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## **CHAPTER 7**

# **Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: a randomised controlled trial**

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## ABSTRACT

### Background

Cryotherapy is widely used for the treatment of cutaneous warts in primary care. However, evidence favours salicylic acid application. We compared the effectiveness of these treatments as well as a wait-and-see approach.

### Methods

Consecutive patients with new cutaneous warts were recruited in 30 primary care practices in the Netherlands between May 1, 2006, and Jan. 26, 2007. We randomly allocated eligible patients to one of three groups: cryotherapy with liquid nitrogen every two weeks, self-application of salicylic acid daily or a wait-and-see approach. The primary outcome was the proportion of participants whose warts were all cured at 13 weeks. Analysis was on an intention-to-treat basis. Secondary outcomes included treatment adherence, side effects and treatment satisfaction. Research nurses assessed outcomes during home visits at 4, 13 and 26 weeks.

### Results

Of the 250 participants (age 4 to 79 years), 240 were included in the analysis at 13 weeks (loss to follow-up 4%). Cure rates were 39% (95% confidence interval [CI] 29%–51%) in the cryotherapy group, 24% (95% CI 16%–35%) in the salicylic acid group and 16% (95% CI 9.5%–25%) in the wait-and-see group. Differences in effectiveness were most pronounced among participants with common warts ( $n = 116$ ): cure rates were 49% (95% CI 34%–64%) in the cryotherapy group, 15% (95% CI 7%–30%) in the salicylic acid group and 8% (95% CI 3%–21%) in the wait-and-see group. Cure rates among the participants with plantar warts ( $n = 124$ ) did not differ significantly between treatment groups.

### Interpretation

For common warts, cryotherapy was the most effective therapy in primary care. For plantar warts, we found no clinically relevant difference in effectiveness between cryotherapy, topical application of salicylic acid or a wait-and-see approach after 13 weeks. (ISRCTN42730629)

## INTRODUCTION

Cutaneous warts are common.<sup>1-3</sup> Up to one-third of primary school children have warts, of which two thirds resolve within two years.<sup>4,5</sup> Because warts frequently result in discomfort,<sup>6</sup> 2% of the general population and 6% of school-aged children each year present with warts to their general practitioner.<sup>7,8</sup> The usual treatment is cryotherapy with liquid nitrogen or, less frequently, topical application of salicylic acid.<sup>9-12</sup> Some physicians choose a wait-and-see approach because of the benign natural course of warts and the risk of side effects of treatment.<sup>10,11</sup>

A recent Cochrane review on treatments of cutaneous warts concluded that available studies were small, poorly designed or limited to dermatology outpatients.<sup>10,11</sup> Evidence on cryotherapy was contradictory,<sup>13-18</sup> whereas the evidence on salicylic acid was more convincing.<sup>19-23</sup> However, studies that compared cryotherapy and salicylic acid directly showed no differences in effectiveness.<sup>24,25</sup> The Cochrane review called for high-quality trials in primary care to compare the effects of cryotherapy, salicylic acid and placebo.

We conducted a three-arm randomised controlled trial to compare the effectiveness of cryotherapy with liquid nitrogen, topical application of salicylic acid and a wait-and-see approach for the treatment of common and plantar warts in primary care.

## METHODS

### Participants

Between May 1, 2006, and Jan. 26, 2007, 30 family practices from the Leiden Primary Care Research Network in the Netherlands invited all patients aged four years and older who attended the clinic with one or more new cutaneous warts to participate. We defined new cutaneous warts as those on the skin that were diagnosed in family practice and had not been treated by a physician or dermatologist in the previous year, regardless of previous self-treatment with over-the-counter medication. We excluded immunocompromised patients and patients with genital warts, seborrheic warts or warts larger than 1 cm in diameter. Patients who fulfilled the inclusion criteria and agreed to participate were visited at home by a trained research nurse, who confirmed their eligibility. Informed consent (child as well as parental informed consent for participants less than 18 years of age) was obtained, and baseline characteristics were collected.

## Study design and randomization

We stratified patients by location of warts: plantar (warts on the soles of the feet) or common (warts on the hands or other locations).<sup>26</sup> Participants who had both plantar and common warts were stratified according to where the majority of their warts were located. We used opaque, sealed envelopes that were numbered based on a computerised randomization list delivered by an independent statistician to conceal allocation. After stratification by location of warts and by number of warts (< six warts v. ≥ six warts), random allocation of participants to treatment groups was done without blocking. The study protocol was approved by the medical ethical committee of the Leiden University Medical Center.

## Treatment protocols

One of us (K.Z) trained all participating general practitioners and assistants working in their practices in the three 13-week treatment protocols, which were designed to reflect best practice.<sup>10,24</sup> Training consisted of a one-hour interactive practical session, during which all tools and techniques were demonstrated; real warts were not used in the demonstrations. For cryotherapy, we used a high-intensity regimen of one session every two weeks until all warts were completely gone. During each session, the participant received three serial applications in which a wad of cotton wool saturated with liquid nitrogen was moved around on the wart. Each application was executed until a frozen halo of 2 mm around the base of the wart appeared (usually after 2–10 seconds).

For the topical application of salicylic acid, we used a white petroleum jelly containing 40% salicylic acid. We chose this concentration to provide a stronger treatment than over-the-counter products, which usually contain 17% salicylic acid. Participants assigned to this group were asked to apply the salicylic acid every day until the warts were completely gone. They were instructed to cover the surrounding skin with tape to protect healthy skin and apply the salicylic acid on top of the wart with another piece of tape. Before each subsequent daily application, they used a file to pare the softened surface area of the wart. Participants assigned to the wait-and-see group were informed about the benign natural course of warts and were advised not to undergo treatment (apart from over-the-counter medication) for at least 13 weeks.

After the 13-week treatment period, all participants who still had warts could switch to another treatment according to their own preferences. Participants were free to use over-the-counter medication during the entire follow-up period but were asked to report all usage.

## Outcome measures

Trained research nurses assessed outcomes during home visits at 4, 13 and 26 weeks of follow-up, independently of the treating physicians. A wart was considered cured if it was no longer visible (skin colour and skin lines were reestablished) and could not be palpated anymore by hand. The primary outcome measure was the proportion of participants whose warts were all cured at 13 weeks. Research nurses assessed side effects, newly developed warts (which were not included in the primary outcome assessment) and adherence to treatment. Treatment adherence was considered adequate if participants had received cryotherapy at least every three weeks, had self-administered salicylic acid at least four days per week and had not undergone any cointervention (treatment of warts other than over-the-counter medication).

In addition, participants were asked to rate treatment burden using a 10-point scale (1 = no burden, 10 = the worst imaginable burden). A scores of six or higher was considered to reflect a substantial burden. Participants rated treatment satisfaction using a five-point scale (one = very unsatisfied, five = very satisfied); those with a score of four or five were considered to be satisfied.

Research nurses, general practitioners and participants were not blinded to treatment allocation. For quality control, 5% of the assessments were directly supervised by experienced general practitioners (J.E. and K.Z.).

## Statistical analysis

We chose a sample size that would provide 80% power, at a significance level of 5%, to detect an absolute increase in the cure rate of 20% between the two active treatment groups. Based on a literature review, we expected salicylic acid to be most effective, with a 70% cure rate.<sup>10,11</sup> A total of 91 patients were required per treatment arm.

We used the  $\chi^2$  test for all comparisons of cure rates and percentages. In our primary analysis, we compared cure rates between the three treatment arms on an intention-to-treat basis. We also calculated relative risks, risk differences and numbers needed to treat for cryotherapy versus salicylic acid, cryotherapy versus wait-and-see approach, and salicylic acid versus wait-and-see approach.

In secondary analyses, we compared cure rates between the three study arms (a) with patients lost to follow-up considered not cured, (b) after excluding patients who had both plantar and common warts, (c) at 26 weeks' follow-up, (d) using individual warts as the unit of analysis instead of patients and (e) per protocol cure rates based on reported treatment adherence.

Subgroup analyses were pre-planned for location of warts (common wart group v. plantar wart group), age clusters (4– 12 years v.  $\geq 12$  years), number of warts per participant, and

duration of warts ( $\leq$  six months v.  $>$  six months). We formally tested for effect modification of treatment by location of warts using a logistic regression model.

Lastly, we compared the percentages of patients with side effects and considerable treatment burden between the two active treatment arms, and the percentages of patients satisfied with treatment between the three arms.

An abridged version of our study protocol can be found at [www.controlled-trials.com/ISRCTN42730629/warts](http://www.controlled-trials.com/ISRCTN42730629/warts).

## RESULTS

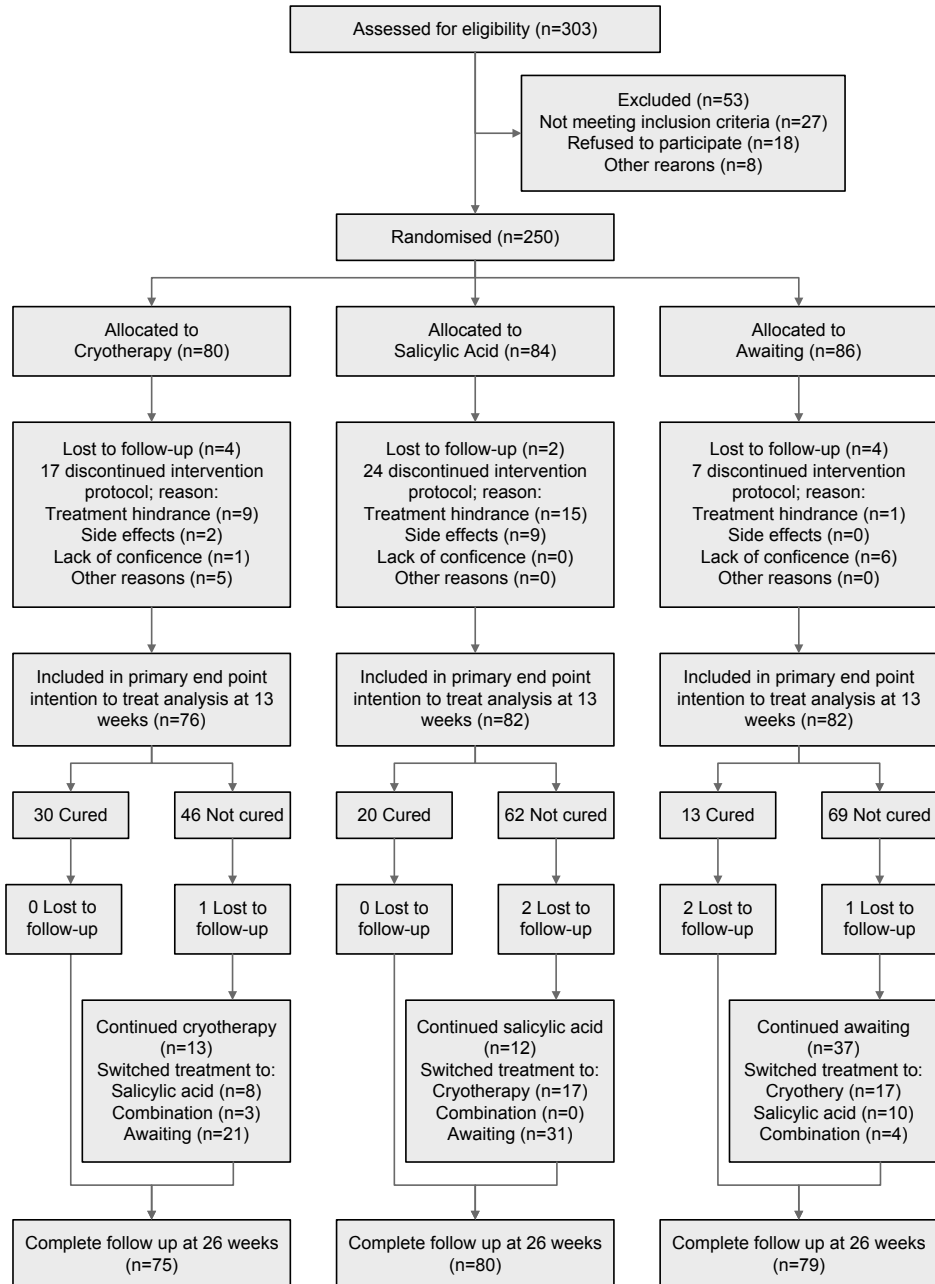
### Patient characteristics

Of 303 patients recruited, we excluded 53, mainly because they had already received treatment in the previous year or refused to participate (Figure 7.1). We randomly assigned the remaining 250 participants to the cryotherapy ( $n = 80$ ), topical salicylic acid ( $n = 84$ ) and wait-and-see ( $n = 86$ ) groups. Baseline characteristics did not differ significantly between the groups (Table 7.1). Seven per cent of the participants reported that they had received treatment for warts more than one year before enrolment; 35% reported that they had treated their warts with one or more of the following over-the-counter medications or methods in the past with no success: dimethyl ether propane cryotherapy (18%), ointment containing salicylic acid at a concentration lower than the study ointment (12%), cutting away the warts themselves (6%) and other alternatives (6%). At study entry, 34% of the participants stated that they preferred cryotherapy, 35% salicylic acid and 4% a wait-and-see approach (no preference given by 27%). Of the 250 participants, 122 (49%) were stratified into the common wart group and 128 (51%) into the plantar wart group. In the common wart group, 103 participants (84%) had warts on their hands, 19 (16%) had them on parts of the body other than hands or soles of the feet, and 13 (11%) also had plantar warts. In the plantar wart group, 22 participants (17%) also had common warts. Baseline characteristics were similar between the common and plantar wart groups except for age distribution and duration of warts.

### Follow-up and treatment adherence

At 13 weeks, 10 participants (4%) were lost to follow up (8 refused further participation, 1 had entered by error because the wart was diagnosed as a seborrheic wart, and 1 was lost for unknown reasons). Overall, 48 (20%) of the remaining 240 participants stopped the assigned treatment protocol (see Appendix 7.1). During the 13-week follow-up period, 61 participants (25%) had one or more new warts; no participants were referred to dermatology outpatient clinics.

Figure 7.1. Flowchart.





**Table 7.1.** Participant characteristics at baseline (n=250)

	Treatment arm		
	Cryotherapy (n=80)	Salicylic acid (n=84)	Awaiting (n=86)
Female sex	45 (56)	54 (64)	50 (58)
Age groups			
4 to 12 years	33 (41)	36 (43)	39 (45)
≥ 12 years	47 (59)	48 (57)	47 (55)
Number of warts (median, IQR)	2 (1 to 3)	2 (1 to 4)	2 (1 to 5)
Size of warts in millimetre (median, IQR)	4 (3 to 5)	4 (3 to 5)	4 (3 to 5)
Hindrance*	55 (69)	63 (75)	70 (81)
Location†			
Common wart group	41 (51)	40 (48)	41 (48)
Plantar wart group	39 (49)	44 (52)	45 (52)
Wart duration			
< six months	31 (39)	37 (44)	34 (40)
≥ six months	49 (61)	47 (56)	52 (61)‡
Treatment preference at baseline			
Cryotherapy	33 (41)	24 (29)	29 (34)
Salicylic Acid	22 (28)	33 (39)	32 (37)
Awaiting	6 (8)	2 (2)	2 (2)
No preference	19 (24)‡	25 (30)	23 (27)

Values are number of participants (percentage of participants) unless stated otherwise. IQR = Inter Quartile Range.

\* Presence of pain, irritation or esthetical annoyance.

† We stratified randomization according to location, but we did not sample according to stratification (number of participants with common warts and number of participants with plantar warts were equivalent by chance).

‡ Sum of percentages is ≠ 100 due to rounding off.

## Effectiveness of treatment

At 13 weeks, the cure rates were 39% (95% confidence interval [CI] 29%–51%) after cryotherapy, 24% (95% CI 16%–35%) after salicylic acid and 16% (95% CI 9.5%–25%) after the wait-and-see protocol, for a relative risk of 1.6 (95% CI 1.0–2.6) for cryotherapy versus salicylic acid. Because the effectiveness of treatments differed between the common wart group and the plantar wart group ( $p$  for interaction 0.007), we report outcomes for all patients as well as by location of warts (Tables 7.2 and 7.3).

In the common wart group, cryotherapy was most effective, with a cure rate of 49% (95% CI 34%–64%) at 13 weeks (Tables 7.2 and 7.3). Further stratification by age and by duration of warts gave similar findings.

**Table 7.2.** Overall effectiveness of treatments at 13 weeks, stratified according to location of warts (n=240)

	Treatment arm				P-value*		
	Cryotherapy		Salicylic acid			Awaiting	
	n	% (95%CI)	n	% (95%CI)			n
All participants (n=240)							
All	30/76	39 (29 to 51)	20/82	24 (16 to 35)	13/82	16 (10 to 25)	0.001
Age groups							
4 to 12 years	16/31	52 (35 to 68)	15/36	42 (27 to 58)	11/38	29 (17 to 45)	0.056
≥ 12 years	14/45	31 (20 to 46)	5/46	11 (5 to 23)	2/44	5 (1 to 15)	0.001
Wart duration							
< six months	19/30	63 (46 to 78)	14/37	38 (24 to 54)	10/32	31 (18 to 49)	0.012
≥ six months	11/46	24 (14 to 38)	6/45	13 (6 to 26)	3/50	6 (2 to 16)	0.012
Common wart group (n=116)							
All	19/39	49 (34 to 64)	6/39	15 (7 to 30)	3/38	8 (3 to 21)	<0.001
Age groups							
4 to 12 years	6/12	50 (25 to 75)	2/12	17 (5 to 45)	1/15	7 (2 to 25)	0.010
≥ 12 years	13/27	48 (31 to 66)	4/27	15 (6 to 32)	2/23	9 (2 to 27)	0.001
Wart duration							
< six months	10/12	83 (55 to 95)	2/11	18 (5 to 48)	2/13	15 (4 to 42)	0.001
≥ six months	9/27	33 (19 to 52)	4/28	14 (6 to 31)	1/25	4 (<1 to 20)	0.006
Plantar wart group (n=124)							
All	11/37	30 (17 to 46)	14/43	33 (20 to 47)	10/44	23 (13 to 37)	0.46
Age groups							
4 to 12 years	10/19	53 (32 to 73)	13/24	54 (35 to 72)	10/23	43 (26 to 63)	0.54
≥ 12 years	1/18	6 (<1 to 26)	1/19	5 (<1 to 25)	0/21	0 (0 to 15)	0.34
Wart duration							
< six months	9/18	50 (29 to 71)	12/26	46 (29 to 65)	8/19	42 (23 to 64)	0.63
≥ six months	2/19	11 (3 to 31)	2/17	12 (3 to 34)	2/25	8 (2 to 25)	0.77

Values are number of participants cured / number of participants in intention to treat analysis at 13 weeks, and percentages of participants cured (95% confidence intervals). A participant is cured when all warts present at baseline are gone.

\* 2-sided chi-square, comparing three treatment groups.

**Table 7.3.** Relative measures of effect between the three treatment arms, depending on location of warts (n=240)

	Relative Risk (95%CI)	Risk Difference (95%CI)	NNT* (95%CI)†
All participants (n=240)			
Cryotherapy versus Awaiting	2.49 (1.41 to 4.41)	0.24 (0.10 to 0.37)	4 (3 to 10)
Salicylic Acid versus Awaiting	1.54 (0.82 to 2.88)	0.09 (-0.04 to 0.21)	12 (-27 to 5)
Cryotherapy versus Salicylic Acid	1.62 (1.01 to 2.59)	0.15 (0.01 to 0.29)	7 (3 to 145)
Common wart group (n=116)			
Cryotherapy versus Awaiting	6.17 (1.99 to 19.16)	0.41 (0.23 to 0.59)	2 (2 to 4)
Salicylic Acid versus Awaiting	1.95 (0.52 to 7.24)	0.07 (-0.07 to 0.22)	13 (-15 to 5)
Cryotherapy versus Salicylic Acid	3.17 (1.42 to 7.07)	0.33 (0.14 to 0.53)	3 (2 to 7)
Plantar wart group (n=124)			
Cryotherapy versus Awaiting	1.31 (0.63 to 2.73)	0.07 (-0.12 to 0.26)	14 (-8 to 4)
Salicylic Acid versus Awaiting	1.43 (0.72 to 2.87)	0.10 (-0.09 to 0.29)	10 (-11 to 4)
Cryotherapy versus Salicylic Acid	0.91 (0.47 to 1.76)	-0.03 (-0.23 to 0.18)	35† (-4 to 6)

\* Number needed to treat for benefit (95% confidence intervals), i.e. number of patients needed to get specific treatment in order to cure one more patient of all warts. When negative, the value becomes the number needed to treat for harm.

In the plantar wart group, the cure rate at 13 weeks did not differ between the treatment arms (Tables 7.2 and 7.3). Further stratification revealed that cure rates were considerably lower among participants 12 years and older than among younger participants. Also, cure rates were lower among participants whose warts had been present for six or more months at baseline than among those whose warts had been present for a shorter duration (Table 7.2).

### Sensitivity analysis

The results at 26 weeks were concordant with the results at 13 weeks (see Appendix 7.2). The same was true when we considered that all patients lost to follow-up were not cured, or when we excluded participants with both common and plantar warts from the analysis. Per-protocol analysis and analysis of the cure rate of individual warts at 13 weeks showed the same significant results as our primary analysis (see Appendix 7.3 and 7.4).

### Side effects and treatment satisfaction

In both wart groups, participants experienced more side effects after cryotherapy than after topical salicylic acid application (Table 7.4). In the common wart group, 31% (95% CI 19%–46%) of the participants reported considerable treatment burden after cryotherapy and 54% (95% CI 39%–68%) after salicylic acid treatment ( $p = 0.040$ ). Furthermore,

**Table 7.4.** Reported side effects at 13 weeks in the active treatment groups, stratified according to location of warts (n=152)

	Treatment arm		P-value*
	Cryotherapy (n=37)	Salicylic acid (n=38)	
Common wart group			
Number of side effects			0.012
0	5 (14)	8 (21)	
1	8 (22)	19 (50)	
2, 3 or 4	24 (65)	11 (29)	
Type of side effects			
Pain	29 (78)	5 (13)	<0.001
Blistering	22 (59)	2 (5)	<0.001
Scarring	8 (22)	-	0.003
Skin irritation	6 (16)	27 (71)	<0.001
Skin pigmentation	3 (8)	2 (5)	0.62
Bleeding after filing	-	6 (16)	0.012
Crust	3 (8)	-	0.075
Plantar wart group			
	(n=37)	(n=40)	
Number of side effects			<0.001
0	3 (8)	14 (35)	
1	14 (38)	19 (48)	
2, 3 or 4	20 (54)	7 (18)	
Type of side effects			
Pain	31 (84)	4 (10)	<0.001
Blistering	16 (43)	5 (13)	0.003
Scarring	1 (3)	-	0.298
Skin irritation	6 (16)	21 (53)	0.001
Skin pigmentation	3 (8)	2 (5)	0.58
Bleeding after filing	-	1 (3)	0.34
Crust	1 (3)	-	0.30
Other minor side effects	4 (11)	4 (10)	0.91

Values are number of participants with side effect (percentage of participants with side effect). Data were missing for three participants with common warts and three participants with plantar warts.

\* 2-sided chi-square, comparing two treatment groups.

† Five out of nine participants with scars reported that their scars had disappeared at 26 weeks.

69% (95% CI 53%–82%) of participants were satisfied with treatment after cryotherapy, as compared with 24% (95% CI 13%–39%) after salicylic acid treatment and 22% (95% CI 12%–38%) after the wait-and-see protocol ( $p < 0.001$ ). In the plantar wart group, there were no differences in treatment burden or satisfaction between the three treatment groups.

## INTERPRETATION

In this pragmatic three-arm randomised controlled trial conducted in family practices, we found that cryotherapy was the most effective therapy for common warts (mainly on hands), with 49% of patients cured after 13 weeks. Despite the fact that cryotherapy caused more frequent and more severe side effects than topical salicylic acid application, patients were most satisfied when treated with cryotherapy. For plantar warts, we found no clinically relevant difference between the treatment arms. Regardless of treatment, children with plantar warts showed relatively high cure rates (about 50%), whereas plantar warts in adolescents and adults were highly persistent (cure rates of about 5%).

Although our overall relative risk of 1.5 between salicylic acid treatment and the wait-and-see protocol was similar to the relative risk of 1.6 from pooled data in the recent Cochrane review, our overall cure rates of 24% in the salicylic acid group and 16% in the wait-and-see group were lower than the cure rates of 73% and 48% in the Cochrane review at similar follow-up.<sup>10,11</sup> This marked difference is most likely due to variation in study design and study population. Our primary care setting, pragmatic design, wide inclusion criteria, excellent follow-up and intention-to-treat analysis led to results that were easy to interpret and directly applicable to daily practice in primary care. In contrast, the two other studies comparing cryotherapy and salicylic acid treatment, which involved dermatology outpatients, excluded patients who had more than five warts, those with warts on locations other than the location under investigation, and non-attending or noncompliant patients (in our study 20% of participants included in the analysis were non-compliant).<sup>24,25</sup> Other factors may also be at play, such as age of the patients and duration of warts before treatment, which our study showed to be significantly associated with cure rates.

Our follow-up at 26 weeks showed that the effects of treatment of common warts were sustainable. In the plantar wart group, in contrast to statistically equal effectiveness at 13 weeks, both of the active treatments might have higher cure rates than a wait-and-see approach in the long term. These findings suggest that the effect of active treatments on plantar warts is delayed or that more aggressive treatment is needed because of the callosity overlying the warts.<sup>14</sup>

### Limitations

As in daily practice, salicylic acid was applied by the participants themselves, which could reduce effectiveness compared with treatments applied by health professionals. However, we explicitly recorded participants' adherence to standardised treatment protocols, and intention-to-treat cure rates were concordant with results of the per-protocol analyses.

The participating patients and family practices were aware of the treatment allocations, because the pragmatic study design and treatment options did not secure realistic blinding.

Furthermore, the research nurses who assessed outcomes were aware of the treatment allocations, because the appearance of the skin after treatment usually revealed the specific treatment and because the large proportion of children often spontaneously reported the specific treatment.

## Conclusion

Although earlier evidence favoured topical salicylic acid application over cryotherapy for the treatment of cutaneous warts, the results of our randomised controlled trial provides evidence to support the use of cryotherapy over salicylic acid treatment, for common warts only. For plantar warts, we found no clinically relevant difference between cryotherapy, salicylic acid treatment or a wait-and-see approach after 13 weeks.

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**Appendix 7.1.** Treatment adherence

Overall, 48 (20%) participants discontinued treatment protocol after 13 weeks (Figure 7.1), of which 32 (13%) did not receive treatment adequately, and 16 (6.7%) used a co-intervention in addition to treatment protocol (table). In addition, ten participants reported the additional use of OTC medication such as low-dose salicylic acid-containing ointments, dimethylether propane cryotherapy, and Thuja-oil. Stratification in the common wart and plantar wart group did not reveal additional information.

Adherence to treatment protocol at 13 weeks (n=240)

	Treatment arm		
	Cryotherapy, n=76	Salicylic acid, n=82	Awaiting, n=82
Adhered to treatment protocol	59 (78)	58 (71)	75 (91)
Permitted additional use of OTC treatment <sup>°</sup>	3 (4)	1 (1)	6 (7)
Discontinued treatment protocol	17 (22)	24 (29)	7 (9)
Category of discontinuation			
Did not receive treatment adequately <sup>^</sup>	14 (18)	18 (22)	-
Used co-intervention	3 (4)*	6† (7)	7 (9)‡
Reason for discontinuation			
Treatment burden	9 (12)	15 (18)	1 (1)
Side effects	2 (3)	9 (11)	-
Lack of confidence	1 (1)	-	6 (7) §
Other reason	5 (7)§	-	-

Values are number of participants (percentage of participants).

\* Participants had used salicylic acid application.

† Participants had used cryotherapy.

‡ Three participants had used cryotherapy, two salicylic acid, and two a combination of both.

§ Sum of percentages ≠ total due to rounding off.

<sup>°</sup> Such as low-dose salicylic acid-containing (17%) ointments, dimethylether propane cryotherapy, or Thuja-oil.

<sup>^</sup> Participants did not receive treatment adequately when cryotherapy had been applied less than every three weeks, or when salicylic acid had been administered less than four days per week.

**Appendix 7.2.** Outcomes at 26 weeks.

At 26 weeks, another six (2%) were lost to follow-up (four refusing further participation, one moving out of the region and one for unknown reasons). After the 13 week protocols, participants that had not been cured were free to switch therapies (or continue the same). They reported to have most frequently switched to or continued a wait-and-see policy for the next 13 weeks (47% in cryotherapy, 52% in salicylic acid, and 54% in wait-and-see). Stratification in the common wart and plantar wart group did not reveal additional information. In all participants combined and in the common wart group, the differences found at 13 weeks persisted for the next 13 weeks (table). In the plantar wart group, the cure rates increased in cryotherapy and salicylic acid arms, but did not change considerably in wait-and-see group (table)

Effectiveness of treatments at 26 weeks\*, stratified according to location of warts (n=234)

	Treatment arm						P-value†
	Cryotherapy		Salicylic acid		Awaiting		
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	
All participants (n=234)	42/75	56 (45 to 67)	32/80	40 (30 to 51)	20/79	25 (17 to 36)	<0.001
Common wart group (n=113)	24/38	63 (47 to 77)	12/38	32 (19 to 47)	10/37	27 (15 to 43)	0.001
Plantar wart group (n=121)	18/37	49 (33 to 64)	20/42	48 (33 to 62)	10/42	24 (13 to 39)	0.022

Values are number of participants cured / number of participants analyzed at 26 weeks, and percentages of participants cured (95% confidence intervals). A participant is cured when all warts present at baseline are gone.

\* After the 13 week protocols, participants were free to switch to any other therapy.

† 2-sided chi-square, comparing three treatment groups.

**Appendix 7.3.** Per-protocol analysis of effectiveness of treatments at 13 weeks, stratified according to location of warts (n=192)

	Treatment arm						P-value*
	Cryotherapy		Salicylic acid		Awaiting		
	n	% cured (95%CI)	n	% cured (95%CI)	n	% cured (95%CI)	
All participants (n=192)	26/59	44 (32 to 57)	18/58	31 (21 to 44)	11/75	15 (8.4 to 24)	<0.001
Common wart group (n=88)	18/30	60 (42 to 75)	4/24	17 (6.7 to 36)	1/34	3 (<1 to 15)	<0.001
Plantar wart group (n=104)	8/29	28 (15 to 46)	14/34	41 (26 to 58)	10/41	24 (14 to 39)	0.66

Values are number of participants cured / number of participants in per-protocol analysis, and percentages of participants cured (95% confidence intervals). A participant is cured when all warts present at baseline are gone.

\* 2-sided chi-square, comparing three treatment groups.

**Appendix 7.4.** Overall effectiveness of treatments at 13 weeks according to the number of individual warts cured (n=737)

	Treatment group						P-value*
	Cryotherapy		Salicylic acid		Awaiting		
	n	% cured (95% CI)	n	% cured (95% CI)	n	% cured (95% CI)	
All warts (n=737)	96/202	48 (41 to 54)	78/273	29 (24 to 34)	59/262	23 (18 to 28)	<0.001
Common warts (n=366)	66/104	63 (54 to 72)	30/146	21 (15 to 28)	10/116	8.6 (4.7 to 15)	<0.001
Plantar warts (n=371)	30/98	31 (22 to 40)	48/127	38 (30 to 46)	49/146	34 (26 to 42)	0.73

Values are number of individual warts cured / number of individual warts in intention to treat analysis at 13 weeks, and percentages of individual warts cured (95% confidence intervals). A wart is cured when wart is gone visually as well as palpably.

\* 2-sided chi-square, comparing three treatment groups.

