psychosocial model might be an effective treatment for patients with CLBP. If RF denervation is considered, it should be provided in the context of a multidisciplinary treatment and not as a stand-alone treatment.

### Key messages

Box 1 provides an overview of what is known, what this thesis adds, and future challenges as the key messages of this thesis.



### **WHAT IS ALREADY KNOWN ON THIS TOPIC**

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- The diagnostic accuracy of patient history and physical examination for diagnosing chronic low back pain (CLBP) originating from the facet joints is controversial.
- Radiofrequency (RF) denervation is a commonly used treatment for patients with CLBP in the Netherlands and internationally.
- There is insufficient high-quality evidence for the effectiveness and cost-effectiveness of RF denervation for patients with CLBP.

### **WHAT THIS THESIS ADDS**

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- There is still insufficient evidence about the diagnostic accuracy of patient history and/or physical examination items to diagnose CLBP originating from the facet joints.
- The trials in this thesis are the first to evaluate whether RF denervation added to a standardised exercise programme is effective and cost-effective for patients with CLBP originating from the facet joints, SI-joints and/or discs.
- No added value of RF denervation to decrease pain or improve functional status for CLBP originating from the facet joints was found. Statistically significant effects for pain reduction, improved functional status and global perceived recovery in the short term for patients with chronic SI-joint pain, and only for pain reduction in patients with pain from multiple sources were found.
- RF denervation cannot be considered cost-effective when added to a standardised exercise programme for patients with CLBP originating from the facet joints, SI-joints and/or discs.
- The course of symptoms for patients with CLBP participating in a randomised controlled trial is comparable to the course of symptoms in clinical practice.

### **FUTURE CHALLENGES**

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- Improving diagnostics of CLBP.
- The identification of patients with CLBP who are likely to benefit from RF denervation in a multidisciplinary setting.
- To identify values that constitute the smallest worthwhile effect of interventions for patients with CLBP.

**Box 1. Key messages of this thesis**

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