Onychomycosis in Primary Care Practice

Major challenges from a minor ailment

Roeland Michiel Watjer

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General Introduction

GENERAL INTRODUCTION

Background

Onychomycosis, the fungal infection of nail tissue, is frequently presented in general practice due to its high prevalence amongst the general population.[1,2] From a broader perspective, the nails are part of the skin appendages, and onychomycosis is therefore considered a dermatologic condition.[3,4] In Dutch general practice, skin conditions, including onychomycosis, are the second most frequently presented health concerns after musculoskeletal problems, contributing to an estimated 14% of all consultations.[5,6] Although the different skin conditions presented in general practice are numerous and specific incidence rates regarding onychomycosis are lacking, mycotic skin infections are the most common, having an incidence rate of 41.6 per 1000 patients in Dutch general practice. Of all mycotic skin infections, onychomycosis and tinea pedis are the most common.[7] As such, onychomycosis can be considered a typical example of a common condition frequently presented to the Dutch general practitioner.[8,9]

Onychomycosis is primarily caused by dermatophytes, mostly Trichophyton rubrum and related species. However, onychomycosis can also be caused by yeasts, mainly Candida species, and non-dermatophyte molds, such as Aspergillus spp.[10] Toenails are substantially more often affected than fingernails, and the proportion of causative pathogens differs for finger- and toenails. Toenail onychomycosis is most frequently caused by dermatophytes, whereas onychomycosis of the fingernails is predominantly caused by Candida species.[11-13]

The mean prevalence of onychomycosis in population-based studies varies between 4.3% and 5.5%.[1,14] This makes onychomycosis the most common cause of all nail-related diseases.[1,14] The prevalence reported for patients visiting hospital clinics is higher (8.9%).[1] This is also the case for patients with predisposing comorbidities or advancing age: between 8.8% to one-third of diabetic patients are affected, and the prevalence reported for patients >60 years increases to >20%.[15-19] In contrast, onychomycosis in children is much less common than in adults, with a pooled prevalence of <1%, and fingernails are more frequently affected than toenails.[19,20]

Despite that onychomycosis was already described as early as 1853 by Georg Meissner, who discovered its fungal nature, this 'minor ailment' persists today, posing different challenges to patients and their general practitioners regarding diagnosis, treatment, and prognosis.[10,21-25] These challenges, which form the basis of this dissertation, are outlined in the next paragraphs.

Clinical presentation and burden

Although most patients will initially only notice the visual changes caused by the fungal spread and often do not have more pressing symptoms such as pain or discomfort,

discarding onychomycosis as merely a cosmetic concern would be shortsighted. Numerous studies have shown that in a substantial part of patients, onychomycosis has a significant negative effect on the quality of life due to associated shame, discomfort, and anxiety.[26-29] In contrast, some studies suggest that others may not even be aware of having mild, early-stage onychomycosis due to non-apparent nail changes or absence of symptoms.[30-32] It would be interesting to know how many patients could be considered 'subclinically' affected, but sufficient data on this topic is lacking.[30-32] Patients with more evident symptoms may initially try over-the-counter medications or other home remedies before considering medical consultation.[2,22] Those with persisting or more pressing symptoms will eventually consult their general practitioner, most likely to confirm their suspected diagnosis and to be informed about possible treatment options.[33]

Diagnostic challenges

Onychomycosis is often considered to be easily diagnosed on physical examination.[2,33] This notion is also supported by the current guideline on mycotic skin infections of the Dutch College of General Practitioners (NHG-standaard), which states that confirmatory testing for onychomycosis is usually not required.[11,33,34] However, the differential diagnosis is broad, and previous diagnostic studies have shown a potential but considerable risk (10-25%) of making an incorrect diagnosis.[10,34-36] This is important because patients might be unnecessarily exposed to particularly oral treatment, given the required treatment duration and potential side effects. However, most diagnostic studies were performed in hospital settings by specialists other than general practitioners, not necessarily representative of Dutch general practice.[23]

Another challenge concerning the diagnostic process is to determine the extent of affliction i.e. the severity of onychomycosis. This is an important clinical aspect to consider as studies have shown that the more severe the affliction gets, the less likely the affected nails will respond to treatment, including oral treatment.[22,37] Having a clinical tool to assess severity could help the general practitioner to choose the most suitable treatment, as well as to predict and evaluate response to treatment. Such an instrument was developed by Carney et al., the Onychomycosis Severity Index (OSI), which is now frequently used to assess severity in clinical trials.[22,37,38] However, the OSI has been primarily validated for use by dermatologists and not for use by general practitioners.[38,39]

Antimycotic treatment

In recent decades, multiple therapeutic studies have shown that the most effective way to treat onychomycosis is by systemic antimycotic treatment i.e. oral antifungals.[37] However, even oral treatment does not guarantee success.[37] To evaluate the efficacy of any type of treatment, it is important to consider the different definitions or types of cure regarding the treatment of onychomycosis. Clinical cure of onychomycosis is defined as

a normal-looking nail after treatment. Mycological cure implies negative confirmatory testing such as direct microscopy (potassium-hydroxide, KOH), polymerase chain reaction (PCR), fungal culture, or, preferably, a combination of tests. Note here that mycological cure can be possible even if the nail is visually still affected. Achieving both clinical and mycological cure is considered complete cure, the most important primary outcome measure in clinical trials.[22,37] Regarding the efficacy of oral antifungal treatment for toenail onychomycosis, the clinical cure rates vary from 36.8-57.5% for terbinafine and 14.4-51.9% for azoles such as itraconazole. Mycological cure rates are generally higher, ranging from 47.4-75.5% and 18.6-66.8% for terbinafine and azoles, respectively.[37]

Besides these variations in treatment success, other potential downsides to systemic treatment exist. Due to physiologically slow nail growth, especially in toenails, an extensive oral treatment period of three months and often longer is required.[34] Furthermore, even after successful treatment, there is a substantial risk of recurrence within the first years after treatment, ranging from 3-33% for terbinafine and 37-55% for azoles.[22,37] Also, the use of oral treatment may be limited due to important drug-drug interactions. Regarding terbinafine, these primarily consist of medications metabolized by the CYP2D6 enzyme, most importantly antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors), beta-blockers such as metoprolol, and other antiarrhythmic drugs. Regarding itraconazole, some CYP3A4 metabolized medications are contraindicated, including simvastatin, midazolam, domperidone, dabigatran, quetiapine, and medications that prolong the QT interval.[33] Last but not least, oral antimycotics may have potentially serious side effects, ranging from severe skin reactions to fulminant hepatic failure.[40-44]

Therefore, effective topical treatment could be an important alternative to oral treatment, avoiding potential interactions and side effects described above. The Cochrane review by Foley et al. in 2020 provides a comprehensive overview of topical antifungals and device-based interventions.[22] Sufficient evidence showed that efinaconazole, ciclopirox, and tavaborole were significantly more effective than placebo. Adverse reactions are usually mild, transient, and limited to localized erythema, discomfort, e.g. burning sensation, or changes in shape or colour of the nail exposed.[22] However, the required treatment period is longer, mostly 6-12 months, and clinical cure rates reported so far are lower than for oral treatment (4.1-16.2%), with a wider range in mycological cure rates (30.3-94.5%).[22] When considering Dutch general practice, the most effective topical antifungals included in the Cochrane review are either unavailable (efinaconazole, tavaborole) or not registered for use in onychomycosis (ciclopirox). Topical miconazole (Daktarin®), readily available in the Netherlands, and the more practical once-weekly amorolfine (Loceryl®) available in surrounding countries, were not included in the Cochrane review due to the lack of randomized studies.[22,45] This left the current Dutch guideline without the required evidence to provide solid recommendations on topical

treatments for use in Dutch general practice.[33] The uncertainty about the efficacy of the available topical antifungals was therefore considered a knowledge gap and put on the national research agenda of the Dutch College of General Practitioners in 2018.[46]

Prognostic implications of onychomycosis

Although onychomycosis may be limited to minor visual nail changes in many patients, for others, onychomycosis can be the cause of substantial symptoms and burden, decreasing the affected patient's quality of life.[26,29] Furthermore, onychomycosis may contribute to long-term negative health outcomes in susceptible patients, especially in patients with diabetes.[25,47] This is important since the prevalence of onychomycosis is increased in patients with diabetes and other immunocompromised states, with up to one-third of diabetic patients affected compared to 4.3-5.5% of the general population.[26] Subsequently, the risk of developing complications from onychomycosis, such as bacterial skin infections and lower leg ulcers, is also significantly increased in patients with diabetes.[24,47-50] The development of a diabetic ulcer is the cause of substantial healthcare costs and morbidity due to e.g. secondary bacterial infections, hospital admissions, and surgeries, ultimately leading to lower-extremity amputations and increased overall mortality.[51,52] Therefore, early identification of patients at risk of developing ulcerative complications could reduce the impact of onychomycosis and potentially prevent part of these negative health outcomes.[24,50,52] However, the relationship between onychomycosis and ulcerative complications in patients with diabetes has not been well studied in primary care.[49,53]

THESIS OUTLINE

This thesis consists of three parts, addressing the three clinical stages and their specific challenges in the care path for toenail onychomycosis presented in general practice: diagnosis, treatment, and prognosis.

In Part I, the research focuses on diagnostic challenges. In Chapter 2, the accuracy of the clinical diagnosis of onychomycosis is addressed, as onychomycosis is often assumed to be easily recognizable and effectively diagnosed based on history and physical examination. Secondly, the reliability of the existing Onychomycosis Severity Index (OSI) to assess onychomycosis severity in primary care settings is addressed in Chapter 3.

In Part II, onychomycosis therapy is addressed. A clinical case report describes a severe skin reaction from oral terbinafine (Chapter 4), illustrating potential harms from systemic treatment and serving as an introduction to finding an effective topical treatment. Subsequently, topical treatments for onychomycosis in Dutch general practice are studied through a randomized double-blind, placebo-controlled trial that evaluates

the efficacy of two frequently used but not well-studied topical antifungals, miconazole and amorolfine (Chapter 5).

In Part III, the prognostic implications of onychomycosis in patients with Diabetes are addressed through a large longitudinal cohort study based on routine care data, investigating the association between onychomycosis and ulcerative complications (Chapter 6).

Finally, a general discussion and summary (Chapter 7) provides the overall findings, a comparison with previous literature, methodological considerations, and aims to reflect on implications for daily practice. A Dutch summary is provided at the end.

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Part I

Diagnostic Considerations in General Practice

The accuracy of clinical diagnosis of onychomycosis in Dutch general practice: a diagnostic accuracy study

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ABSTRACT

Background: Onychomycosis, the most common cause of nail dystrophy, is generally diagnosed by clinical examination. Current guidelines for Dutch general practice advise confirmatory testing only in cases of doubt or insufficient response to treatment. However, making a correct diagnosis can be challenging given the wide variety of clinical features and differential diagnosis.

Aim: To establish accuracy of clinical diagnosis of onychomycosis by GPs.

Design & setting: A diagnostic accuracy study based on GPs' clinical diagnosis of primary care patients suspected of onychomycosis.

Method: Using 137 complete datasets from the Onycho Trial, diagnostic accuracy of clinical diagnosis as the index test was compared with confirmatory testing as the reference test. A sensitivity analysis was performed to determine diagnostic values for different combinations of index and reference test. Logistical regression was used to assess which clinical characteristics were associated with the positive predictive value (PPV) of the index test.

Results: Clinical accuracy, that is the PPV of the index test, was 74.5%. Sensitivity analysis showed no significant difference in diagnostic values. Male sex and a history of any previous treatment significantly increased clinical accuracy with an odds ratio (OR) of 3.873 (95% confidence interval [CI] = 1.230 to 12.195, $P = 0.021$) and OR 4.022 (95% CI = 1.075 to 15.040, $P = 0.039$), respectively.

Conclusion: The study demonstrated that the GPs' clinical diagnosis of onychomycosis was insufficiently accurate to initiate treatment without confirmatory testing. Further research is needed to investigate how to increase clinical accuracy and reduce potentially unnecessary exposure to treatment.

INTRODUCTION

Onychomycosis is a very common nail problem. It accounts for more than half of all nail-related disease and around 30% of fungal skin infections in Europe and North America.[1-3] On average 4.3% of adults are affected, although rates vary between 2% and 14%, increasing substantially with increasing age.[4-7] Onychomycosis can lead to discolouration, thickening, and separation from the nail bed; the great toenail is most often affected.[8-9] The chance of a self-limiting course is very low.[10]

In general, onychomycosis has an indolent disease course, although some patients experience pain and discomfort through thickening of the nail and may develop complications such as recurring dermatomycosis or secondary bacterial infection.[9] Additionally, several studies have shown significant decrease in nail-related quality of life in affected individuals.[11-15]

According to a Cochrane review, the most effective treatment is oral terbinafine or an imidazole for 3 months.[16] However, oral treatment may have potentially serious side effects including severe skin rash and liver injury.[17] Weighing potential adverse reactions against onychomycosis' indolent disease course, physicians might be reluctant in prescribing oral treatment especially for milder cases. Onychomycosis is often diagnosed on clinical examination. Accuracy of clinical diagnosis varies between different specialists. Dermatologists' clinical diagnosis was confirmed by laboratory testing in 93% of cases, compared with 81% for GPs.[18] Another study found podiatrists to be superior in clinically diagnosing onychomycosis with an accuracy of 80.8%, compared with 75.3% for dermatologists and 66.2% for GPs.[19]

In current Dutch general practice guidelines, antifungal treatment may be started solely based on clinical examination. Confirmatory testing by potassium hydroxide (KOH) preparation, fungal culture, or polymerase chain reaction (PCR) for fungal DNA is advised only when in doubt or in the case of treatment failure.[10] These tests also have varying accuracies and generally modest sensitivity. KOH is the most sensitive (85%), followed by PCR (73%) and culture, which is the least sensitive (54%).[20,21] To increase diagnostic accuracy, it is recommended to use a combination of different confirmatory tests.[21-23]

Given the varying accuracies of tests, patients could be unnecessarily exposed to treatment and its potential side effects. Confirmatory testing of clinically suspected cases could reduce potential overtreatment. To make a decision whether or not to use confirmatory testing in general practice, one needs to know the accuracy of clinical diagnosis.

This study aimed to determine the accuracy of clinical diagnosis of onychomycosis by GPs compared with confirmatory testing. Second, the study aimed to assess which clinical features have a significant impact on predicting confirmatory testing outcome.

METHODS

Study design

The accuracy of clinical diagnosis was investigated using data from the Onycho Trial, a randomised double-blind placebo-controlled trial (RCT), investigating the effectiveness of topical treatment with miconazole (Daktarin) or amorolfine (Loceryl) compared with placebo for mild to moderately severe onychomycosis in Dutch general practice (https://trialsearch.who.int/Trial2.aspx?TrialID=NL8193). Clinical diagnosis by the GPs involved was determined by the index test; confirmatory testing of the affected nail samples was used as the reference standard.

Regarding the index test, the conclusion of three independent observers was used based on standardised photographs taken during screening for the Onycho Trial, and these were compared with results of confirmatory testing. A positive clinical diagnosis by at least two out of three observers was regarded an overall positive clinical diagnosis; only one or no observer making a positive diagnosis was regarded as a negative clinical diagnosis. The three observers were two senior GPs (JE and TN) and one GP in training (RW). All observers were blinded for treatment allocation, clinical information recorded, and each other's assessments.

For confirmatory testing, a positive result from any one of three testing methods used (KOH, PCR, or culture) was considered a positive reference test. PCR consisted of lab developed real-time PCR assays designed to detect trichophyton and microsporum species, based on the assay described by Wisselink et al. and an assay to detect *Trichophyton rubrum*.[24] Note that not all participants received all three types of confirmatory tests. All patients did receive KOH and additional PCR testing, but fungal culture was only performed for determination purposes in case of a positive KOH with negative PCR results and in case of a positive dermatophyte PCR with a negative *T. rubrum* species PCR. This was in accordance with standard work-up protocols of the affiliated departments of dermatology and microbiology.

Finally, the clinical diagnosis was considered to be correct if the overall clinical diagnosis made by the observers was in agreement with the overall confirmatory test result.

Patients

All study participants (aged 18–70 years) with mild onychomycosis recruited and screened for the Onycho Trial, between October 2019 and January 2022, were considered for analysis. The majority of patients were recruited from the general public

through social media; others were directly or indirectly referred by GPs affiliated with the regional research collaboration 'Extramural Leiden Academic Network' (ELAN).

Data collection

All data originated from the ongoing Onycho Trial. Castor Electronic Data Capture (EDC), a cloud-based data management system, was used to record all data. Only datasets consisting of complete data, on both clinical diagnosis and laboratory test results, were used for the analyses.

Statistical analysis

Diagnostic values, that is, sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) representing the accuracy of the clinical diagnosis, were calculated using 2 × 2 tables, with clinical diagnosis as the index test and the overall result of confirmatory testing as the reference test. To compare observers, diagnostic values were calculated for each observer separately. For the level of agreement between observers, descriptive statistics and inter-observer reliability (Fleiss' kappa) were calculated.

To evaluate differences between possible combinations of index and reference test and to compare these to the primary combination chosen, a sensitivity analysis was performed constructing 2 × 2 tables for all possible combinations between number of observers making a positive clinical diagnosis (1 out of 3 up to 3 out of 3) and all possible combinations for confirmatory testing. Diagnostic values were calculated for each combination and their 95% CI using Wilson's score method for binomial proportions.

Uni- and multivariate logistic regression analyses (forced entry and stepwise methods) were performed to assess whether any of the patient characteristics were significantly associated with the accuracy of clinical diagnosis, calculating ORs and their 95% CIs. For categorical data, the lowest or least severe category was chosen as the reference group.

Finally, a subgroup analysis was performed for the significantly associated characteristics found by multivariate regression. For all analyses performed, a P value of <0.05 was considered statistically significant.

Statistical analyses for both sensitivity and regression analyses were conducted using IBM SPSS (version 25).

Sample size

To calculate the required sample size for the binary outcome, that is, having onychomycosis or not, the following equation was used: $n = 2\,(z\alpha_{/2} + z\beta)^2 \bar{p}(1 - \bar{p})/d^2$, with an alpha of 0.05 and a power of 90%. Setting the PPV of combined confirmatory

testing at 100% and the estimated accuracy of clinical diagnosis of GPs at 70%, which was based on available literature, the expected difference was 30%.[19] Using these numbers, a minimum of 30 was required for both groups resulting in a total sample size of 60 patients.

RESULTS

Patient selection

Of 140 available records, 137 had complete data necessary for analyses. For the other three not all observers had provided the required input, or results of confirmatory testing were still pending or not performed (Figure 1). Regarding the incomplete records, the first patient was excluded at intake owing to metformin use, not collecting any further data. The second did not receive a clinical diagnosis from all three observers as required for analyses. For the third patient, no PCR test was performed owing to shortages caused by the COVID-19 pandemic, required for the reference standard (Figure 1). Since the reasons for these incomplete observations were unrelated to the potential value of the outcome, these data were considered to be missing at random; that is, not causing bias.

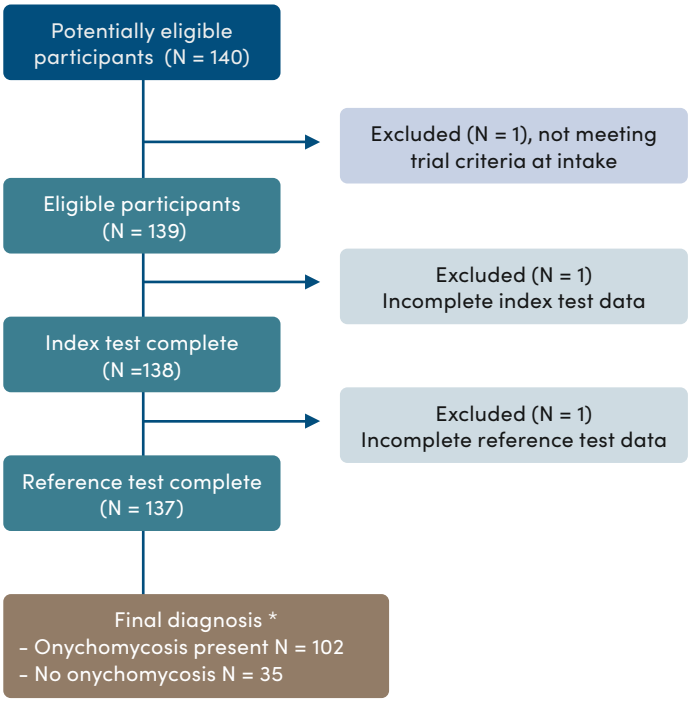

Figure 1 Participant flow diagram
* Confirmed by at least 2 out of 3 observers

Patient characteristics

Table 1 shows the study population's characteristics and risk factors for onychomycosis. The majority (59.1%) of the patients were aged >50 years and had moderate-to-severe onychomycosis (based on Onychomycosis Severity Index[25] of 3–4 toenails and moderate symptoms for 1 year). The vast majority (83.2%) had tried any form of treatment including oral antifungal medication, to which only 17 patients (12.4%) had been exposed explicitly. All previous treatments, including home remedies, were self-reported; no data were available to verify type, timing, or duration of any treatment.

Table 1 Participant characteristics

	Total (N = 137)
Demographic Factors	
Mean age, years (SD)	52.0 (12.5)
- 0-25 years (%)	4 (3)
- 26-50 years (%)	52 (38)
- 51-75 years (%)	81 (59)
Male (%)	60 (44)
Skin type (Fitzpatrick skin types), %	
- Very Fair, Fair and Medium	133 (97)
- Olive, Brown and Black	4 (3)
Clinical Factors	
Affected area of index toenail (%)	
- 1-10	6 (4)
- 11-25	31 (23)
- 26-50	57 (42)
- 51-75	34 (25)
- 76-100	9 (6)
OSI-score (%)	
- Mild (0-5)	20 (15)
- Moderate (6-15)	70 (51)
- Severe (16-35)	47 (34)
Mean total affected toenails (SD)	3.8 (1.9)
Time since onset (≥1 year) (%)	118 (86)
Score ONYCHO-questionnaire (%)	
- Good (67-100)	47 (34)
- Moderate (34-66)	83 (61)
- Poor (0-33)	7 (5)

Table 1 Participant characteristics (continued)

	Total (N = 137)
Risk Factors	
History tinea pedis (%)	78 (57)
Family members with onychomycosis (%)	31 (23)
Presence of dermatological disease (%)	40 (29)
History of oral treatment (%)	23 (17)
History of any previous treatment (%)	114 (83)
History of use of immunosuppressives (%)	17 (12)
Frequent use of public pool or spa (≥5 visits/year) (%)	49 (36)
Consistent use of flip flops during these visits (%)	32 (23)
History of smoking or active smoker (%)	57 (42)

OSI = Onychomycosis Severity Index

Accuracy of clinical diagnosis

Of 137 patients included, 102 were correctly diagnosed, that is, confirmed by laboratory testing; 35 were incorrectly diagnosed (Table 2). Clinical accuracy, that is, the PPV, was 74.5% (95% CI = 66.2% to 81.3%). Comparing clinical accuracy, there was no significant difference between the different observers (Table S1). Regarding inter-observer agreement, there was unanimous agreement on a positive clinical diagnosis in 127 of 137 cases (92.7%). However, for the remaining cases where at least one observer considered an alternative diagnosis, in none of these cases all three observers agreed, resulting in a Fleiss' kappa of −0.025.

Table 2 2 x 2 Table clinical accuracy of index test

		Confirmatory Testing [a]		
		Positive	Negative	Total
Clinical diagnosis by GP [b]	**Yes**	102 (74.5%) [c]	35	137
	No	0	0 [d]	0
	Total	102 [e]	35	137

[a] At least 1 out of 3 confirmatory tests (potassium hydroxide [KOH], polymerase chain reaction [PCR], culture) positive. [b] At least 2 out of 3 observers positive diagnosis. [c] *P* value for positive predictive value (PPV) = 0.000 with 95% CI = 0.961 to 1.000. [d] *P* value for specificity = 0.000 with 95% CI = 0.000 to 0.036. [e] *P* value for sensitivity = 0.000 with 95% CI = 0.964 to 1.000.

Sensitivity analysis of clinical diagnosis

Table 3 shows the sensitivity analysis for differences in diagnostic values between the possible combinations of index and reference tests. The index test was divided into three groups based on the number of observers confirming clinical diagnosis (1 out of 3 up to 3 out of 3). For the reference test all possible combinations were used (see Table S2–S4).

The diagnostic values for the first two groups were the same: a sensitivity of 100% and PPV of 27.3% to 74.5%, depending on the combination of confirmatory tests. Since all patients received a positive clinical diagnosis by at least one or two observers, specificity was 0% and NPV could not be calculated.

Compared with the first two groups, sensitivity was slightly lower for the third group (3 out of 3), ranging from 92.6%–95.1%; PPVs were roughly equal, between 27.4% and 76.4%. Specificity was 4.9%–14.3 and NPVs were between 50.0% and 75.0%.

Table 3 Sensitivity analysis

		N	Sensitivity, % [95% C.I.]	Specificity, % [95% C.I.]	Positive predictive value, % [95% C.I.]	Negative predictive value, % [95% C.I.]
Clinical diagnosis	**Confirmatory test**					
1 out of 3	KOH or PCR or culture	137	100 [95.5 – 100]	0 [0 – 12.3]	74.5 [66.2 – 81.3]	–
	KOH	139	100 [95.1 – 100]	0 [0 – 9.8]	67.6 [59.1 – 75.2]	–
	PCR	137	100 [93.8 – 100]	0 [0 – 7.1]	53.3 [44.6 – 61.8]	–
	Culture	68	100 [87.1 – 100]	0 [0 – 12.3]	48.5 [36.4 – 60.9]	–
	KOH & PCR	137	100 [96.6 – 100]	0 [0 – 3.4]	50.4 [41.7 – 59.0]	–
	KOH & culture	68	100 [84.5 – 100]	0 [0 – 6.7]	39.7 [28.3 – 52.3]	–
	PCR & culture	66	100 [80.0 – 100]	0 [0 – 9.6]	30.3 [19.9 – 43.0]	–
	KOH & PCR & culture	66	100 [78.1 – 100]	0 [0 – 9.2]	27.3 [17.4 – 39.8]	–

Table 3 Sensitivity analysis (continued)

		N	Sensitivity, % [95% C.I.]	Specificity, % [95% C.I.]	Positive predictive value, % [95% C.I.]	Negative predictive value, % [95% C.I.]
2 out of 3 [a]	KOH or PCR or culture [a]	137	100 [95.5 – 100]	0 [0 – 12.3]	74.5 [66.2 – 81.3]	–
	KOH	139	100 [95.1 – 100]	0 [0 – 9.8]	67.6 [59.1 – 75.2]	–
	PCR	137	100 [93.8 – 100]	0 [0 – 7.1]	53.3 [44.6 – 61.8]	–
	Culture	68	100 [87.1 – 100]	0 [0 – 12.3]	48.5 [36.4 – 60.9]	–
	KOH & PCR	137	100 [96.6 – 100]	0 [0 – 3.4]	50.4 [41.7 – 59.0]	–
	KOH & culture	68	100 [84.5 – 100]	0 [0 – 6.7]	39.7 [28.3 – 52.3]	–
	PCR & culture	66	100 [80.0 – 100]	0 [0 – 9.6]	30.3 [19.9 – 43.0]	–
	KOH & PCR & culture	66	100 [78.1 – 100]	0 [0 – 9.2]	27.3 [17.4 – 39.8]	–
3 out of 3	KOH or PCR or culture	137	95.1 [88.4 – 98.2]	14.3 [5.4 – 31.0]	76.4 [67.9 – 83.3]	50 [20.1 – 79.9]
	KOH	139	94.7 [87.5 – 98.0]	11.1 [4.2 – 24.8]	69 [60.2 – 76.7]	50 [20.1 – 79.9]
	PCR	137	94.5 [85.8 – 98.2]	9.4 [3.9 – 19.9]	54.3 [45.3 – 63.1]	60 [27.4 – 86.3]
	Culture	68	93.9 [78.4 – 98.9]	5.7 [1.0 – 20.5]	48.4 [35.9 – 61.2]	50 [9.2 – 90.8]
	KOH & PCR	137	94.2 [85.1 – 98.1]	8.8 [3.6 – 18.9]	51.2 [42.2 – 60.1]	60 [27.4 – 86.3]
	KOH & culture	68	92.6 [74.2 – 98.7]	4.9 [0.8 – 17.8]	39.1 [27.4 – 52.1]	50 [9.2 – 90.8]
	PCR & culture	66	95 [73.1 – 99.7]	6.5 [1.7 – 18.9]	30.6 [19.9 – 43.8]	75 [21.9 – 98.7]
	KOH & PCR & culture	66	94.4 [70.6 – 99.7]	6.3 [1.6 – 18.2]	27.4 [17.2 – 40.4]	75 [21.9 – 98.7]

[a] Combination used for logistical regression analysis.
KOH = potassium hydroxide. PCR = polymerase chain reaction.

Logistical regression analysis

Table 4 shows the logistical regression analyses for correct clinical diagnosis for the primary combination of at least 2 out 3 observers diagnosing onychomycosis and at least 1 out of 3 confirmatory tests being positive. Univariate analysis showed male sex

to increase the odds of a correct clinical diagnosis with an OR of 2.889 (95% CI = 1.233 to 6.770; P = 0.015).

Multivariate analysis showed male sex (OR 3.873, 95% CI = 1.230 to 12.195; P = 0.021) and history of any previous treatment (OR 4.022, 95% CI = 1.075 to 15.040; P = 0.039) were significantly associated with a correct diagnosis. Stepwise forward and backward methods did not reveal any additional significant contributors.

Table 4 Logistical regression analysis correct diagnosis general practitioners

	Univariate analysis			**Multivariate analysis**		
	OR	**95% C.I.**	**p-value**	**OR**	**95% C.I.**	**p-value**
Demographic Factors						
Age (years)	1.009	0.979 -1.041	0.548	1.066	0.983 – 1.157	0.124
- 0-25 years	Reference Group		0.278	Reference Group		0.175
- 26-50 years	4.200	0.526 – 33.543	0.176	0.965	0.040 – 23.419	0.982
- 51-75 years	2.522	0.335 – 18.983	0.369	0.162	0.003 – 8.986	0.374
Gender (male)	**2.889**[a]	1.233 – 6.770	**0.015**[a]	**3.873**[a]	1.230 – 12.195	**0.021**[a]
Skin type (Fitzpatrick 4-6)	1.030	0.104 – 10.240	0.980	0.510	0.030 – 8.581	0.640
Clinical Factors						
Percentage of the index toenail affected, %						
- 1-10	Reference Group		0.256	Reference Group		0.218
- 11-25	1.818	0.312 – 10.582	0.506	5.042	0.335 – 75.802	0.242
- 26-50	4.182	0.741 – 23.594	0.105	10.212	0.499 – 209.180	0.132
- 51-75	2.778	0.472 – 16.374	0.259	2.077	0.071 – 60.829	0.671
- 76-100	8.000	0.580 – 110.268	0.120	10.660	0.143 – 794.910	0.282
OSI-score						
- Mild (0-5)	Reference Group		0.117	Reference Group		0.214
- Moderate (6-15)	1.256	0.439 – 3.596	0.670	0.488	0.075 – 3.194	0.454
- Severe (16-35)	3.077	0.908 – 10.425	0.071	2.192	0.146 – 32.856	0.570
Total affected toenails	0.998	0.815 – 1.223	0.986	0.962	0.714 – 1.297	0.802
Time since onset (years)	1.028	0.980 – 1.078	0.266	1.040	0.977 – 1.107	0.217

Table 4 Logistical regression analysis correct diagnosis general practitioners (continued)

	Univariate analysis			**Multivariate analysis**		
	OR	**95% C.I.**	**p-value**	**OR**	**95% C.I.**	**p-value**
Time since onset (>1 year)	1.048	0.348 – 3.153	0.934	0.377	0.074 – 1.926	0.241
Score ONYCHO-questionnaire						
- Good (67-100)	Reference Group		0.889	Reference Group		0.427
- Moderate (34-66)	1.204	0.534-2.716	0.654	1.983	0.652 – 6.029	0.228
- Poor (0-33)	0.956	0.164 – 5.556	0.960	0.919	0.091 – 9.231	0.943
Risk Factors						
History tinea pedis	2.154	0.988 – 4.696	0.054	2.735	0.953 – 7.855	0.062
Family members with onychomycosis	0.794	0.325 – 1.940	0.613	1.300	0.363 – 4.660	0.687
Presence of a different dermatological disease	1.261	0.530 – 3.003	0.600	1.664	0.482 – 5.764	0.420
History of oral treatment	0.582	0.223 – 1.521	0.269	0.294	0.074 – 1.164	0.081
History of any previous treatment	1.719	0.658 – 4.491	0.269	**4.022** [a]	1.075 – 15.040	**0.039** [a]
History of use of immunosuppressives	0.584	0.199 – 1.719	0.329	0.550	0.128 – 2.370	0.423
Frequent use of public swimming pools, saunas or spas (≥5 visits/year)	0.923	0.416 – 2.048	0.844	1.284	0.390 – 4.229	0.682
Consistent use of flip flops during these visits	1.038	0.417 – 2.585	0.935	0.932	0.279 – 3.114	0.909
History of smoking or active smoker	0.798	0.368 – 1.731	0.568	0.369	0.131 – 1.040	0.059

OSI = Onychomycosis Severity Index.
Statistical significance is indicated by [a] and bold text.

Subgroup analysis

Based on multivariate regression, subgroup analysis was performed for both sex and history of any previous treatment. For sex, the PPV for males was 85.0% compared with 66.2% for females. For participants with and without a history of previous treatment, this was 76.3% and 65.2%, respectively (see Table S5-6).

DISCUSSION

Summary

This study demonstrated an overall accuracy of clinical diagnosis of onychomycosis by GPs of 74.5%, meaning that 25.5% of cases could not be confirmed by laboratory testing and could be considered incorrect. These patients are at risk of receiving unnecessary antifungal treatment if no confirmatory testing were performed. Male sex and a history of any previous treatment significantly increased the odds of making a correct diagnosis.

Strengths and limitations

All data used originated from participants recruited from both general public and general practice; the observers performing clinical diagnosis were all practicing GPs and did not have additional training, making the results representative of other primary care settings.

All clinical diagnoses were made independently from other observers, without the knowledge of confirmatory test results, limiting observer bias.

Although there is still debate on what should be considered the gold standard for confirmatory testing, a combination of tests is often recommended.[20,22,23,26,27] For this study, at least one of three tests being positive was considered sufficient to minimize incorrect exclusion of true cases of onychomycosis. This is consistent with daily practice where normally a single confirmatory test is performed when in doubt.[10,18] If one of the other recommended approaches would have been applied, clinical accuracy would have been lower, as shown in Table 3.

Regarding the sample-size calculation, a limitation was that a sensitivity of 100% was applied to the reference standard. A more conservative approach would be to take the sensitivity of 85% from the KOH test, the highest of the confirmatory tests used. Using the same calculation, the required sample size would have been a total of 132 patients.

In addition, selection bias was an inherent consequence, with all data originating from an RCT. All patients were specifically recruited for having onychomycosis. This is likely the reason that there were no cases in which a majority of observers (2 out of 3) diagnosed something other than onychomycosis. This is reflected by a specificity of 0% (Table 2), and signifies an underestimation of true clinical accuracy by GPs.

Another limitation is that clinical diagnosis in daily practice is made by a single GP instead of a group. Although sensitivity analysis showed no difference in diagnostic values between 1 out of 3 or 2 out of 3 observers, accuracy could be lower in daily practice.

Although GPs were blinded to each other's clinical diagnosis and test results, they were aware their assessment was part of the inclusion process for the trial, potentially leading to observer bias. When in doubt, onychomycosis might have been diagnosed too easily, increasing the chance of inclusion; and vice versa, an alternative diagnosis might have been preferred, promoting milder cases to increase the chance of response to treatment. Given the incentive of inclusion, the former seems more likely and GPs are probably better in diagnosing onychomycosis in daily practice than this study suggests.

Comparison with existing literature

Li et al. found a clinical accuracy of 75.4%, which is consistent with the present study findings.[19] However, clinical diagnosis primarily was made by specialists other than GPs, who were likely more experienced in diagnosing nail disease. In addition, only microscopy was used for confirmation, potentially underestimating accuracy of clinical diagnosis. Kuijpers and Tan found an accuracy of 81% for GPs.[18] Although higher than the 74.5% found in the present study, dermatologists had an accuracy of 93%, supporting that experience improves accuracy. Using three different tests, the chance of confirming fungal infection was actually increased and therefore a correct diagnosis. Thus, an accuracy of 74.5% is arguably representative for GPs and other primary care settings.

Implications for research and practice

In conclusion, the study demonstrates a significant chance of an incorrect clinical diagnosis without confirmatory testing in primary care, especially in female patients or patients without any previous treatment. Not performing a confirmatory test could lead to unnecessary patient exposure to antifungal treatments. The authors, therefore, would not currently recommend GPs advise therapy without confirmatory testing. With 67.9% of cases confirmed by KOH alone against relative low costs, initial KOH testing would be a reasonable approach (Table 3).

To decrease observer bias, further studies to improve validity of results should ideally include all, or at least a broader spectrum of, nail disorders and all levels of severity as far as onychomycosis is concerned. Besides reducing bias by study design, future studies could obtain additional variables that might significantly influence clinical accuracy.

Despite its limitations, this study underlines the importance of confirmatory testing, especially when considering treatment. Further research is necessary to optimise the accuracy of the clinical diagnosis by GPs and reduce the number of patients unnecessarily exposed to treatment.

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DECLARATIONS

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Ethical approval: No approval from the Dutch Medical Ethics Committee was required for this study. The overarching Onycho Trial was approved by the Dutch Medical Ethics Committee Leiden-Den Haag-Delft (CCMO ref. NL68851.058.19, project ref. P19.055 dd. 26-08-2019)
Provenance: Freely submitted; externally peer reviewed.
Data: The dataset relied on in this article is available from the corresponding author on reasonable request.

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SUPPLEMENTARY DATA

Table S1 2 x 2 Tables clinical accuracy per general practitioner

		Confirmatory test		
		Positive	**Negative**	**Total**
Diagnosis first general practitioner	Onychomycosis	102 (75%)	34	136
	Other	0	1	1
	Total	102	35	137
Diagnosis second general practitioner	Onychomycosis	99 (73.9%)	35	134
	Other	3	0	3
	Total	102	35	137
Diagnosis third general practitioner	Onychomycosis	100 (76.3%)	31	131
	Other	2	4	6
	Total	102	35	137

Table S2 2 x 2 Tables at least 1/3 clinical onychomycosis diagnosis with all combinations

		Minimum 1 out 3 GPs diagnose onychomycosis		
Confirmatory test		**Yes**	**No**	**Total**
Minimum KOH, PCR or culture positive	Yes	102	0	102
	No	35	0	35
	Total	137	0	137
Minimum KOH positive	Yes	94	0	94
	No	45	0	45
	Total	139	0	139
Minimum PCR positive	Yes	73	0	73
	No	64	0	64
	Total	137	0	137
Minimum fungal culture positive	Yes	33	0	33
	No	35	0	35
	Total	68	0	68
Minimum KOH & PCR positive	Yes	69	0	69
	No	68	0	68
	Total	137	0	137
Minimum KOH & fungal culture positive	Yes	27	0	27
	No	41	0	41
	Total	68	0	68

Table S2 2 x 2 Tables at least 1/3 clinical onychomycosis diagnosis with all combinations (continued)

		Minimum 1 out 3 GPs diagnose onychomycosis		
Confirmatory test		**Yes**	**No**	**Total**
Minimum PCR & fungal culture positive	Yes	20	0	20
	No	46	0	46
	Total	66	0	66
Minimum KOH, PCR & fungal culture positive	Yes	18	0	18
	No	48	0	48
	Total	66	0	66

Table S3 2 x 2 Tables at least 2/3 clinical onychomycosis diagnosis with all combinations

		Minimum 2 out 3 GPs diagnose onychomycosis		
Confirmatory test		**Yes**	**No**	**Total**
Minimum KOH, PCR or culture positive	Yes	102	0	102
	No	35	0	35
	Total	137	0	137
Minimum KOH positive	Yes	94	0	94
	No	45	0	45
	Total	139	0	139
Minimum PCR positive	Yes	73	0	73
	No	64	0	64
	Total	137	0	137
Minimum fungal culture positive	Yes	33	0	33
	No	35	0	35
	Total	68	0	68
Minimum KOH & PCR positive	Yes	69	0	69
	No	68	0	68
	Total	137	0	137
Minimum KOH & fungal culture positive	Yes	27	0	27
	No	41	0	41
	Total	68	0	68
Minimum PCR & fungal culture positive	Yes	20	0	20
	No	46	0	46
	Total	66	0	66

Table S3 2 x 2 Tables at least 2/3 clinical onychomycosis diagnosis with all combinations (continued)

		Minimum 2 out 3 GPs diagnose onychomycosis		
Confirmatory test		**Yes**	**No**	**Total**
Minimum KOH, PCR & fungal culture positive	Yes	18	0	18
	No	48	0	48
	Total	66	0	66

Table S4 2 x 2 Tables at least 3/3 clinical onychomycosis diagnosis with all combinations

		Minimum 3 out 3 GPs diagnose onychomycosis		
Confirmatory test		**Yes**	**No**	**Total**
Minimum KOH, PCR or culture positive	Yes	97	5	102
	No	30	5	35
	Total	127	10	137
Minimum KOH positive	Yes	89	5	94
	No	40	5	45
	Total	129	10	139
Minimum PCR positive	Yes	69	4	73
	No	58	6	64
	Total	127	10	137
Minimum fungal culture positive	Yes	31	2	33
	No	33	2	35
	Total	64	4	68
Minimum KOH & PCR positive	Yes	65	4	69
	No	62	6	68
	Total	127	10	137
Minimum KOH & fungal culture positive	Yes	25	2	27
	No	39	2	41
	Total	64	4	68
Minimum PCR & fungal culture positive	Yes	19	1	20
	No	43	3	46
	Total	62	4	66
Minimum KOH, PCR & fungal culture positive	Yes	17	1	18
	No	45	3	48
	Total	62	4	66

Reliability of the Onychomycosis Severity Index in Primary Care

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Submitted

ABSTRACT

Background: The Onychomycosis Severity Index was designed to quantify onychomycosis severity and was validated by dermatologists. The aim of this study was to assess the reliability of the Onychomycosis Severity Index when applied in primary care.

Methods: Three general practitioners assigned Onychomycosis Severity Index scores to a set of standardized pictures of primary care patients' toenails affected by mild to moderately severe onychomycosis. To evaluate inter-observer reliability in terms of absolute agreement, being of primary interest, Intraclass Correlation Coefficients were calculated. In addition, Cronbach's alpha was calculated to assess consistency. To evaluate intra-observer or test-retest reliability, repeated scores on a subset of pictures were compared by calculating their corresponding coefficients.

Results: For inter-observer reliability in terms of absolute agreement, comparing scores for 280 pictures, the Intraclass Correlation Coefficient was 0.578 (95% CI 0.458 - 0.671); Cronbach's alpha was 0.834 (95% CI 0.797 - 0.865). Regarding intra-observer or test-retest reliability, comparing repeated scores for 80 pictures, the mean corresponding coefficient was 0.650 (95% CI 0.501 – 0.761).

Conclusions: Although showing good consistency as illustrated by Cronbach's alpha, the Onychomycosis Severity Index when used in primary care shows poor to moderate inter-observer reliability and poor to good intra-observer reliability. Based on these findings, we would not recommend applying the OSI in its current form in primary care; reliability should be improved by adaptation of the OSI for broader- and primary care use.

BACKGROUND

Onychomycosis, a chronic infection of the nails caused by dermatophytes, non-dermatophyte molds, or yeasts is very common, having an estimated population-based prevalence of 4.3% in Europe and North America.[1-3] As a result, onychomycosis is frequently presented in general practice.[1] If treatment is required, oral terbinafine is the first choice.[4] Despite being less effective than systemic treatment, local therapy could be an alternative for milder, superficial cases given the potential side effects of systemic treatment.[2,4]

The severity of onychomycosis is an important factor to account for when treatment is considered.[5] Being able to assess severity could aid in choosing the appropriate treatment since topical treatment is considered more appropriate for mild onychomycosis while more advanced stages of onychomycosis require oral treatment.[2,4] However, there is currently no standard method for grading the severity of onychomycosis in primary care, and choosing the right treatment can be challenging.[5] In addition, such an instrument could also be used to measure response to treatment or select patients that would benefit from early referral to specialist care, which would be of great value to primary care.

Carney et al. proposed a visual classification system for assessing onychomycosis severity: the Onychomycosis Severity Index (OSI).[6] This grading system consists of three subscores for different clinical features combined in a simple formula, resulting in a score from 0 to 35 points. The OSI was developed by a consensus group of dermatology experts on nail disease. An initial reliability assessment was performed by comparing the scores of multiple dermatologists on different pictures of onychomycotic nails. Since it was developed and tested in a different, secondary care setting, the OSI cannot be directly applied to primary care. Although used in multiple studies to evaluate treatment efficacy, it is currently unknown whether the OSI would be reliable in primary care; no research has been done on this topic as yet.[7]

Therefore, the aim of this study was to evaluate the usefulness of the OSI as an instrument to quantify onychomycosis severity in primary care by assessing inter- and intra-observer variability between different general practitioners (GPs).

METHODS

Design

The design of this study was a reliability assessment. Data used originated from the Onycho Trial (ICTRP NL8193, https://trialsearch.who.int/), evaluating the efficacy of topical treatment for mild to moderately severe onychomycosis in primary care. To assess the clinical severity of onychomycosis at baseline and follow-up visits at three and six months, standardized pictures of patients' toenails were scored independently by three different GPs, using the OSI for the index toenail, defined as the largest and most affected toenail. We examined if the OSI scores given by the different observers for the same picture were reliable by assessing both inter- (or between) observer and intra-observer (test-retest) variability, calculating the corresponding Intraclass Correlation Coefficients (ICC), using the appropriate settings for model, type, and definition.[8,9]

Participants

Participants were referred by their GP or recruited from the general public via social media. Potentially eligible patients were invited for face-to-face screening and intake. All patients signed informed consent and approval was given by the medical ethical committee (approval number NL68851.058.19).

Data

The primary data used for the reliability assessment consisted of standardized pictures taken as part of the Onycho Trial, at baseline, and during follow-up visits (Figure 1).

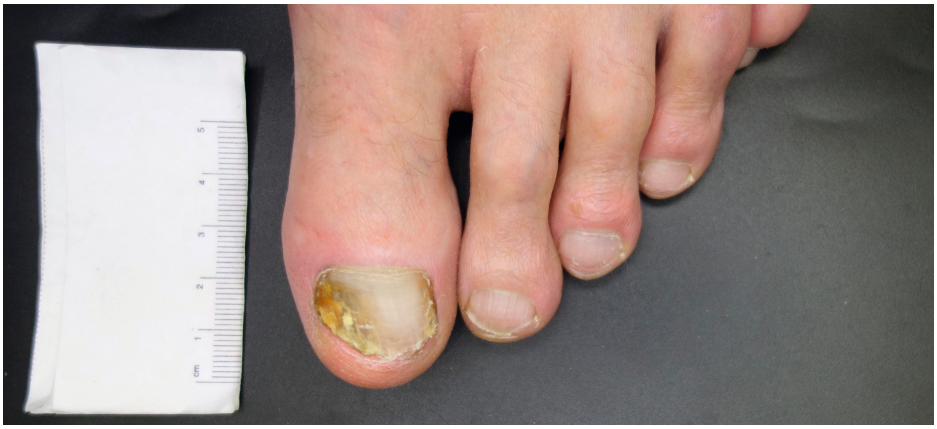

Figure 1 Example of standardized picture

To be able to calculate inter- or between-observer reliability, an OSI score provided by all three observers was required. To assess intra-observer i.e. test-retest reliability,

each observer provided an additional, second OSI score to a subset of pictures. Pictures with missing observations were considered incomplete and left out of the analyses.

Onychomycosis Severity Index

The OSI is composed of three subscores representing clinical features of nail involvement by onychomycosis. These clinical features are the proportion of the nail affected (in percentage groups from 0-5 points), the proximity from the distal tip of the nail to the matrix (in quartiles up to matrix involvement, 0-5 points), and thirdly the presence or absence of two signs of severe infection: subungual hyperkeratosis i.e. thickening of ≥ 2mm and/or subungual accumulation of fungal material i.e. dermatophytoma (0 or 10 points). The subscores are combined in a simple formula ([subscore 1 x subscore 2] + [subscore 3]) to calculate the final OSI score ranging from 0 to 35 points maximum.[6]

Observers

The observers consisted of two senior GPs (JE, TB) and one GP in training (RW). The instructions in the article of Carney et al. were used to apply the OSI score to the pictures presented. Given the double-blinded nature of the trial, the observers were unaware of treatment allocation and blinded for each other's clinical evaluation including OSI scores. Regarding the intra-observer or test-retest reliability assessment, observers were also blinded for their previous scores with a minimum of at least 2 weeks in between repeated observations.

Sample size calculation and statistical analysis

Based on the formulas proposed by Bujang et al., derived from Walter et al., a minimum sample size of 39 pictures was calculated to be required for the assessment of inter-observer reliability (*k* = 3 observers, power 0.80, alpha 0.05 and levels of agreement $R_0 = 0.5$ and $R_1 = 0.7$) [10,11]. For the analysis of intra-observer reliability, i.e. test-retest reliability (*k* = 2 observers, equal power, alpha, and levels of agreement) a sample size of 63 pictures was calculated to be required.[10,11]

Since the OSI score consists of numerical data, interclass correlation coefficients were used to assess inter- and intra-observer reliability (instead of the kappa statistic). Following the instructions by McGraw and Koo for calculating inter-observer reliability, the appropriate model, type, and definition were chosen to represent the correct aim and assumptions for the OSI [8,9]: A two-way random model was selected to be able to generalize results to GPs outside our group of observers; Single measures were chosen since average OSI scores are of less relevance in clinical practice; Finally, absolute agreement was considered the appropriate definition given our aim to compare exact OSI scores and not consistency between GPs. In addition, to evaluate for differences in reliability between the different subscores of the OSI, the corresponding ICCs were calculated for each subscore using the same settings. ICC values of < 0.5 were considered poor; values of 0.50 - 0.75, 0.75 - 0.90 and > 0.90 were considered

moderate, good, and excellent, respectively. In addition, 95% confidence interval (CI) values were calculated to improve the interpretation of results.[9]

For intra-observer or test-retest reliability assessment, a two-way mixed model was used since the OSI scores compared originated from the same observer; for type and definition, single-measures and absolute agreement were chosen, respectively, since two single OSI scores were compared.

For the sake of comparison, we calculated Cronbach's alpha being a frequently reported measure for inter-observer reliability and also reported by Carney et al. Values of > 0.7 indicate high consistency. However, in contrast to the settings for the ICC, as stated above, Cronbach's alpha is based on consistency and average measures. Given the intended clinical use of the OSI, the comparison of absolute, single OSI scores between different observers and their corresponding ICC values were considered the appropriate measures rather than Cronbach's alpha since the latter is based on consistency and mean scores.[12]

Analyses for calculating both Cronbach's alpha and selected ICCs were performed using SPSS (version 27.0.0.0).

RESULTS

Participants

A total of 193 patients were invited for face-to-face screening and intake of which 189 patients had complete observations required for this study. Table 1 describes their baseline characteristics.

All standardized pictures taken during screening and follow-up visits resulted in a total of 343 individual pictures (Figure 2). 280 pictures were scored by all three observers and thus used for inter-observer analysis; 80 pictures were scored twice by each observer and used for intra-observer analysis.

Table 1 Participant characteristics

	Total N = 189
Demographic Factors	
Mean age, years (SD)	52 (12.8)
- 0-25 years (%)	6 (3)
- 26-50 years (%)	72 (38)
- 51-75 years (%)	111 (59)
Male (%)	84 (44)

Table 1 Participant characteristics (continued)

	Total N = 189
Clinical Factors	
Percentage of the index toenail affected, %	
- 1-10 (%)	9 (5)
- 11-25 (%)	40 (21)
- 26-50 (%)	75 (40)
- 51-75 (%)	50 (26)
- 76-100 (%)	15 (8)
OSI-score	
- Mild (0-5) (%)	26 (14)
- Moderate (6-15) (%)	94 (50)
- Severe (16-35) (%)	69 (36)
Mean number of affected toenails (SD)	3.8 (1.9)
Time since onset >1 year (%)	126 (86)

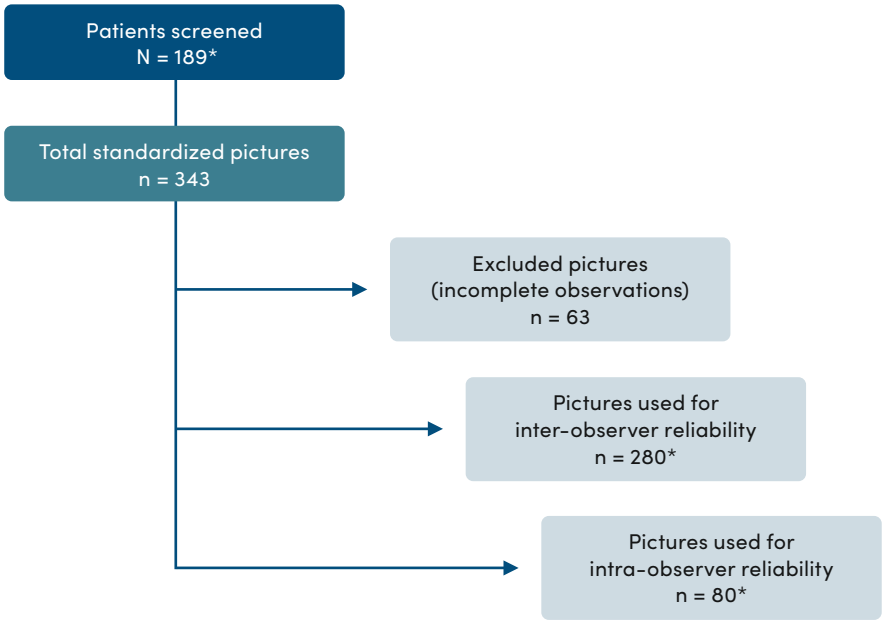

Figure 2 Flow-chart of data collection and pictures used for reliability assessment
N = number of patients, n = number of pictures, * = complete data/observations

OSI scores

Regarding the 280 pictures used for inter-observer analysis, the mean OSI for all three observers was 12.5 points. For each single observer, the means and standard deviations (SD) were 15.0 (8.7), 11.8 (7.8), and 10.6 (7.1) for observers A, B, and C respectively. The distribution of the scores given is shown in Figure 3.

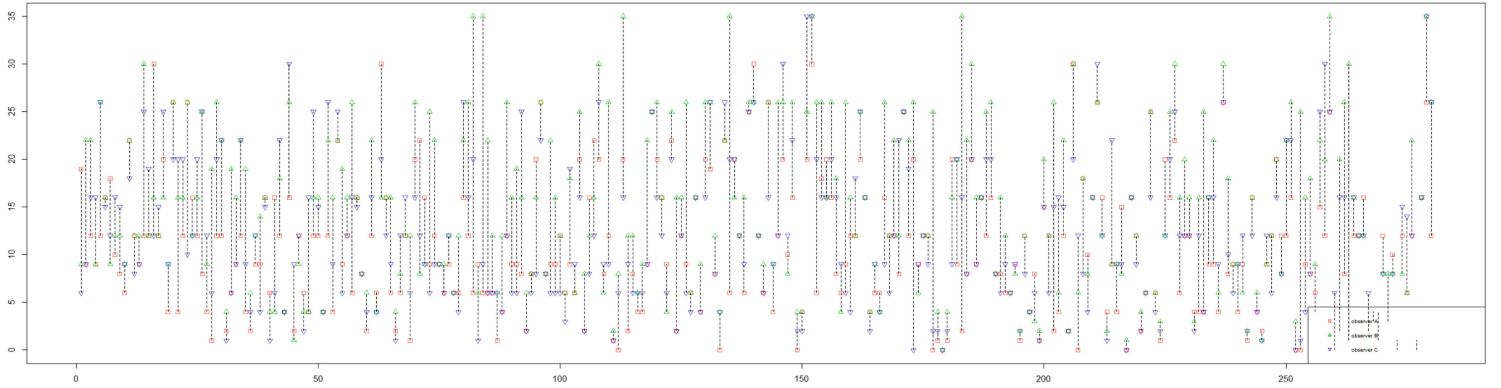

Figure 3 Onychomycosis severity index (OSI) scores given by each observer for inter-observer reliability assessment. 'Picture id' indicates the identification number; 'OSI score' indicates the OSI scores given by the individual observer (A, B, C) as indicated in the legend

Regarding test-retest scores, comparing the first and second observations for the 80 pictures used, the mean scores (SD) were 14.5 (7.1) and 13.9 (6.6) for observer A, 12.8 (7.1) and 11.3 (6.8) for observer B, and 10.9 (6.6) and 11.4 (6.5) for observer C, respectively.

Reliability assessment results

For the analysis of between or inter-observer reliability using observations of the 280 pictures, the ICC calculated was 0.578 with a 95% CI of 0.458 - 0.671 based on a two-way random model, absolute agreement, and single measures. In terms of consistency, Cronbach's alpha, which is based on a two-way mixed model, consistency, and mean scores, was 0.834 with a 95% CI of 0.797 - 0.865.

Comparing the reliability of each of the three subscores of the OSI, the ICC (95% CI) for the proportion of the nail affected was 0.651 (0.587 - 0.708); for the proximity from the distal tip of the nail to the matrix, the ICC (95% CI) was 0.591 (0.506 – 0.665), and for the third component, this was 0.303 (0.219 – 0.387).

Regarding intra-observer or test-retest reliability using the 80 pictures with repeat OSI scores, applying a two-way mixed model, absolute agreement, and single measures, the mean intra-observer ICC (95% CI) for all three observers combined was 0.650 (0.501 – 0.761). For the individual observers, the corresponding ICC values (95% CI) were 0.675 (0.536-0.779), 0.670 (0.523 - 0.777), and 0.606 (0.446 - 0.728) for observers A, B, and C, respectively.

DISCUSSION

Summary

The primary aim was to investigate the reliability of the OSI when used in primary care. We assessed both inter- and intra-observer reliability using standardized pictures of toenail onychomycosis from the Onycho Trial. Inter-observer reliability was poor to moderate indicating that different practitioners provide significantly different scores for the same patient. Regarding intra-observer or test-retest reliability, slightly better results were found indicating that repeated OSI scores, for example, to follow-up on disease progression or response to treatment, are more reliable compared with inter-observer values.

Regarding the subscores, the poor inter-observer reliability of the overall OSI was mostly due to poor agreement on the third aspect of the OSI score, i.e. for hyperkeratosis and dermatophytoma. This could be in part due to the fact pictures taken from one viewpoint were available, limiting the ability to determine the presence and amount of subungual thickening. In daily practice, using physical examination instead of pictures would arguably be easier, potentially improving reliability. However, the first two components only had moderate reliability scores as well. The reason for this could be

that we used different statistical ICC settings, aimed at measuring absolute agreement, being more demanding than other settings likely applied in previous studies. In doing so, consistent but structural differences strongly decrease ICC results illustrated by the relatively low ICC values found, in contrast to Cronbach's alpha of 0.834 which is comparable to previously reported values. We argue the ICC settings as applied, are appropriate given the intended use of the OSI which requires measuring inter-observer reliability in terms of absolute agreement.[9]

Comparison with previous studies

Our results are considerably lower than those reported by Carney et al. who found excellent reliability for the OSI applied by medical specialists with a Cronbach's alpha of 0.98 - 0.99 and ICC values of 0.93 – 0.95.[6] However, it was unclear which model was used for the calculation of the ICCs (two-way random, mixed, or one-way), if reliability was assessed in terms of consistency or absolute agreement, and if means or single measures were compared. Additionally, no confidence intervals were reported which are considered more important than the ICC values itself for the interpretation of results.[9] It is not unthinkable that values reported by Carney et al. were based on consistency and average scores, being more likely to take on higher values. We argue that the correct model, type, and definition need to be reported and should match the intended use of the instrument being evaluated.

Another difference might be the fact that the observers in the study of Carney et al. were all dermatologists and the application of the OSI was done after additional instruction and in consensus.

Strengths and limitations

The key point of this study was the fact that it was the first evaluation of OSI reliability after Carney, specifically for primary care settings. All patients were recruited from primary care and the general public and the observers were actively practicing GPs, making our results representative for many primary care settings. The instructions provided in the article by Carney et al. were thoroughly reviewed and discussed amongst the observers and subsequently used directly to guide our observers in applying the OSI.[6] Given the multitude of clinical problems presented in general practice, formal training of all GPs on OSI use would be practically unfeasible. Therefore, applying the OSI according to the instructions provided in the original article, was in our view the most representative of daily practice if an instrument to grade onychomycosis severity would be implemented.

Methodologically, we reported essential information on the chosen ICC settings frequently lacking in similar studies, making our results more transparent and easier to interpret. In addition, based on our sample size calculations, the number of pictures used to assess inter- and intra-observer reliability were both sufficient.

An important limitation of this study was that we used standardized pictures derived from the Onycho Trial that focused on mild to moderately severe onychomycosis, excluding the most advanced stages. Our results are therefore not generalizable to those patients having severely affected toenails. In addition, the OSI scores included in our assessment were closer together than if all types of severity would have been included. Since a smaller range of scores negatively affects ICC values, our results potentially underestimate true reliability.

CONCLUSION

Considering the intended use of the OSI to quantify onychomycosis severity in primary care and to aid in clinical decision-making, we currently would not recommend implementing this score in primary care in its current form, i.e. without further evaluation or adjustment.

A possible issue to address for future studies to increase reliability could be to design a simple training tool for general practitioners to improve the interpretation of the clinical features of the OSI and its implementation in primary care.

Another aspect to consider, also mentioned by Carney et al. and supported by our findings, is that the third clinical feature of the OSI i.e. the presence or absence of subungual hyperkeratosis or dermatophytoma is the most difficult to determine. Since this feature accounts for 10 of the maximum 35 points, we hypothesize that simplifying or adapting its evaluation could improve the reliability of the OSI for primary care use.

Considering the potential merits of having a validated tool for measuring onychomycosis severity in primary care, more studies would be required to evaluate the reliability of such an instrument in different primary care settings and populations.

LIST OF ABBREVIATIONS

CI Confidence Interval; GP general practitioner; ICC Intraclass Correlation Coefficient; ICTRP International Clinical Trials Registry Platform; OSI Onychomycosis Severity Index; SD standard deviation

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The authors thank all participants from the Onycho Trial, the departments' contributing research staff, and GPs who helped promote the Onycho Trial.

DECLARATIONS

Ethics approval and consent to participate: All patients signed informed consent and approval was given by the Medical Ethics Committee Leiden – The Hague - Delft (approval number NL68851.058.19).

Consent for publication: Written consent was given for Figure 1.

Availability of data and materials: The datasets used and analysed for this study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests

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Author's contributions: All authors read and approved the final manuscript. RW, TN, MB, and JE: conceptualization; RW, TN, JE: methodology and formal analysis; RW: investigation, writing – original draft; RW, TN, MB, KD, ME, and JE: writing – review and editing; TN and JE: supervision.

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Part II

Treatment of Onychomycosis in Dutch General Practice

Severe drug eruption from oral terbinafine for mild onychomycosis - a case report from family practice and literature review – "Just an innocent little pill?"

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ABSTRACT

Onychomycosis is the most prevalent nail disease and is frequently encountered in clinical practice. Despite having multiple therapeutic options, of which systemic antifungals are the most effective, treatment is not always mandatory in all patients. Especially when considering systemic treatment, the risk of adverse reactions may outweigh the potential benefits of treatment. In this case report, we present a clinical case of a 49-year-old male patient with a blank past medical history who experienced a severe drug eruption from terbinafine prescribed for mild onychomycosis that required discontinuation of terbinafine, additional evaluation, and treatment of this adverse reaction.

INTRODUCTION

Onychomycosis, a fungal infection of the nail caused by dermatophytes, yeasts, and non-dermatophyte molds, is the most common nail disease with an estimated prevalence of 4.3% in North America and Europe and a worldwide estimated prevalence of 5.5%, respectively.[1,2] However, the prevalence of onychomycosis can increase markedly with advancing age, with underlying conditions such as diabetes, or in different continents and climates.[3-6] Although frequently having an indolent course, onychomycosis is considered not to resolve spontaneously.[7-10] Onychomycosis severity can range from mild, affecting only a limited portion of the nail, to severe, involving the majority of the nail plate, the nail matrix and/or causing substantial subungual hyperkeratosis and dermatophytomas.[11] Regardless of severity, many patients find the associated changes disfiguring and bothersome, and in a considerable number of patients onychomycosis can affect the quality of life.[12-15] In contrast, onychomycosis remains asymptomatic in many patients, often unaware of having onychomycosis in the first place.[2,3,6,16,17]

Not only those suffering from evident symptoms or complications but also those with predominantly cosmetic concerns will consult their physician. Requests for treatment are not seldomly driven by commercial campaigns that draw attention to onychomycosis and frame it as ugly, unhygienic, and a disease that requires treatment.[18] However, according to current guidelines, treatment is not always mandatory.[19,20] Physicians may suffice by providing the necessary information, and, if applicable, reassurance. Satisfactory for some, other patients may persist in their request. If treatment is indicated, oral terbinafine for a minimum of 3 months is recommended.[19-22] In terms of cure rates, terbinafine achieves 70% mycological, and 38% complete cure, the latter consisting of both clinical and mycological cure.[23] Despite being the most effective option, a 38% chance of complete cure could arguably be regarded as modest; at the end of the day, patients will primarily be interested in normal-looking nails after completing their treatment. Even after successful treatment with terbinafine, a recurrence rate of 33% after an average of 36 months, is significant.[21,24] Moreover, terbinafine can have potentially serious side effects such as severe skin reactions, and cases of liver failure have been described.[25-27]

In this case report, we present a case of a patient who developed a serious adverse reaction to terbinafine, illustrating an important potential harm of oral antifungal treatment prescribed for onychomycosis. Written informed consent was received on July 30th, 2023.

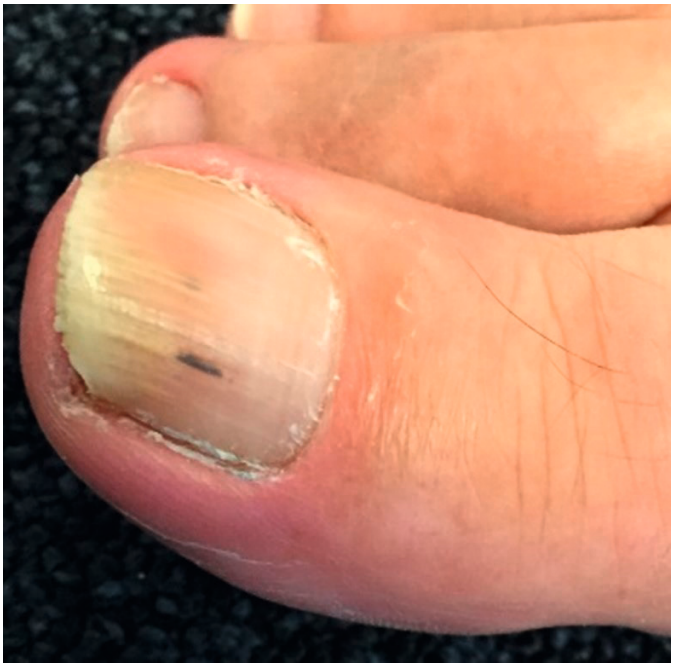

Figure 1 The nail as presented before starting terbinafine

CASE DESCRIPTION

A 49-year-old male patient with a blank medical history visited our practice because of a discolored greater toenail. Normally rarely attending the clinic, he was embarrassed about his abnormal-looking nail. Having tried multiple home remedies, he decided to make an appointment. He explained that at first only the greater toenail was affected. Now it seemed to be spreading to adjacent nails which disconcerted him. After reading information on the internet, he opted for oral terbinafine. There were no mechanical issues, pain, or concomitant infections present. On examination, his toenail was moderately affected (Figure 1). Given the patient's preference, and after explaining the expected results and potential side effects, the attending physician provided the requested prescription.

Eleven days later, he returned to the clinic with a red, non-itching macular rash on his chest and axillary region (Figure 2). Suspecting a mild allergic reaction, fexofenadine 180 mg o.d. was prescribed and terbinafine was discontinued. Four days later, fexofenadine not having improved his symptoms, he returned to the practice again. His upper body had turned 'completely red' (Figure 3). On examination, a confluencing erythematosquamous rash was seen, suggestive of exfoliative dermatitis.[28] A severe

allergic reaction to terbinafine was suspected and after consulting a dermatologist, prednisolone 30 mg o.d. was started and the patient was referred to the dermatologist.

On examination, we observed an erythrodermic patient with a diffuse erythematosquamous rash with collarette-shaped desquamations, extending from the neck over the entire torso, to the arms and thighs. The lower legs and hands were showing smaller erythematosquamous papules. No bullae or vesicles were present. The oral mucosa and eyes were not affected, and his temperature was normal. To exclude a drug rash with eosinophilia and systemic symptoms (DRESS syndrome), a blood test was performed, showing an elevated ESR (25 mm/h), leukocytosis (27.8*109/L), but no eosinophilia or other blood count abnormalities, nor any abnormal liver or kidney function tests. Thus, the dermatologist's conclusion was a severe drug eruption from oral terbinafine in the form of exfoliative dermatitis, confirming our suspected diagnosis. The consulting dermatologist decided not to perform a skin biopsy due to the highly suggestive history and findings on physical examination. Prednisolone was continued, and topical treatments in the form of betamethasone, Calmurid, and vaseline paraffin ointment, were added. Three weeks later, returning to our practice for follow-up, the rash was fully resolved and the skin had returned to normal.

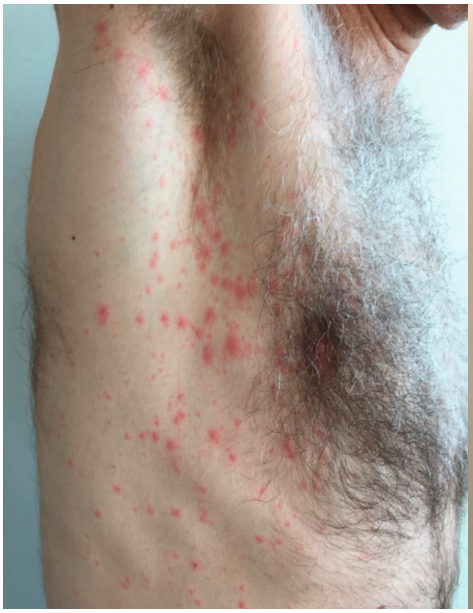

Figure 2 The skin reaction after 11 days

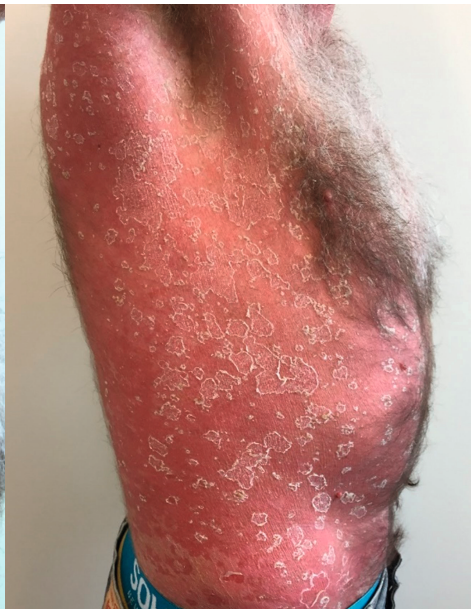

Figure 3 The skin reaction after 15 days

DISCUSSION

Case evaluation

This case represents an example of a severe drug reaction to terbinafine, a relatively rare but well-known adverse event.[29] Although our patient was very much bothered by the cosmetic changes caused by the fungal infection, the onychomycosis was mild and without additional consequences or complications that otherwise would have warranted treatment. Oral terbinafine provided an opportunity to rid this patient of his onychomycosis but also exposed him to potential adverse reactions, as illustrated.

Review of the literature

As for most antifungals, the primary mechanism of action of terbinafine is the inhibition of fungal membrane production and ergosterol synthesis.[30,31] Terbinafine belongs to the group of allylamines and works as a non-competitive inhibitor of the enzyme squalene epoxidase, preventing the conversion of squalene to squalene-epoxide.[8] The most common adverse reactions associated are headaches, gastrointestinal symptoms, and rashes.[31] Less common adverse reactions include visual disturbances, dysgeusia, and transient transaminitis.[31] Regarding the skin, rashes not otherwise specified (6%), pruritus (3%), and urticaria (1%) are most frequently reported.[32] Specific cutaneous conditions linked to terbinafine use include fixed drug eruption, erythema multiforme, erythema annulare centrifugum-like eruption, sub-acute lupus erythematosus, flare-ups of psoriasis, psoriasis de novo, and more severe reactions such as exfoliative dermatitis, acute generalized exanthematous pustulosis, and toxic epidermal necrolysis.[32-34] There are no specific incidence rates available for specific skin reactions, including exfoliative dermatitis in our case.[32] Although most adverse reactions to terbinafine are mild and do not warrant discontinuation, some are more severe, and even cases of fulminant liver failure requiring liver transplantation have been reported.[35] However, as for adverse skin reactions, incidence rates for specific hepatic reactions are lacking and only rough estimates are mentioned, for example, "0.01%" or "less than 1 in 1000".[8,32,36,37] Regarding alternative treatments for onychomycosis as opposed to oral terbinafine, other systemic antifungals or topical treatments might have been considered. However, alternative systemic antifungal treatments pose similar risk to adverse reactions, and topical treatments, although carrying a much lower risk of serious adverse reactions, are unfortunately significantly less effective than systemic antifungal treatment.[21,38] Our case was an example of a rare but severe cutaneous adverse reaction to terbinafine in the form of exfoliative dermatitis that warranted the discontinuation of terbinafine and the addition of systemic corticosteroid treatment.

CONCLUSION

Patients visiting their family physician often wish to receive a form of treatment, hoping this will resolve their problem. However, many problems presented do not require pharmacological treatment. Some issues can't be solved at all, some are self-limiting in nature and only require symptomatic treatment, and some problems do not warrant treatment despite having multiple treatment options. A mild case of onychomycosis, without an increased risk of complications, is a good example of the latter, since treatment is not always warranted in such cases. Physicians, however, may be tempted to prescribe treatment to comply with the expectations of the patient, rather than making a choice primarily based on medical necessity or urgency. As for any treatment, physicians should weigh the severity, burden, and expected outcome of a disease, against the potential harms of the treatment considered. Oral antifungal treatment for onychomycosis not only cures less than half of patients treated, with onychomycosis recurring in one-third of patients, but also has the potential of causing serious adverse reactions as illustrated. The principle of "primum non nocere" incorporated in the Hippocratic oath and roughly translated to "abstain from all intentional wrong-doing and harm", still holds. When confronted with medical challenges and having to choose between treatment with an uncertain outcome or watchful waiting, the latter is often the better choice.

ACKNOWLEDGMENTS

We would like to thank the patient who so kindly consented to the publication of his case report.

DECLARATIONS

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Conflict of interests: The authors declare that there are no conflicts of interest.

Author contribution statement: R.W. and J.E. were responsible for the conceptualization, J.E., K.Q., T.B. and M.N. provided the resources and data, R.W. was responsible for writing the original draft, J.E. and T.B. provided supervision, and J.E., K.Q., M.N and T.B. were all involved in the reviewing and editing process.

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How effective is topical miconazole or amorolfine for mild to moderately severe onychomycosis in primary care: the Onycho Trial – a randomised double-blind placebo-controlled trial

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ABSTRACT

Objectives: To evaluate the efficacy of topical miconazole or amorolfine compared to placebo for mild to moderately severe onychomycosis.

Design: Randomized, double-blind, placebo-controlled trial, with computer-generated treatment allocation at a 1:1:1 ratio.

Setting: Primary care, recruitment from February 2020 to August 2022.

Participants: 193 patients with suspected mild to moderately severe onychomycosis were recruited via general practices and from the general public, 111 of whom met study criteria. The mean age of participants was 51 (SD 13.1), 51% were female and onychomycosis was moderately severe (mean OSI 12.1 [SD 8.0]).

Interventions: Once-daily miconazole 20mg/g or once-weekly amorolfine 5% nail lacquer solution was compared with placebo (denatonium benzoate solution).

Main outcome measures: Complete, clinical and mycological cure at six months. Secondary outcomes were clinical improvement, symptom burden, quality of life, adverse effects, compliance, patient-perceived improvement and treatment acceptability.

Results: Based on intention-to-treat analysis, none of the participants receiving miconazole or amorolfine reached complete cure compared with two in the placebo group (OR not estimable [n.e.], p = 0.493, and OR n.e., p = 0.240, respectively). There was no evidence of a significant difference between groups regarding clinical cure (OR n.e., p = 0.493, and OR 0.47, 95% CI 0.04 to 5.45, p = 0.615), while miconazole and amorolfine were less effective than placebo at reaching both mycological cure (OR 0.25, 95% CI 0.06 to 0.98, p = 0.037, and OR 0.23, 95% CI 0.06 to 0.92, p = 0.029, respectively) and clinical improvement (OR 0.26, 95% CI 0.08 to 0.91, p = 0.028 and OR 0.25, 95% CI 0.07 to 0.85, p = 0.021, respectively). There was no evidence of a significant difference in disease burden, quality of life, adverse reactions, compliance, patient-perceived improvement or treatment acceptability.

Conclusions: Topical miconazole and amorolfine were not effective in achieving complete, clinical, or mycological cure of mild to moderately severe onychomycosis, nor did they significantly alleviate severity or symptom burden. These treatments should therefore not be advised as monotherapy to treat onychomycosis.

Trial registration: WHO ICTRP NL8193 (https://trialsearch.who.int/)

INTRODUCTION

Onychomycosis is the most common cause of abnormal toenails, accounting for over half of all nail-related diseases.[1,2] Toenail onychomycosis is primarily caused by dermatophytes, most frequently *Trichophyton rubrum*, and to a lesser extent by yeasts or non-dermatophyte molds.[3-5] With an estimated prevalence of 4.3% in the general population, increasing to over 20% in patients aged ≥60, toenail onychomycosis is common in Europe and North America and often seen in general practice.[1,6-8] Clinical signs and symptoms may vary significantly, with some patients unaware of their onychomycosis, while others suffer from progressive thickening, discoloration, separation from the nail bed, or even nail plate destruction.[3,7,9,10] Onychomycosis can also cause pain and decrease quality of life, especially in the severely affected,[11,12] as well as complications such as recurring fungal and bacterial skin infections.[13,14]

In patients experiencing few or no symptoms, treatment might not be strictly warranted.[7,12,15] For patients requiring treatment, oral terbinafine is the recommended and most effective treatment option.[12,15,16] However, oral treatment can have serious adverse effects such as severe cutaneous reactions, or cause hepatotoxicity ranging from mild transaminitis to fulminant liver failure.[17-20] Hence, oral treatment is disadvised for patients with liver disease, hypersensitivity or at risk of drug-drug interactions. Topical treatment would be a welcome alternative, not only for those with contraindications for systemic treatment but also in general, given its low risk profile.[21] Previous studies investigating the efficacy of topical antifungals were carried out in outpatient settings in specialized clinics not necessarily representative of primary care.[21] Furthermore, studies have shown that severe cases, e.g. involving the matrix, do not respond well to topical treatment.[16,21,22] Based on previous results and general availability, miconazole and amorolfine are potentially suitable for treating mild to moderately severe onychomycosis in primary care.[22-27] Although effective at treating dermatomycosis, miconazole is not well-studied in the treatment of onychomycosis, and the evidence available on the efficacy of amorolfine is of low-quality.[21-27]

Our aim was to investigate the efficacy of these commonly-used topical antifungals in the primary care treatment of mild to moderately severe onychomycosis. In this randomized, double-blind placebo-controlled trial, we compared topical miconazole or topical amorolfine with placebo.

METHODS

Trial design

The Onycho Trial was a double-blind, placebo-controlled trial designed to investigate the efficacy of topical antifungal treatment in Dutch general practice (ICTRP NL8193 https://trialsearch.who.int/). The study consisted of three parallel arms: two topical

antifungals, miconazole and amorolfine, and a placebo group, with randomization at the individual patient level and an allocation ratio of 1:1:1.
The study was approved by the designated medical ethics committee of Leiden-Den Haag-Delft (METC-LDD) on August 26th, 2019 (NL68851.058.19), conducted and coordinated by RW, under the supervision of TB and JE, at the department of Primary Care and Public Health (PHEG) of the Leiden University Medical Center (LUMC). This trial was reported in accordance with the CONSORT statement and guidelines.[28,29]

Participants and setting

The Onycho Trial focused on primary care patients with mild to moderately severe onychomycosis, defined as 10-75% involvement of the index toenail without matrix involvement or spikes. The index toenail was defined as the largest, most affected toenail. Initially, the minimum involvement was set at 25% for ease of interpretation. One month into the trial, and after including six participants, this was lowered to 10% to increase the inclusion of milder cases and to accommodate the Onychomycosis Severity Index (OSI) as a measure of severity as approved by the ethics committee.[30]
Additional criteria included age 18 to 70, no more than three affected toenails per foot, no oral antifungal treatment within six months prior to enrolment, and no clinically apparent tinea pedis. Patients using contraindicated medication (metformin, phenytoin, and coumarins) were excluded, as well as patients with contraindicated conditions (pregnant or lactating women), or conditions potentially affecting nail growth (stage III-IV peripheral arterial occlusive disease, or cancers treated with immuno- or chemotherapy). There were no patients receiving topical antifungal treatment at the time of enrolment.
Patients suspected of having onychomycosis were referred by participating GPs or recruited from the general public through social media, with pre-screening via email or telephone. Eligible patients were invited for face-to-face screening at the department or the participant's home. Screening and follow-up visits at 3 and 6 months after the start of treatment were performed by the department's research staff under supervision of observers RW (GP in training), TB and JE (practicing GPs). At each visit, protocolized clinical evaluations were performed, including the administration of validated questionnaires. Using a small portable photobooth, standardized photographs were taken and independently evaluated by the observers for patient selection and response to treatment. Finally, fungal infection of the nail sample collected during screening was confirmed by the LUMC's departments of Dermatology and Medical Microbiology, using a standardized work-up of potassium hydroxide preparation, polymerase chain-reaction and culture. This was repeated at the final visit after 6 months of treatment.

All patients signed informed consent at the screening visit. All clinical data were recorded using Castor's Electronic Data Capture (EDC) System® (Castor).

Patient and public involvement

There was no formal patient or public involvement in the design of this study.

Interventions

Topical treatment of affected toenails consisted of once-daily application of miconazole 20mg/g (Daktarin®), or once-weekly amorolfine hydrochloride 5% (Loceryl®) nail lacquer according to regular user instructions for a period of 6 months. Placebo consisted of daily application of denatonium benzoate solution (Byte-X®, used to prevent nail biting) chosen for its resemblance in look, smell and consistency to the other antifungal lacquers. A thorough literature search was performed which yielded no studies suggesting antifungal properties of denatonium benzoate.[31-35]

All medications were prepared, packaged and distributed by the LUMC's trial pharmacy. Trial medication consisted of two vials, one for Monday to Saturday, and another for Sunday, identical for all participants regardless of treatment allocation. For participants in the miconazole group, both vials contained miconazole. For the amorolfine group, the Monday to Saturday vial contained denatonium benzoate solution, while the Sunday vial contained amorolfine. For the placebo group both vials contained denatonium benzoate solution. All participants received identical written instructions that included once daily application of one layer of nail lacquer solution after cleaning the nail with acetone provided. For Sundays, participants were additionally instructed to file the nail surface before applying treatment, all according to user instructions.

Outcomes

Our primary outcome measure was the proportion of patients achieving complete cure, consisting of both clinical and mycological cure of the index toenail at 6 months. Secondary outcome measures were clinical improvement (defined as either ≤10% involvement of the index toenail or as ≥40% reduction), symptom burden as expressed by the ONYCHO questionnaire score,[15] quality of life based on the Short Form-12 survey,[36,37] adverse effects, therapy compliance, patient-perceived improvement, and treatment acceptability. Adverse effects included local reactions, as well as serious adverse events and suspected unexpected serious adverse reactions. Therapy compliance was defined as having missed no more than two weeks of treatment i.e. <10% of the treatment period. In addition, the effects of treatment on OSI score (range 0-35) and percentage of affected area of the index toenail were measured over time.

Sample size

Based on previous studies, the expected difference in complete cure between antifungal treatment and placebo was set at 40%.[21,22] With a power of 90% and an alpha of 2.5%, applying the Bonferroni correction given the trial's three study arms, the required sample size was 29 patients per group to demonstrate a significant difference (p-value < 0.05). With an anticipated loss-to-follow-up of 20%, we calculated that 36

patients would be required for each group, resulting in a minimum inclusion of 108 patients. No interim analyses were performed.

Randomization

Treatment allocation of included participants was computer-generated in Castor, using non-stratified variable block randomization with block sizes of 6, 9, and 12, and an allocation ratio of 1:1:1 to ensure equally sized groups. The allocation sequence was concealed for observers and research staff involved in screening, enrolment and follow-up. This was not the case for the data manager and pharmacy staff who required access to this information and were not involved in screening, follow-up, analyses of results, or study tasks involving direct contact with participants. After confirmation of successful inclusion, the allocation sequence was initiated by the data manager in Castor and automatically sent to the responsible pharmacy staff.

Blinding

All participants, data collection staff and observers responsible for patient selection and outcome assessment (RMW, TNB, and JAHE) were blinded for treatment allocation and outcome measurements recorded by the other observers. Regardless of treatment allocation, all dispensed trial medications were distributed in identical vials, including identical user instructions to ensure concealment of allocation.

Statistical methods

Descriptive statistics were used to evaluate baseline characteristics, presenting results per treatment group in absolute numbers with corresponding percentages, or as means and standard deviations (SD). To test for statistical differences between the groups, Pearson's χ^2 test or one-way analysis of variance (ANOVA) were used for categorical or numerical data, respectively, with significance defined as a $p<0.05$.

To evaluate treatment effect after 6 months, primary comparisons were miconazole with placebo and amorolfine with placebo. In addition, both antifungals combined were compared with placebo and miconazole was compared with amorolfine. The primary outcome of complete cure, together with underlying clinical and mycological cure as binary outcomes, were evaluated using Pearson's χ^2 or Fisher's exact test, the latter used if ≥1 cells had an expected count <5.

As binary measures, secondary outcomes for clinical improvement (≤10% or ≥40% reduction of affected area), adverse effects, therapy compliance, patient-perceived improvement and treatment acceptability, were also evaluated using χ^2 or Fisher's exact tests. To evaluate the effect of treatment on symptom burden and quality of life, as numerical values based on corresponding questionnaire scores, one-way ANOVA applying Tukey-Kramer's post-hoc test was used to compare mean differences between the groups. The corresponding effect sizes are reported as odds ratios (OR)

with 95% confidence intervals (95% CI) and p-values for the binary outcomes, or as mean differences with p-values for the numerical outcomes, respectively.

In addition, repeated measures ANOVA was used to evaluate the effect of treatment on clinical severity as expressed by the percentages of index toenail affected and OSI scores over time.

For the purpose of intention-to-treat analysis, the last-observation-carried-forward method was applied for both primary and secondary outcome measures, replacing missing numerical values for those of the last observation; for binary outcomes, missing values were replaced by their negative option, that is, not having reached the outcome of interest.

Finally, a per-protocol analysis was done to evaluate treatment effect in compliant patients defined as those that had missed no more than 2 weeks of treatment, as well as a subgroup analysis to evaluate the influence of the affected area of the index toenail at baseline on primary outcome and clinical improvement.

P-values of <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (Version 28).

RESULTS

Participant recruitment

Participants were recruited from February 2020 to August 2022, when the required number of participants was reached. The date of first enrolment was 10 February 2020. Between March and November 2020 recruitment was suspended due to the Covid-19 pandemic. The first subsequent screening visit was 9 December 2020. The last follow-up visit took place on 17 March 2023.

Participant flow

Figure 1 illustrates participant flow. Of 953 respondents, 760 were non-eligible, consisting of 735 who did not meet or were unable to verify criteria, while 25 declined, were unwilling or unable to participate (e.g. for practical reasons). The remaining 193 respondents were eligible and invited for screening and intake.

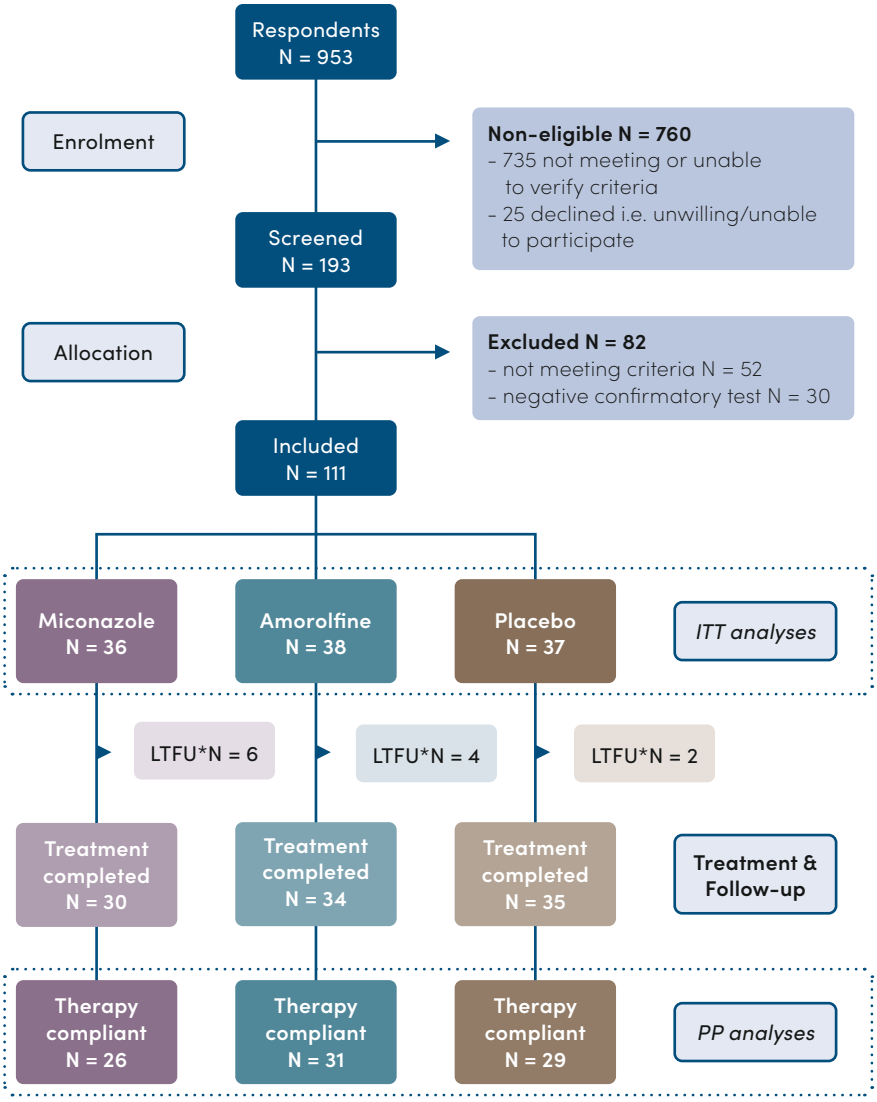

Figure 1 Participant flow
* LTFU = lost to follow-up, ITT = intention-to-treat, PP = per protocol

82 patients were subsequently excluded through screening: 52 of whom did not meet criteria due to extensive involvement *(n = 36)*, less than 10% involvement *(n = 15)*, or use of contraindicated medication *(n=1)*; for the remaining 30 patients, fungal infection could not be confirmed.

Of the 111 patients included and randomized to one of the treatment arms, 99 (89.2%) completed the full treatment period, of whom 86 (77.5%) were also compliant. 12

patients (10.8%) were lost to follow-up: 6 in the miconazole group (due to no effect (n=3), discoloration (n=1), no given reason (n=1), and one never started); 4 in the amorolfine group (due to no effect (n=2), moving (n=1), and pregnancy (n=1)); as well as 2 patients in the placebo group (due to no effect (n=1), and unspecified private circumstances (n=1)).

Baseline data

Table 1 shows the baseline characteristics per treatment group. The overall study population had a mean age at baseline of 51 years (SD 13.1), a slight female predominance (51.4%), and showed moderately severe onychomycosis (mean affliction 41% [SD 15.5], mean OSI 13.0 [SD 5.5]) primarily caused by dermatophyte infection (93.7%). Specific organisms identified are presented in Table S1 in the supplementary data. Most participants reported a moderate symptom burden, with an average ONYCHO questionnaire score of 58.9 (SD 13.8). Regarding risk factors and relevant history, tinea pedis was most commonly reported (56.8%), and a majority had previously treated their nail infection (82.9%), including use of topical antifungals. A minority had previously received oral treatment (10.8%). No statistically significant differences were found between groups at baseline.

Table 1 Participant characteristics at baseline

	Miconazole (N = 36)	Amorolfine (N = 38)	Placebo (N = 37)	p value*
Demographic Factors				
Mean age, years (SD)	53.0 (13.0)	48.1 (13.7)	52.9 (12.1)	0.181
Female, N (%)	18 (50.0)	18 (47.4)	21 (56.8)	0.705
Fitzpatrick skin type 1-3, N (%)	35 (97.2)	37 (97.4)	36 (97.3)	0.999
Clinical Factors				
Affected area of index toenail, mean % (SD)	36.7 (15.9)	44.5 (16.0)	40.5 (14.0)	0.095
Affected area, per category, N (%)				0.220
11-25%	11 (30.6)	6 (15.8)	7 (18.9)	-
26-50%	17 (47.2)	17 (44.7)	22 (59.5)	-
51-75%	8 (22.2)	15 (39.5)	8 (21.6)	-
OSI score, mean (SD)	12.9 (5.6)	13.9 (5.6)	12.0 (5.2)	0.320
OSI category, N (%)				0.466
Mild (0-5)	3 (8.3)	3 (7.9)	5 (13.5)	-
Moderate (6-15)	23 (63.9)	19 (50.0)	23 (62.2)	-
Severe (16-35)	10 (27.8)	16 (42.1)	9 (24.3)	-
Number of affected toenails, mean (SD)	3.6 (1.8)	3.6 (1.6)	3.4 (1.5)	0.782
Time since onset >1 year, N (%)	29 (80.6)	34 (89.5)	33 (89.2)	0.448
ONYCHO-questionnaire score, mean (SD)	60.9 (13.2)	56.7 (14.6)	59.1 (13.7)	0.426

Table 1 Participant characteristics at baseline (continued)

	Miconazole (N = 36)	Amorolfine (N = 38)	Placebo (N = 37)	p value*
ONYCHO-questionnaire category, N (%)				0.761
Good (67-100)	13 (36.1)	10 (26.3)	10 (27.0)	-
Moderate (34-66)	21 (58.3)	24 (63.2)	25 (67.6)	-
Poor (0-33)	2 (5.6)	4 (10.5)	2 (5.4)	-
SF-12 questionnaire score, mean (SD)				
PCS-12 score	52.0 (4.8)	50.8 (5.9)	51.6 (5.3)	0.585
MCS-12 score	43.7 (2.7)	43.1 (3.3)	42.5 (4.2)	0.346
Mycology				0.454
Dermatophyte, N (%)	34 (94.4)	37 (97.4)	33 (89.2)	-
Non-dermatophyte, N (%)	1 (2.8)	1 (2.6)	1 (2.7)	-
Yeast, N (%)	1 (2.8)	0 (0.0)	3 (8.1)	-
Risk Factors				
History tinea pedis, N (%)	17 (47.2)	26 (68.4)	20 (54.1)	0.169
Family members with onychomycosis, N (%)	8 (22.2)	9 (23.7)	11 (29.7)	0.734
Presence of dermatological disease, N (%)	10 (27.8)	11 (28.9)	9 (24.3)	0.897
Previous oral antifungal treatment, N (%)	4 (11.1)	5 (13.2)	3 (8.1)	0.778
Any previous (topical) treatment, N (%)	27 (75.0)	33 (86.8)	32 (86.5)	0.311
Current immunosuppressive use, N (%)	1 (2.8)	0 (0.0)	2 (5.4)	0.353
Frequent public pool or spa visit (≥5x/yr), N (%)	8 (22.2)	18 (47.4)	11 (29.7)	0.061
Consistent flip-flop use at pool/spa visit, N (%)	7 (19.4)	12 (31.6)	5 (13.5)	0.153
Smoking or history of smoking, N (%)	17 (47.2)	11 (28.9)	18 (48.6)	0.155

N = number of patients, SD = standard deviation, PCS-12 = physical health component of SF-12 questionnaire, MCS-12 = Mental health component of SF-12 questionnaire, * p-values are based on Pearson's Chi-square test for categorical data or one-way ANOVA for numerical data

Numbers analysed

All randomized patients (N=111) were included in the intention-to-treat analyses of primary and secondary outcome measures. For the per protocol analysis, only compliant cases were selected (N=86).

Primary and secondary outcomes

Table 2 summarises results for each treatment group at 6 months. No patient in the miconazole and amorolfine group reached complete cure, compared with two in the placebo group. In the amorolfine group one patient reached clinical cure, compared with two in the placebo group. In each antifungal group, 3 patients reached mycological cure, compared with 10 in the placebo group.

Table 2 Summary results after 6 months treatment, per treatment group

	Miconazole (N = 36)	Amorolfine (N = 38)	Placebo (N = 37)
Primary outcome (N, %)			
Complete cure rate	0 (0.0)	0 (0.0)	2 (5.4)
Clinical cure	0 (0.0)	1 (2.6)	2 (5.4)
Mycological cure	3 (8.3)	3 (7.9)	10 (27.0)
Secondary outcomes (N, %)			
Clinical improvement (≤10% affected)	4 (11.1)	4 (10.5)	12 (32.4)
Clinical improvement (≥40% reduction)	0 (0.0)	1 (2.6)	3 (8.1)
Affected area (index toenail), % (SD)	39.9 (26.0)	43.6 (23.9)	28.6 (25.3)
Affected area, per category, N (%)			
0%	0 (0.0)	1 (2.6)	2 (5.4)
1-10%	5 (13.9)	3 (7.9)	10 (27.0)
11-25%	10 (27.8)	6 (15.8)	9 (24.3)
26-50%	11 (30.6)	14 (36.8)	8 (21.6)
51-75%	5 (13.9)	10 (26.3)	5 (13.5)
76-100%	5 (13.9)	4 (10.5)	3 (8.1)
OSI score, mean (SD)	13.7 (7.3)	13.4 (6.1)	9.4 (8.8)
OSI score, per category, N (%)			
Absent (0)	0 (0.0)	2 (5.3)	3 (8.1)
Mild (1-5)	6 (16.7)	2 (5.3)	14 (37.8)
Moderate (6-15)	14 (38.9)	19 (50.0)	10 (27.0)
Severe (16-35)	16 (44.4)	15 (39.5)	10 (27.0)
Number of affected toenails, mean (SD)	3.2 (2.1)	3.1 (1.8)	2.9 (2.0)
ONYCHO-questionnaire score, mean (SD)	57.5 (14.2)	57.4 (16.9)	63.1 (11.3)
ONYCHO score, per category, N (%)			
Good (67-100)	12 (33.3)	13 (34.2)	19 (51.4)
Moderate (34-66)	22 (61.1)	20 (52.6)	17 (45.9)
Poor (0-33)	2 (5.6)	5 (13.2)	1 (2.7)
SF-12 questionnaire score, mean (SD)			
PCS-12 score	52.3 (4.5)	51.2 (4.7)	51.5 (5.0)
MCS-12 score	42.6 (4.9)	42.8 (3.1)	41.6 (4.1)
Adverse effects, N (%)	7 (19.4)	7 (18.4)	8 (21.6)
Compliance (≤14 days missed), N (%)	26 (72.2)	31 (81.6)	29 (78.4)
Perceived improvement, N (%)	12 (33.3)	18 (47.4)	17 (45.9)
Treatment acceptability, N (%)	29 (80.6)	30 (78.9)	28 (75.7)

Legend: N = number of patients, SD = standard deviation, OSI = Onychomycosis Severity Index, PCS-12 = physical health component of SF-12 questionnaire, MCS-12 = mental health component of SF-12 questionnaire

Tables 3 and 4 show the comparison of primary and secondary outcomes for miconazole versus placebo, and for amorolfine versus placebo, respectively. No OR could be calculated for comparisons with zero counts, indicated as 'not estimable'.
As regards complete or clinical cure, there were no statistically significant differences between antifungals and placebo while miconazole and amorolfine were significantly less effective at reaching mycological cure compared with placebo (OR 0.25, 95% CI 0.06 to 0.98, p=0.037, and OR 0.23, 95% CI 0.06 to 0.92, p=0.029, respectively).

Regarding secondary outcomes, the placebo group showed superior clinical improvement, defined as ≤10% involvement after treatment, compared with either miconazole or amorolfine (OR 0.26, 95% CI 0.08 to 0.91, p=0.028, and OR 0.25, 95% CI 0.07 to 0.85, p=0.021, respectively). No statistically significant differences were found for the remaining secondary outcome measures.

The comparison of both antifungals combined versus placebo showed similar results, as presented in supplemental table S2. The results for the comparison of miconazole and amorolfine are presented in supplemental table S3, showing no significant differences between both treatments.

Table 3 Effect size differences at 6 months between **miconazole** and **placebo**

	Miconazole (N = 36)	**Placebo (N = 37)**	**Effect size**	
	N (%)	**N (%)**	**OR (95% CI)**	**p value ***
Primary outcome				
Complete cure	0 (0.0)	2 (5.4)	n.e.	0.493
Clinical cure	0 (0.0)	2 (5.4)	n.e.	0.493
Mycological cure	3 (8.3)	10 (27.0)	**0.245 (0.061-0.982)**	**0.037**
Secondary outcomes				
≤10% affected	4 (11.1)	12 (32.4)	**0.260 (0.075-0.906)**	**0.028**
Reduction ≥40%	0 (0.0)	3 (8.1)	n.e.	0.240
Adverse effects	7 (19.4)	8 (21.6)	0.875 (0.281-2.729)	0.818
Compliance (<14 days missed)	26 (72.2)	29 (78.4)	0.717 (0.246-2.091)	0.542
Perceived improvement	12 (33.3)	17 (45.9)	0.588 (0.228-1.518)	0.271
Treatment acceptability	29 (80.6)	28 (75.7)	1.332 (0.436-4.065)	0.614
	Mean (SD)	**Mean (SD)**	**Mean diff.(95% CI)**	**p-values****
ONYCHO score	57.5 (14.2)	63.1 (11.3)	−5.600 (−13.599-2.398)	0.224
PCS-12 score	52.3 (4.5)	51.5 (5.0)	0.809 (−1.828-3.445)	0.747

Table 3 Effect size differences at 6 months between **miconazole** and **placebo** (continued)

	Miconazole (N = 36)	**Placebo** (N = 37)	**Effect size**	
MCS-12 score	42.6 (4.9)	41.6 (4.1)	0.956 (–1.308-3.219)	0.576

N = number of patients, SD = standard deviation, CI = confidence interval, n.e. = not estimable, diff. = difference, * Fisher's exact instead of Chi-square if >20% of cells with expected frequency <5, ** Tukey-Kramer's post-hoc test for multiple comparisons, **statistically significant results in bold**

Table 4 Effect size differences at 6 months between **amorolfine** and **placebo**

	Amorolfine (N = 38)	**Placebo (N = 37)**	**Effect size**	
	N (%)	**N (%)**	**OR (95% CI)**	**p value**
Primary outcome				
Complete cure	0 (0.0)	2 (5.4)	n.e.	0.240
Clinical cure	1 (2.6)	2 (5.4)	0.473 (0.041-5.451)	0.615
Mycological cure	3 (7.9)	10 (27.0)	**0.231 (0.058-0.924)**	**0.029**
Secondary outcomes				
≤10% affected	4 (10.5)	12 (32.4)	**0.245 (0.071-0.850)**	**0.021**
Reduction ≥40%	1 (2.6)	3 (8.1)	0.306 (0.030-3.088)	0.358
Adverse effects	7 (18.4)	8 (21.6)	0.819 (0.263-2.543)	0.729
Compliance (<14 days missed)	31 (81.6)	29 (78.4)	1.222 (0.393-3.796)	0.729
Perceived improvement	18 (47.4)	17 (45.9)	1.059 (0.427-2.624)	0.902
Treatment acceptability	30 (78.9)	28 (75.7)	1.205 (0.408-3.559)	0.735
	Mean (SD)	**Mean (SD)**	**Mean diff. (95% CI)**	**p-values****
ONYCHO score	57.4 (16.9)	63.1 (11.3)	–5.685 (–13.576-2.206)	0.205
PCS-12 score	51.2 (4.7)	51.5 (5.0)	–0.299 (–2.900-2.302)	0.960
MCS-12 score	42.8 (3.1)	41.6 (4.1)	1.184 (–1.049-3.417)	0.421

N = number of patients, SD = standard deviation, CI = confidence interval, n.e. = not estimable, diff. = difference, * Fisher's exact instead of Chi-square if >20% of cells with expected frequency <5, ** Tukey-Kramer's post-hoc test for multiple comparisons, **statistically significant results in bold**

The effect of treatment on the percentage of affected area and OSI scores over time is illustrated by Figure 2.

Regarding the affected area, repeated measures ANOVA showed an overall significant difference in treatment effect over time between all groups (F(3.4-182.1)=4.8, p=0.002). Using pairwise comparisons, we found that this effect was due to a significant mean difference between amorolfine and placebo (10.7%, 95% CI 0.2 to 21.2, p=0.045) rather

than between miconazole and placebo (5.5%, 95% CI −5.2 to 16.2, p=0.639), with both favouring placebo.

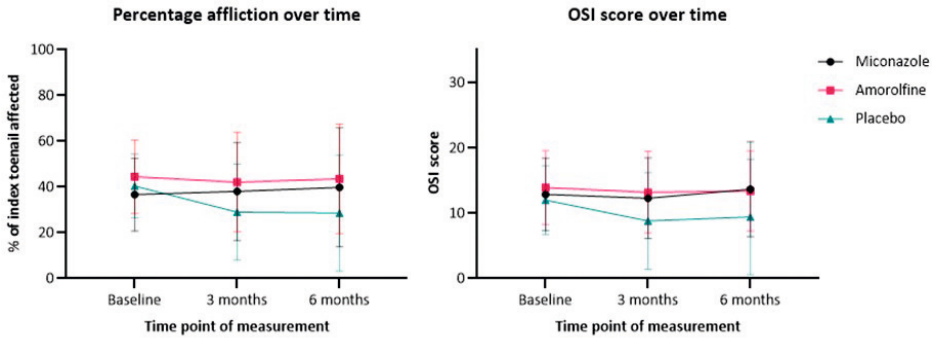

Figure 2 Percentage of index toenail affliction and OSI scores with corresponding confidence intervals over time. Y-axes represent percentage affliction (left) and OSI scores (right). X-axis represents the time point of measurement at baseline and follow-up.

Similarly, we found an overall significant difference in treatment effect on OSI scores over time between all 3 groups (repeated measures ANOVA F(3.6-189.0) = 2.6, p=0.045). Again, this was due to a significant mean difference between amorolfine and placebo (3.2, 95% CI 0.1 to 6.8, p=0.041) rather than between miconazole versus placebo (2.9, 95% CI -0.5 to 6.2, p=0.121), in favour of placebo.

Per protocol analysis

The overall results of the per-protocol analysis are summarized in Table S4. The corresponding statistical tests, comparing miconazole with placebo, amorolfine with placebo, and miconazole with amorolfine, are shown in table S5A-C, respectively. In contrast to the intention-to-treat analysis, we found no significant differences in mycological cure for miconazole versus placebo (OR 0.22, 95% CI 0.04 to 1.15, p=0.082) or for amorolfine versus placebo (OR 0.28, 95% CI 0.07 to 1.19, p=0.073). In addition, neither miconazole nor amorolfine achieved a significant clinical improvement (≤10% affected) when compared with placebo (OR 0.35, 95% CI 0.09 to 1.28, p=0.105 and OR 0.28, 95% CI 0.08 to 1.03, p=0.048, respectively). As for the intention-to-treat analysis, there were no significant differences between amorolfine and miconazole.

Subgroup analysis

The results of the subgroup analysis based on the affected toenail area at baseline are shown in supplemental table S6A,B, comparing miconazole and amorolfine with placebo, respectively. Miconazole was significantly less effective in reaching clinical improvement defined as ≤10% affected area at 6 months for patients having 11-25% involvement at baseline (OR 0.35, 95% CI 0.11 to 1.116, p=0.049) compared with placebo. There were no other significant differences, nor between amorolfine and placebo.

Harms

The number of patients reporting adverse effects of miconazole or amorolfine compared with placebo did not differ significantly (OR 0.88, 95% CI 0.28 to 2.73, p=1.000 and OR 0.82, 95% CI 0.26 to 2.54, p=0.729, respectively). Furthermore, no serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) were reported. The number and specific type of side effects are described in supplemental table S7.

DISCUSSION

Summary

In this primary care study, we investigated whether topical miconazole or amorolfine are effective in the treatment of mild to moderately severe onychomycosis. Neither was effective at reaching complete or clinical cure. Based on intention-to-treat analyses, both antifungals were actually significantly less effective at reaching mycological cure and clinical improvement compared with placebo. By contrast, per-protocol analysis of therapy-compliant patients found no statistically significant differences between groups in mycological cure or clinical improvement. In addition, adverse effects, perceived improvement, acceptability, disease burden or quality of life were not significantly different between the antifungal and placebo groups.

Comparison with previous literature

The efficacy of miconazole has been investigated previously, but in studies that either lacked placebo control, or compared topical to systemic treatments.[25-27] One study reported a high mycological cure rate (60%) at 6 months, but suffered from substantial drop-out (40%) in the treatment group due to inefficacy.[27] Previous investigations have exclusively used miconazole cream, thus the Onycho Trial was the first to apply miconazole as a nail lacquer, as well as the first to compare topical miconazole with placebo in a primary care setting.[21]

Compared to our results, previous studies of amorolfine reported noticeably better complete and mycological cures (38-52% and 60-75%, respectively), although again those studies were not placebo-controlled or blinded.[23,24] A more recent open-label trial (N=1029) reported outcomes more comparable to ours, with complete, clinical and mycological cure rates for amorolfine of 0.96%, 3.8%, and 15.7%, respectively.[38] Although we did not find a significant treatment effect of miconazole or amorolfine as monotherapy, previous studies showed that amorolfine was effective when combined with oral treatment or when used as a prophylactic to prevent recurrence of onychomycosis.[39,40] These methods of application were not included in our study.

In summary, previous studies on miconazole and amorolfine as monotherapy that showed better results were not placebo controlled or blinded. This could explain at least in part the higher cure rates. Our findings support a limited, in our case non-significant

effect of amorolfine and contrast with previously reported cure rates for miconazole, possibly explained by performance and observer bias in previous studies.

Strengths and limitations

An important strength of this trial was the predominance of moderately severe cases, generally considered the most appropriate for topical treatment. Furthermore, selection, treatment and follow-up all took place in an outpatient setting representative of daily practice.
Standardized measurement approaches were used for clinical evaluation as well as confirmatory testing, improving the reliability and reproducibility of our findings. Strict blinding of patients and observers for treatment allocation and evaluations further limited potential bias.

Moreover, we applied accepted, frequently-used outcome measures for complete, clinical and mycological cure, as well as for clinical improvement, allowing our results to be easily compared to those of other trials.[21] In addition, we anticipated criticism levelled at previous studies by evaluating treatment effect on symptom burden and quality of life.[21,22]

A limitation inherent to the selection criteria used in our study is the potential underrepresentation of certain patient groups, most notably those with severe onychomycosis, but also patients with Fitzpatrick skin-type >3 or diabetics excluded due to the risk of metformin-miconazole interactions. Our results are therefore not generalizable to these groups. In view of our inclusion of primarily milder cases, we expect that use of miconazole or amorolfine in a broader population would likely worsen general outcomes.
Importantly, we found a stronger effect of placebo on mycological cure and clinical improvement (to <10%) compared to the antifungal treatments. Nevertheless, it is unlikely that this statistically significant difference was due to antifungal properties of the placebo given the lack of response in the per protocol analysis, although an immune stimulating effect of denatonium benzoate cannot be ruled out.[31-35] Despite the common assumption that onychomycosis does not resolve if untreated, our findings are consistent with some previous trials showing comparable numbers of participants reaching clinical and mycological cure in the placebo groups, supporting the possibility of spontaneous improvement.[21,41-43]

Another limitation was the relatively short treatment period compared to other trials, in particular for reaching complete cure given the slow nail growth.[21] However, miconazole had previously shown significant results at six months and amorolfine had been reported to give no further improvement beyond six months.[22,27] In addition to these factors, we expected that a six-month period would increase willingness to participate and limit potential dropout, as well as better represent daily practice.

Conclusion and future directives

This study supports previous results for topical antifungal treatment of onychomycosis, which have been modest at best and often disappointing in their currently commercially available formulations.[21] Based on our findings, topical treatment of mild to moderately severe onychomycosis with miconazole or amorolfine should not be advised.
As the antifungal efficacy of topical antimycotics in skin infections is well established, previously described poor penetration into nail tissue seems likely to have played an important role in the present and previous studies.[44,45] Further research into topical antifungals may be justified if combined with modalities that enhance antifungal penetration into the nail.[21,45,46]

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DECLARATIONS

Contributors: RMW was first author, and RMW, TNB and JAHE together act as guarantors. RMW, TNB, JAHE, KDQ and MTvdB were involved in the design, planning, conduct and reporting of this study. KS was primarily involved in the conduct, as well as the reporting, MEN was involved in the reporting of the trial, and BJAM was involved in both design and reporting, specifically concerning the statistical analyses. The corresponding author attests that all listed authors meet authorship criteria, and that no others meeting the criteria have been omitted.

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Disclaimer: The views expressed in this publication are those of the authors and not necessarily those of FAZ.

Competing interests: None declared.

Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethical approval: The study was approved by the designated medical ethics committee of Leiden-Den Haag-Delft (METC-LDD) on 26 August 2019 (NL68851.058.19), conducted and coordinated by RMW, under the supervision of TNB and JAHE, at the department of Primary Care and Public Health (PHEG) of the Leiden University Medical Center (LUMC).

Data availability statement: Data are available on reasonable request. The data used for this study are available from the corresponding author on reasonable request.

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SUPPLEMENTAL MATERIALS

Table S1 Mycology results at baseline

	Miconazole (N = 36)	Amorolfine (N = 38)	Placebo (N = 37)
Dermatophyte, N (%)			
T. rubrum	15 (41.7)	17 (44.7)	15 (40.5)
T. mentagrophytes	4 (11.1)	4 (10.5)	2 (5.4)
T. interdigitale	1 (2.8)	1 (2.6)	0 (0.0)
Dermatophyte nos	14 (38.9)	15 (39.5)	16 (43.2)
Non-dermatophyte, N (%)			
Aspergillus spp	0 (0.0)	1 (2.6)	0 (0.0)
Acremonium spp	0 (0.0)	0 (0.0)	1 (2.7)
Non-dermatophyte nos	1 (2.8)	0 (0.0)	0 (0.0)
Yeast, N (%)			
Candida spp	0 (0.0)	0 (0.0)	1 (2.7)
Candida parapilosis	1 (2.8)	0 (0.0)	1 (2.7)
Rodoturula	0 (0.0)	0 (0.0)	1 (2.7)

N = number of patients, nos = not otherwise specified, spp = species

Table S2 Effect size differences at 6 months for both **antifungals** (N=74) vs **placebo** (N=37)

	Antifungal	Placebo	Effect size	
	N (%)	N (%)	OR (95% CI)	p value*
Primary outcome				
Complete cure	0 (0.0)	2 (5.4)	n.e.	0.109*
Clinical cure	1 (1.4)	2 (5.4)	0.24 (0.02 to 2.73)	0.257*
Mycological cure	6 (8.1)	10 (27.0)	**0.24 (0.08 to 0.72)**	**0.007**
Secondary outcomes				
≤10% affected	8 (10.8)	12 (32.4)	**0.25 (0.09 to 0.69)**	**0.005**
Reduction ≥40%	1 (1.4)	3 (8.1)	0.16 (0.02 to 1.55)	0.107
Adverse effects, any	14 (18.9)	8 (21.6)	0.84 (0.32 to 2.24)	0.736
Compliance (<14 days missed)	57 (77.0)	29 (78.4)	0.93 (0.36 to 2.40)	0.872
Perceived improvement	30 (40.5)	17 (45.9)	0.80 (0.36 to 1.78)	0.587
Treatment acceptability	59 (79.2)	28 (75.7)	1.26 (0.49 to 3.24)	0.625

Table S2 Effect size differences at 6 months for both **antifungals** (N=74) vs **placebo** (N=37) (continued)

	Antifungal	Placebo	Effect size	
	Mean (SD)	**Mean (SD)**	**Mean diff. (95% CI)**	**p value****
ONYCHO score	57.4 (15.6)	63.1 (11.3)	-5.6 (-13.6 to 2.3)	0.225
PCS-12 score	51.7 (4.6)	51.5 (5.0)	0.3 (-2.4 to 2.9)	0.854
MCS-12 score	42.7 (4.0)	41.6 (4.1)	2.1 (-1.2 to 3.3)	0.499

N = number of patients, SD = standard deviation, CI = confidence interval, n.e. = not estimable, diff. = difference, * Fisher's exact instead of Chi-square if ≥1 cells with expected frequency <5, ** Tukey-Kramer's post-hoc test for multiple comparisons. **Statistically significant results in bold.**

Table S3 Effect size differences at 6 months for **miconazole** (N=36) vs **amorolfine** (N=38)

	Miconazole	Amorolfine	Effect size	
	N (%)	**N (%)**	**OR (95% CI)**	**p value***
Primary outcome				
Complete cure	0 (0.0)	0 (0.0)	n.e.	n.e.
Clinical cure	0 (0.0)	1 (2.6)	0.51 (0.40 to 0.64)	1.000
Mycological cure	3 (8.3)	3 (7.9)	1.03 (0.45 to 2.38)	1.000
Secondary outcomes				
≤10% affected	4 (11.1)	4 (10.5)	1.03 (0.49 to 2.15)	1.000
Reduction ≥40%	0 (0.0)	1 (2.6)	0.51 (0.40 to 0.64)	1.000
Adverse effects, any	7 (19.4)	7 (18.4)	1.03 (0.58 to 1.86)	0.911
Compliance (<14 days missed)	26 (72.2)	31 (81.6)	0.78 (0.48 to 1.26)	0.339
Perceived improvement	12 (33.3)	18 (47.4)	0.73 (0.44 to 1.23)	0.219
Treatment acceptability	29 (80.6)	30 (78.9)	1.05 (0.58 to 1.92)	0.863
	Mean (SD)	**Mean (SD)**	**Mean diff. (95% CI)**	**p value****
ONYCHO score	57.5 (14.2)	57.4 (16.9)	0.1 (-7.9 to 8.0)	1.000
PCS-12 score	52.3 (4.5)	51.2 (4.7)	1.1 (-1.5 to 3.7)	0.575
MCS-12 score	42.6 (4.9)	42.8 (3.1)	-0.2 (-2.5 to 2.0)	0.968

N = number of patients, SD = standard deviation, CI = confidence interval, n.e. = not estimable, diff. = difference, * Fisher's exact instead of Chi-square if ≥1 cells with expected frequency <5, ** Tukey-Kramer's post-hoc test for multiple comparisons. **Statistically significant results in bold.**

Table S4 Summary results of per protocol analysis

	Miconazole (N = 26)	Amorolfine (N = 31)	Placebo (N = 29)
Primary outcome (N, %)			
Complete cure rate	0 (0.0)	0 (0.0)	2 (6.9)
Clinical cure	0 (0.0)	1 (3.2)	2 (6.9)
Mycological cure	2 (7.7)	3 (9.7)	8 (27.6)
Secondary outcomes (N, %)			
Clinical improvement (≤10% affected)	4 (15.4)	4 (12.9)	10 (34.5)
Clinical improvement (≥40% reduction)	0 (0.0)	1 (3.2)	3 (10.3)
Affected area (index toenail), % (SD)	40.9 (27.7)	43.2 (25.8)	28.5 (27.1)
Affected area, per category, N (%)			
0%	0 (0.0)	1 (3.2)	2 (6.9)
1-10%	4 (15.4)	3 (9.7)	8 (27.6)
11-25%	7 (26.9)	6 (19.4)	7 (24.1)
26-50%	8 (30.8)	9 (29.0)	5 (17.2)
51-75%	2 (7.7)	8 (25.8)	4 (13.8)
76-100%	5 (19.2)	4 (12.9)	3 (10.3)
OSI score, mean (SD)	14.0 (8.1)	13.3 (6.7)	9.1 (9.2)
OSI score, per category, N (%)			
Absent (0)	0 (0.0)	2 (6.5)	3 (10.3)
Mild (1-5)	5 (19.2)	2 (6.5)	11 (37.9)
Moderate (6-15)	8 (30.8)	13 (41.9)	8 (27.6)
Severe (16-35)	13 (50.0)	14 (45.1)	7 (24.1)
Number of affected toenails, mean (SD)	3.0 (2.2)	2.9 (1.7)	2.9 (2.0)
ONYCHO-questionnaire score, mean (SD)	57.8 (13.5)	58.2 (15.9)	63.2 (11.7)
ONYCHO score, per category, N (%)			
Good (67-100)	8 (30.8)	10 (32.3)	14 (48.3)
Moderate (34-66)	17 (65.4)	18 (58.1)	14 (48.3)
Poor (0-33)	1 (3.8)	3 (9.7)	1 (3.4)
SF-12 questionnaire score, mean (SD)			
PCS-12 score	51.8 (4.7)	51.4 (4.5)	51.8 (4.7)
MCS-12 score	42.6 (5.2)	42.7 (3.2)	42.2 (3.6)
Adverse effects, N (%)	5 (19.2)	7 (22.6)	4 (13.8)
Perceived improvement, N (%)	11 (42.3)	17 (54.8)	15 (51.7)
Treatment acceptability, N (%)	25 (96.2)	27 (87.1)	25 (86.2)

Legend: N = number of patients, SD = standard deviation, OSI = Onychomycosis Severity Index, PCS-12 = physical health component of SF-12 questionnaire, MCS-12 = mental health component of SF-12 questionnaire.

Table S5A Effect size difference for **miconazole** and **placebo**, per protocol

	Miconazole (N = 26)	**Placebo (N = 29)**	**Effect size**	
	N (%)	N (%)	OR (95% CI)	p value *
Primary outcome				
Complete cure	0 (0.0)	2 (6.9)	n.e.	0.492
Clinical cure	0 (0.0)	2 (6.9)	n.e.	0.492
Mycological cure	2 (7.7)	8 (27.6)	0.22 (0.04 to 1.15)	0.082
Secondary outcomes				
≤10% affected	4 (15.4)	10 (34.5)	0.35 (0.09 to 1.28)	0.105
Reduction ≥40%	0 (0.0)	3 (10.3)	n.e.	0.238
Adverse effects	5 (19.2)	4 (13.8)	1.49 (0.35 to 6.26)	0.721
Perceived improvement	11 (42.3)	15 (51.7)	0.68 (0.24 to 1.99)	0.485
Treatment acceptability	25 (96.2)	25 (86.2)	4.00 (0.42 to 38.35)	0.355
	Mean (SD)	**Mean (SD)**	**Mean diff.(95% CI)**	**p-values****
ONYCHO score	57.8 (13.5)	63.2 (11.7)	–5.4 (–14.4 to 3.5)	0.322
PCS-12 score	51.8 (4.7)	51.8 (4.7)	0.0 (–3.0 to 3.0)	1.000
MCS-12 score	42.6 (5.2)	42.2 (3.6)	0.4 (–2.2 to 3.0)	0.922

N = number of patients, SD = standard deviation, CI = confidence interval, n.e. = not estimable, diff. = difference, * Fisher's exact instead of Chi-square if ≥1 cells with expected frequency <5, ** Tukey-Kramer's post-hoc test for multiple comparisons. **Statistically significant results in bold.**

Table S5B Effect size differences for **amorolfine** and **placebo**, per protocol

	Amorolfine (N = 31)	**Placebo (N = 29)**	**Effect size**	
	N (%)	N (%)	OR (95% CI)	p value*
Primary outcome				
Complete cure	0 (0.0)	2 (6.9)	n.e.	0.229
Clinical cure	1 (3.2)	2 (6.9)	0.45 (0.04 to 5.25)	0.606
Mycological cure	3 (9.7)	8 (27.6)	0.28 (0.07 to 1.19)	0.073
Secondary outcomes				
≤10% affected	4 (12.9)	10 (34.5)	0.28 (0.08 to 1.03)	0.048
Reduction ≥40%	1 (2.1)	3 (10.3)	0.29 (0.03 to 2.95)	0.346
Adverse effects	7 (22.6)	4 (13.8)	1.83 (0.47 to 7.03)	0.379
Perceived improvement	17 (54.8)	15 (51.7)	1.13 (0.41 to 3.13)	0.809
Treatment acceptability	27 (87.1)	25 (86.2)	1.08 (0.24 to 4.79)	1.000

Table S5B Effect size differences for **amorolfine** and **placebo**, per protocol (continued)

	Amorolfine (N = 31)	**Placebo (N = 29)**	**Effect size**	
	Mean (SD)	**Mean (SD)**	**Mean diff.(95% CI)**	**p-values****
ONYCHO score	58.2 (15.9)	63.2 (11.7)	–5.0 (–13.6 to 3.5)	0.345
PCS-12 score	51.4 (4.5)	51.8 (4.7)	–0.4 (–3.3 to 2.4)	0.935
MCS-12 score	42.7 (3.2)	42.2 (3.6)	0.4 (–2.0 to 2.9)	0.897

N = number of patients, SD = standard deviation, CI = confidence interval, n.e. = not estimable, diff. = difference, * Fisher's exact instead of Chi-square if ≥1 cells with expected frequency <5, ** Tukey-Kramer's post-hoc test for multiple comparisons.

Table S5C Effect size differences for **miconazole** and **amorolfine**, per protocol

	Miconazole (N = 26)	**Amorolfine (N = 31)**	**Effect size**	
	N (%)	N (%)	OR (95% CI)	p value*
Primary outcome				
Complete cure	0 (0.0)	0 (0.0)	n.e.	n.e.
Clinical cure	0 (0.0)	1 (3.2)	0.54 (0.42 to 0.68)	1.000
Mycological cure	2 (7.7)	3 (9.7)	0.87 (0.29 to 2.64)	1.000
Secondary outcomes				
≤10% affected	4 (15.4)	4 (12.9)	1.11 (0.52 to 2.38)	1.000
Reduction ≥40%	0 (0.0)	1 (3.2)	0.54 (0.42 to 0.68)	1.000
Adverse effects	5 (19.2)	7 (22.6)	0.89 (0.43 to 1.87)	0.757
Perceived improvement	11 (42.3)	17 (54.8)	0.76 (0.43 to 1.36)	0.346
Treatment acceptability	25 (96.2)	27 (87.1)	2.40 (0.41 to 14.2)	0.362
	Mean (SD)	**Mean (SD)**	**Mean diff.(95% CI)**	**p-values****
ONYCHO score	57.8 (13.5)	58.2 (15.9)	-0.4 (-9.2 to 8.4)	0.994
PCS-12 score	51.8 (4.7)	51.4 (4.5)	0.4 (-2.5 to 3.4)	0.934
MCS-12 score	42.6 (5.2)	42.7 (3.2)	-0.5 (-2.6 to 2.5)	0.999

N = number of patients, SD = standard deviation, CI = confidence interval, n.e. = not estimable, diff. = difference, * Fisher's exact instead of Chi-square if ≥1 cells with expected frequency <5, ** Tukey-Kramer's post-hoc test for multiple comparisons.

Table S6A Subgroup analysis for affected area at baseline - effect size differences at 6 months between **miconazole** and **placebo**

	Miconazole $N^{11-25\%} = 11$ $N^{26-50\%} = 17$ $N^{51-75\%} = 8$	**Placebo** $N^{11-25\%} = 7$ $N^{26-50\%} = 22$ $N^{51-75\%} = 8$	**Effect size**	
	N (%)	N (%)	OR (95% CI)	p value *
Primary outcome				
Complete cure				
11-25%	0 (0.0)	0 (0.0	n.e.	n.e.
26-50%	0 (0.0)	1 (4.5)	0.55 (0.42 to 0.74)	1.000
51-75%	0 (0.0)	1 (12.5)	0.47 (0.27 to 0.80)	1.000
Clinical cure				
11-25%	0 (0.0)	0 (0.0)	n.e.	n.e.
26-50%	0 (0.0)	1 (4.5)	0.55 (0.42 to 0.74)	1.000
51-75%	0 (0.0)	1 (12.5)	0.47 (0.27 to 0.80)	1.000
Mycological cure				
11-25%	0 (0.0)	1 (14.3)	0.35 (0.19 to 0.67)	0.389
26-50%	2 (11.8)	8 (36.4)	0.39 (0.11 to 1.40)	0.140
51-75%	1 (12.5)	1 (12.5)	1.00 (0.23 to 4.40)	1.000
Secondary outcomes				
≤10% affected				
11-25%	2 (18.2)	5 (71.4)	**0.35 (0.11 to 1.16)**	**0.049**
26-50%	2 (11.8)	6 (27.3)	0.52 (0.15 to 1.81)	0.426
51-75%	0 (0.0)	1 (12.5)	0.47 (0.27 to 0.80)	1.000
Reduction ≥40%				
11-25%	0 (0.0)	0 (0.0)	n.e.	n.e.
26-50%	0 (0.0)	1 (4.5)	0.55 (0.42 to 0.74)	1.000
51-75%	0 (0.0)	2 (25.0)	0.43 (0.23 to 0.80)	0.467

N = number of patients, OR = odds ratio, CI = confidence interval, n.e. = not estimable, * Fisher's exact instead of Chi-square if ≥1 cells with expected frequency <5, **statistically significant results in bold.**

Table S6B Subgroup analysis for affected area at baseline - effect size differences at 6 months between **amorolfine** and **placebo**

	Amorolfine **N $^{11-25\%}$ = 6** **N $^{26-50\%}$ = 17** **N $^{51-75\%}$ = 15**	**Placebo** **N $^{11-25\%}$ = 7** **N $^{26-50\%}$ = 22** **N $^{51-75\%}$ = 8**	**Effect size**	
	N (%)	N (%)	OR (95% CI)	p value *
Primary outcome				
Complete cure				
11-25%	0 (0.0)	0 (0.0)	n.e.	n.e.
26-50%	0 (0.0)	1 (4.5)	0.55 (0.42 to 0.74)	1.000
51-75%	0 (0.0)	1 (12.5)	0.32 (0.17 to 0.59)	0.348
Clinical cure				
11-25%	1 (16.7)	0 (0.0)	0.42 (0.21 to 0.81)	0.462
26-50%	0 (0.0)	1 (4.5)	0.55 (0.42 to 0.74)	1.000
51-75%	0 (0.0)	1 (12.5)	0.32 (0.17 to 0.59)	0.348
Mycological cure				
11-25%	2 (33.3)	1 (14.3)	1.67 (0.55 to 5.02)	0.559
26-50%	1 (5.9)	8 (36.4)	0.21 (0.03 to 1.36)	0.052
51-75%	0 (0.0)	1 (12.5)	0.32 (0.17 to 0.59)	0.348
Secondary outcomes				
≤10% affected				
11-25%	3 (50.0)	5 (71.4)	0.63 (0.20 to 1.97)	0.592
26-50%	1 (5.9)	6 (27.3)	0.29 (0.05 to 1.81)	0.113
51-75%	0 (0.0)	1 (12.5)	0.32 (0.17 to 0.59)	0.348
Reduction ≥40%				
11-25%	0 (0.0)	0 (0.0)	n.e.	n.e.
26-50%	1 (5.9)	1 (4.5)	1.16 (0.28 to 4.85)	1.000
51-75%	0 (0.0)	2 (25.0)	0.29 (0.15 to 0.56)	0.111

N = number of patients, OR = odds ratio, CI = confidence interval, n.e. = not estimable, * Fisher's exact instead of Chi-square if ≥1 cells with expected frequency <5.

Table S7 Reported side effects

	Miconazole (N=7)	Amorolfine (N=7)	Placebo (N=8)
Local side effects	n	n	n
Itch	0	4	2
Irritation	2	4	4
Burning sensation	2	1	2
Discoloration of surrounding skin	0	1	0
Inflammation/infection	1	0	2
Redness	1	4	4
Skin rash	0	0	1
Urticaria	0	0	0
Discoloration of nails	4	1	0
Pain	1	0	0
Dystrophy	1	0	0
Peeling	0	0	1
TOTAL	12	15	16
Systemic side effects			
Allergic reactions	0	0	0
SAEs	0	0	0
SUSARs	0	0	0

N = number of patients, n = number of adverse reactions, SAEs = serious adverse events, SUSARs = suspected unexpected serious adverse reactions.

Part III

Prognostic Implications in Patients with Diabetes

Association between onychomycosis and ulcerative complications in diabetic patients: a longitudinal cohort study in Dutch general practice

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ABSTRACT

Introduction: Diabetic foot ulcers are feared complications of diabetes mellitus (DM), requiring extensive treatment and hospital admissions, ultimately leading to amputation and increased mortality. Different factors contribute to the development of foot ulcers and related complications. Onychomycosis, being more prevalent in patients with diabetes, could be an important risk factor for developing ulcers and related infections. However, the association between onychomycosis and diabetic complications has not been well studied in primary care.

Research design and methods: To determine the impact of onychomycosis on ulcer development and related complications in patients with diabetes in primary care, a longitudinal cohort study was carried out using routine care data from the Extramural Leiden University Medical Center Academic Network. Survival analyses were performed through Cox proportional hazards models with time-dependent covariates.

Results: Data from 48 212 patients with a mean age of 58 at diagnosis of DM, predominantly type 2 (87.8%), were analysed over a median follow-up of 10.3 years. 5.7% of patients developed an ulcer. Onychomycosis significantly increased the risk of ulcer development (HR 1.37, 95% CI 1.13 to 1.66), not affected by antimycotic treatment, nor after adjusting for confounders (HR 1.23, 95% CI 1.01 to 1.49). The same was found for surgical interventions (HR 1.54, 95% CI 1.35 to 1.75) and skin infections (HR 1.48, CI 95% 1.28 to 1.72), again not affected by treatment and significant after adjusting for confounders (HR 1.32, 95% CI 1.16 to 1.51 and HR 1.27, 95% CI 1.10 to 1.48, respectively).

Conclusions: Onychomycosis significantly increased the risk of ulcer development in patients with DM in primary care, independently of other risk factors. In addition, onychomycosis increased the risk of surgeries and infectious complications. These results underscore the importance of giving sufficient attention to onychomycosis in primary care and corresponding guidelines. Early identification of onychomycosis during screening and routine care provides a good opportunity for timely recognition of increased ulcer risk.

INTRODUCTION

According to the International Diabetes Federation, an estimated 537 million people worldwide suffer from diabetes mellitus (DM).[1] In 2019, 1.1 million patients with diabetes were registered in Dutch primary care, about 7% of the adult population.[2] Complications of DM are the cause of significant morbidity and medical costs.[3] With the prevalence of DM projected to continue to rise, prevention and management of diabetic complications are becoming increasingly important.[2] One of the most feared complications of DM is the diabetic foot, which includes diabetic foot ulcers.[4] Ulcers often require extensive treatment and hospitalization, and can ultimately lead to lower extremity amputation.[5] To prevent ulcer development and its consequences, early recognition of patients at risk is essential.[6] Various risk factors for ulcer development have been identified. The most prominent are prior ulcer or amputation, neuropathy, foot deformity, focal pressure points, and peripheral arterial disease.[7] Furthermore, male gender, signs of microangiopathy, including visual impairment, poor glycaemic control (i.e., elevated glycated haemoglobin A1c levels), insulin therapy, and onychomycosis were identified as additional significant risk factors.[8,9] Regarding the latter, patients with diabetes are more prone to fungal infections in general and onychomycosis in particular: up to one-third of patients with diabetes are estimated to have onychomycosis compared to 4.3% in the general population.[10,11] Although onychomycosis is often considered a nuisance and unesthetic at most, numerous studies have shown onychomycosis to have a substantial negative effect on the quality of life and predispose patients to complications such as bacterial infections, especially in patients with diabetes.[12-14] However, the underlying pathophysiologic mechanism that explains the relationship between onychomycosis and diabetic complications remains unclear.[15,16] Although previous studies suggest onychomycosis may be an important risk factor for ulcer development, this relationship has not been well studied in primary care.[7,17]

The aim of this study was to assess if onychomycosis, treated or not, is a risk factor for diabetic foot ulcers, and secondly, for related complications in primary care. Therefore, we conducted a longitudinal cohort study using routine-care data of patients with diabetes from primary care.

METHODS

Study design

This study was designed as a longitudinal, retrospective cohort using routine-care data from primary care patients with DM. The date of diagnosis of DM was considered the start of follow-up; the end of follow-up was either development of an outcome, date of death, deregistration or data extraction. Using predefined risk factors, primarily onychomycosis and secondarily antimycotic treatment and related, often underlying conditions, both exposed and unexposed individuals were identified. Following patients forward in time, the incidences of the outcomes of interest were compared between the two groups.[18] Ulcer development was considered the primary outcome; hospital referrals, surgical interventions (performed within primary care) and the bacterial skin infections, cellulitis and erysipelas, were secondary outcomes.

Data and setting

Routine-care data from primary care practices affiliated with the Extramural Leiden University Medical Center (LUMC) Academic Network (ELAN) were used. ELAN is a collaboration between Dutch general practitioners (GPs) and the Department of Public Health and Primary Care from the LUMC, in the western part of the Netherlands. ELAN periodically extracts and stores these data in its database in compliance with local and European privacy legislation.[19,20] The investigators had no access to the ELAN database used to create the dataset for analysis. The data used to create the dataset provided to the investigators were extracted on 11 May 2022.

Participants

The records of all patients with diabetes, regardless of subtype, were extracted. Based on the intended analyses, patient records meeting the following criteria were selected:

1. Date of diagnosis of DM recorded.
2. Age between 0 and 100.
3. Date of exposure (risk factor) and event (complication) recorded, that is, time between diagnosis of DM and exposure or outcome of interest known.
4. Exposure or event occurred after diagnosis of DM and before deregistration, death or data extraction, that is, during follow-up.

Regarding the latter, since the start of follow-up was defined as the date on which the diagnosis of DM was established, only exposures and events occurring after baseline were used for analyses.

Patient and public involvement

It was not appropriate to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

Measurements and outcomes

Regarding exposures and outcome measures, the diagnoses and comorbidities extracted were coded using the International Classification of Primary Care coding system and their corresponding dates of registration. Similarly, data on medication, referrals and interventions were extracted using their corresponding coding systems.

Besides onychomycosis, the available risk factors of interest were tinea pedis, peripheral artery disease, venous insufficiency, ankle oedema, psoriasis, lichen planus, eczema, neuropathy, smoking and antimycotic treatment. In addition, age and sex were also considered potential confounders and used for analyses.

Our primary outcome measure was ulcer development. Secondary outcome measures were hospital referrals, surgical interventions performed within primary care, that is, minor procedures such as debridement, and infectious complications (cellulitis and erysipelas). Only hospital referrals related to DM referring to surgery, internal medicine or dermatology, were used for analyses. Cellulitis and erysipelas, although coded differently, were combined since both entities are used interchangeably. The same was done for ulcus cruris and diabetic foot ulcers, combining them into a single variable for ulcers. In case two variables were combined and a patient was diagnosed with having both, the diagnosis that occurred first, that is, with the shortest time to diagnosis of DM, was used for analysis.

Statistical analyses

Descriptive statistics were used to analyse patient characteristics at baseline and to describe the occurrence of both exposures and outcomes during follow-up.

Since exposures and outcomes of interest were not constant over time, that is, occurring at different moments during follow-up, these were considered to be time-dependent covariates. Therefore, to answer our research questions, Cox-proportional hazards (PHs) models with time-dependent covariates were used, thus taking into account the time between baseline and diagnosis of an exposure or event. The PH assumption was checked by testing whether the covariates interacted significantly with time. In case of violation, the corresponding HR was modelled as a time-dependent effect by including an interaction term between the logarithm of time and the covariate.

To answer our research questions, three models were constructed. First, the association between onychomycosis and ulcer development was evaluated as single predictor (univariate model), then adjusted for antimycotic treatment (first multivariate model), and finally for all potential confounders mentioned above (second multivariate model). The PHs assumption (PH) was violated for age and neuropathy in the last model, hence corrected for by including the interaction terms with the logarithm of time in the corresponding model.

Regarding secondary outcomes, the associations between onychomycosis and hospital referrals, surgeries and bacterial skin infections were evaluated. The same set of models, that is, a univariate model, a multivariate model to adjust for antimycotic treatment and a final multivariate model to adjust for all confounders combined, were used for each of the secondary outcomes, respectively. Again, the interaction terms with the logarithm of time were used for the covariates for which the PH assumption was violated. These were neuropathy and smoking in the final multivariate model for hospital referrals, age and ankle oedema in the final model for surgical interventions, and age in the final model for bacterial skin infections.

P values of <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (V.28).

RESULTS

Patient characteristics

The initial data extraction consisted of 50 292 patient records. After applying the criteria as described, 48 212 records were selected for analysis. Patient characteristics are shown in table 1. Our sample included 22 877 women (47.5%) and 25 335 men (52.5%). The mean age at baseline was 58.3 years (SD 15.7). The vast majority of patients (87.8%) were diagnosed with type 2 DM; only 6.5% had type 1 DM and the remaining cases (5.7%) were unspecified.

Table 1 Patient characteristics at baseline, that is, start of follow-up

Patients, total (N)	**48,212**
Mean age at onset of DM in years (SD)	58.3 (15.7)
Gender, N (%)	
Male	25,335 (52.5)
Female	22,877 (47.5)
Type of Diabetes Mellitus, N (%)	
Type 1	3,131 (6.5)
Type 2	42,312 (87.8)
Unspecified	2,769 (5.7)

DM, diabetes mellitus.

The median follow-up time was 10.3 years (IQR 10.8). Exposures and events recorded during follow-up are presented in table 2.

The cumulative incidence of onychomycosis in our sample was 4.1%. Regarding the other exposures, ankle oedema (13.5%) and eczema (12.2%) were most frequently recorded.

During follow-up, 6.2% of patients received any form of antimycotic treatment. In total, 2771 patients (5.7%) developed an ulcer after a median of 8.8 years (IQR 9.6). Regarding the secondary outcomes, surgical interventions occurred most frequently (12.8%) after a median of 7.8 years (IQR 8.9), followed by infections (10.1%) after a median 7.7 years (IQR 9.4). 6.3% needed a hospital referral after a median of 7.4 years (IQR 9.2).

Table 2 Exposures and events during follow-up

	N (cumulative incidence, %)
Total cohort	48,212
Exposures	
Onychomycosis	1,959 (4.1)
Tinea pedis	2,006 (4.2)
Peripheral arterial disease	2,381 (4.9)
Venous insufficiency	275 (0.6)
Ankle edema	6,494 (13.5)
Psoriasis	1,193 (2.5)
Lichen ruber planus	166 (0.3)
Eczema	5,870 (12.2)
Neuropathy	3,287 (6.8)
Smoking	2,930 (6.1)
Antimycotic treatment	
Any type	3,005 (6.2)
Local	2,777 (5.8)
Systemic	228 (0.5)
Events	
Ulcer	2,771 (5.7)
Cellulitis/erysipelas	4,889 (10.1)
Hospital referral	3,060 (6.3)
Surgical intervention	6,149 (12.8)

Primary outcome: ulcer development

The results for the association between onychomycosis and ulcer development are shown in table 3. In univariate analysis, onychomycosis was significantly associated with ulcer development (HR 1.37, 95% CI 1.13 to 1.66). After adjusting for antimycotic treatment and all confounders combined, onychomycosis remained significantly associated with ulcer development (HR 1.37, 95% CI 1.13 to 1.66 and HR 1.23, 95% CI 1.01 to 1.49, respectively).

Secondary outcomes

The results, describing the association between onychomycosis and our secondary outcome measures, are also shown in table 3.

Onychomycosis was significantly associated with hospital referrals in univariate analysis (HR 1.24, 95% CI 1.02 to 1.52). Adjusting for treatment did not significantly alter this association (HR 1.27, 95% CI 1.04 to 1.55). However, when adjusted for all confounders, onychomycosis was not significantly associated with hospital referrals (HR 1.17, 95% CI 0.96 to 1.43).

Onychomycosis was also significantly associated with surgical interventions in primary care (HR 1.54, 95% CI 1.35 to 1.75). Antimycotic treatment did not significantly influence this association (HR 1.46, 95% CI 1.29 to 1.66), nor did adjustment for all confounders combined (HR 1.32, 95% CI 1.16 to 1.51).

Finally, onychomycosis was significantly associated with the bacterial infections cellulitis/erysipelas (HR 1.48, 95% CI 1.28 to 1.72), again not significantly affected by treatment (HR 1.45, 95% CI 1.25 to 1.68), nor after adjusting for all confounders (HR 1.27, 95% CI 1.10 to 1.48).

Table 3 Cox proportional-hazards models for effect of onychomycosis on primary and secondary outcome measures

Outcome	Onychomycosis		Univariate model		Adjusted for antimycotic treatment		Multivariate model *	
	Yes (%)	No (%)	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Primary								
Ulcer	140 (5.1)	2,631 (94.9)	1.37 (1.13 - 1.66)	0.001	1.37 (1.13 - 1.66)	0.001	1.23 (1.01-1.49)	0.036
Secondary								
Hospital referral	186 (6.1)	2874 (93.6)	1.24 (1.02-1.52)	0.035	1.27 (1.04-1.55)	0.021	1.17 (0.96-1.43)	0.128
Surgical intervention	427 (6.9)	5722 (93.1)	1.54 (1.35-1.75)	<0.001	1.46 (1.29-1.66)	<0.001	1.32 (1.16-1.51)	<0.001
Cellulitis / erysipelas	317 (6.5)	4572 (93.5)	1.48 (1.28-1.72)	<0.001	1.45 (1.25-1.68)	<0.001	1.27 (1.10-1.48)	0.001

* Adjusted for: age, sex, peripheral arterial disease, venous insufficiency, ankle oedema, tinea pedis, psoriasis, lichen planus, eczema, neuropathy, smoking, antimycotic treatment (any)

CONCLUSIONS

Summary

Our study demonstrated that onychomycosis in primary care patients with diabetes was significantly associated with the development of an ulcer compared with patients without onychomycosis. Even when adjusted for antimycotic treatment and additional confounders, onychomycosis remained independently associated with ulcer development. The same association was found for bacterial skin infections and surgical procedures in primary care.

Comparison with existing literature

Our results confirm the association between onychomycosis and ulcer development previously found in other populations, establishing its important role in patients with diabetes, independently from already well-established risk factors like vascular disease, neuropathy and pre-existing skin disease.[7,8,21]

Boyko et al. found an adjusted HR of 1.58 (95% CI 1.16 to 2.16) in their final multivariate model but used prospective data from veterans, predominantly male (98%) and of higher average age (62.4) attending internal medicine clinics, that is, a different setting.[8] Monteiro-Soares et al., in their endeavour to optimize the prediction model as proposed by Boyko, also found a significant association between onychomycosis and ulcer development using data from patients attending a tertiary podiatry clinic. However, they did not include the effect of time, thus limited to logistical regression analyses and unable to produce HR's to compare our results with.[22]

Furthermore, we were able to confirm the association between onychomycosis and surgical interventions as well as bacterial skin infections in primary care, previously suspected but not sufficiently supported by clinical evidence.[16,23]

Strengths and limitations

The major strength of this study was the ability to analyse data from a large cohort of primary care patients, our results therefore being representative for primary care settings in general. Although the association between onychomycosis and ulcer development has been described as mentioned above, this is the first study that establishes this association in primary care.[8]

In addition, we specifically evaluated the effect of antimycotic treatment on the association between onychomycosis and diabetic complications, which was addressed in the systematic review of Monteiro et al., but not previously done.[7,8,24] Since onychomycosis increased the hazard for developing an ulcer, one might speculate that antimycotic treatment would decrease this hazard. However, it did not, suggesting that antimycotic treatment was not effective in preventing ulcers or that antimycotic

treatment merely represents a selection of patients with more severe disease burden, already more prone to ulcer development due to other contributing factors.

An important limitation due to the use of observational, routine-care data, was our inability to proof a causal relationship between onychomycosis and ulcer development. The finding that antimycotic treatment did not significantly affect the association between onychomycosis and ulcers also suggests that onychomycosis is probably a marker rather than a direct cause of ulcer development.

Another limitation is the inherent level of uncertainty that comes with routine-care data. For example, coding is not always accurate and registration has improved over the last decades; effects based on data registered by GPs in the past might differ from data more recently registered. This could lead to over-reporting or under-reporting. Also, looking at the cumulative incidence of onychomycosis in our study sample, a lower number was found than reported by population-based studies likely due to the fact not all patients consulted their GP.[10] However, it is unlikely that these data-registration limitations would be different for those with or without onychomycosis within our study population, therefore probably not affecting our results.

In parallel, specific groups of patients were likely to be checked more often by their GP, for example, those having more severe disease. Their chance of being diagnosed with onychomycosis would be higher compared with healthier individuals, which potentially could have introduced confounding by indication and an overestimation of the association found. However, when correcting for all confounders, the independent and significant contribution of onychomycosis remained intact, pleading against a substantial effect from this form of confounding.
Finally, we only analysed a prespecified, available set of variables, not including important predictors of previous ulcers or amputations. Our results therefore only represent ulcer risk in those without prior ulcers or amputation.

Implications for practice and future perspectives

In conclusion, our study demonstrates that onychomycosis is independently associated with ulcer development in patients with diabetes in primary care. As ulcers may precede lower extremity amputations and ultimately increase mortality, our findings support the clinical relevance of onychomycosis in patients with diabetes, emphasising the importance of recognising fungal toenail infections in diabetes care.[25-27] Therefore, we would recommend all healthcare professionals involved in the care of patients with diabetes within primary care, to systematically check for the presence of onychomycosis during routine care.
Investigating if treatment of onychomycosis could reduce the risk of diabetic ulcer development and related complications by a prospective study design could be an important next scientific step.

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DECLARATIONS

Contributors: All authors read and approved the final manuscript. RW: guarantor. RW, JE and TB: conceptualisation. RW, KH, LG and TB: methodology and formal analysis. RW, KH and LG: investigation, data curation, writing. RW, JE, KQ, MN and TB: review. TB and JE: supervision. Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

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Ethics approval: Medical Ethics Committee Leiden Den-Haag Delft (METC-LDD), reference number G21.206. The METC-LDD decided that, in accordance with national regulations, further approval by an institutional review board was not necessary, that is, a waiver was granted and the study was exempted since the study was not subject to the Medical Research Involving Human Subjects Act, according to the guidelines of the Central Committee on Research Involving Human Subjects (CCMO). For additional information in English, refer to: https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/yourresearch-is-it-subject-to-the-wmo-or-not or in Dutch: https://wetten.overheid.nl/jci1.3:c:BWBR0009408&z=2022-03-15&g=2022-0315

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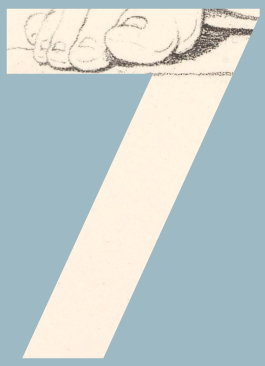

General Discussion and Summary

ONYCHOMYCOSIS IN DUTCH GENERAL PRACTICE

Dermatologic conditions, after musculoskeletal problems, are the second most frequent reason for consultation in Dutch general practice.[1] Fungal infections of the skin and its appendages, including the nails, have a reported incidence of 41.6 per 1000 patients in Dutch general practice. Although specific incidence and prevalence rates for onychomycosis in Dutch general practice are lacking, the prevalence of onychomycosis in the general population is estimated to be between 4.3% and 5.5%.[2,3] As onychomycosis and tinea pedis combined form the majority of all mycotic infections, onychomycosis is also very commonly presented in Dutch general practice.[1,4]

AIMS OF THIS THESIS

Part I of this thesis focused on the diagnostic process of onychomycosis in general practice and addressed our **first aim**: to **identify and evaluate diagnostic challenges** of onychomycosis in general practice.
Firstly, regarding the diagnosis, there could be debate about the assumption that onychomycosis can be easily diagnosed without additional confirmatory testing, i.e. based on history and physical examination, as the national guideline currently implies.[5] Based on previous findings, the majority of clinical diagnoses are indeed correct.[6-8] Nonetheless, these studies also indicate a substantial risk of overdiagnosis of 10-25% i.e., a false positive diagnosis, which could lead to unnecessary exposure to treatment.[6-8] Therefore, we evaluated the **accuracy of the clinical diagnosis of onychomycosis** in **Chapter 2** to investigate to what extent onychomycosis can be sufficiently diagnosed, i.e., correctly diagnosed on history and physical examination without confirmatory testing, using the data from the Onycho Trial described in Chapter 5. Since only confirmed cases could be included in the trial, an important step in the selection process was to confirm that the clinical diagnosis of onychomycosis was correct. To do so, we compared the clinical diagnoses made by the observers with the results of the confirmatory tests from the Department of Dermatology and Medical Microbiology, thereby determining the diagnostic accuracy of the clinical diagnosis of onychomycosis.
Secondly, focusing on onychomycosis severity, we evaluated the **reliability of the Onychomycosis Severity Index** (OSI) used in general practice in **Chapter 3**. The OSI is a measuring tool developed to quantify onychomycosis severity, primarily for research purposes.[9] Establishing onychomycosis severity, however, could also be useful in clinical practice as previous clinical trials have shown that the more severe the onychomycosis becomes, the poorer the response to treatment tends to be.[10] Therefore, reliably determining onychomycosis severity could help predict and evaluate treatment response, and help choose the appropriate treatment approach.[9]

In **Part II** of this thesis, therapeutic challenges of onychomycosis are addressed. As illustrated by our case report in **Chapter 4**, the most effective treatment option, systemic

antifungal therapy, can potentially have serious side effects.[11] Understandably, patients and physicians may be reluctant towards oral treatment.[5,12] Topical treatment could avoid this concern since side effects from topical antifungals are mostly absent and, if they develop, are usually limited to localized redness, mild discomfort, or temporary colour changes.[13] Hence, to support the search for effective alternatives to systemic treatment, our **second aim** was to **evaluate the efficacy of topical antifungals** available in Dutch general practice. This topic was also considered relevant by the Dutch College of General Practitioners due to the lack of evidence on topical treatments in Dutch general practice and was put on the National Research Agenda of the Dutch College of General Practitioners in 2018.[14] Topical treatments of interest in the Dutch setting would be miconazole (Daktarin®), which is readily available, and amorolfine (Loceryl®), which is available in surrounding countries but is more practical in its use, only requiring a once or twice-weekly application.[15-17] However, both topical antifungals were not previously well studied, i.e., in comparative and randomized trials.[13] Therefore, to determine whether topical treatments in the Dutch setting could effectively treat or at least improve onychomycosis, we conducted a randomized, double-blind, placebo-controlled trial discussed in **Chapter 5.**

Finally, focusing on the prognosis and implications of onychomycosis in **Part III**, our **third aim** was to **explore the potential impact** of onychomycosis in Dutch general practice, especially since onychomycosis is often seen as a harmless inconvenience and therefore could mistakenly be dismissed as a merely cosmetic concern.[5] However, looking more closely at the impact of onychomycosis on patients' well-being, several studies indicate that onychomycosis can cause a considerable burden and negatively affect a patient's quality of life.[18,19] Previous studies also suggest that onychomycosis could increase the risk of complications, particularly ulcer development and infectious complications in patients with diabetes.[20-23] Identifying patients at risk of complications at an early stage could reduce the impact and potentially prevent ulcerative complications of onychomycosis in primary care.[21,24] However, the previously suggested association between onychomycosis and ulcerative complications is primarily based on data from hospitals and specialized clinics.[20,25] To study **the association between onychomycosis and ulcerative complications in patients with diabetes** in general practice, we performed a large retrospective cohort study using routine-care data from the Dutch general practices affiliated with the LUMC through the Extramural Leiden Academic Network (ELAN), described in **Chapter 6**.

RESEARCH PRIORITIES

In summary, this thesis had three main research priorities:

1. To **identify and evaluate diagnostic challenges** by answering two questions: to what extent onychomycosis can be clinically diagnosed without confirmatory testing, and if onychomycosis severity can be reliably assessed in general practice;
2. To answer the question for Dutch general practitioners if **topical antifungal treatment could be effective** for treating mild to moderately severe onychomycosis using topical antifungals available in Dutch general practice as an alternative to systemic antifungals;
3. To study **the association of onychomycosis** with ulcerative complications in patients with diabetes, thereby investigating onychomycosis as a clinically important **prognostic risk factor** as opposed to a cosmetic concern.

STUDY SETTING AND FRAMEWORK

No specific theoretical model or conceptual framework was used for the studies in this thesis to answer our research questions. However, one could take the clinical setting of a typical Dutch general practice as the basic ground for the conceptual framework for this thesis, since this is the setting where a patient with a nail problem would typically present. The initial questions would likely concern the diagnosis: "What is it that I have? Could it be a fungal nail infection or something else?". Subsequently, questions regarding treatment would be addressed: "If so, what can be done about it?". Another type of question that could be considered by the practitioner but is also relevant to the patient, would be regarding the prognosis i.e. progression over time and potential consequences: "Can it resolve spontaneously? Does it have any (long-term) negative effect? And if so, would this justify a different approach to treatment or follow-up?".
The framework described above provides an important context that should be taken into consideration when comparing our study results to those of other researchers, especially when other studies are performed in different settings or under different circumstances.

ACCURACY OF THE CLINICAL DIAGNOSIS OF ONYCHOMYCOSIS

Summary of findings

In **Chapter 2**, we evaluated the extent to which Dutch general practitioners are able to clinically diagnose onychomycosis through the evaluation of 137 standardized, high-resolution photographs from patients screened for the Onycho Trial. We found a positive predictive value, i.e., a correct clinical diagnosis in 74.5% of cases, which means

a substantial risk of 25.5% of making a false positive diagnosis. A false positive diagnosis could lead to overtreatment and unnecessary exposure to antifungal treatment.

Comparison with previous literature

Comparing our results to previous diagnostic studies, Li et al. found an overall accuracy of 75.4% for the clinical diagnoses of onychomycosis.[7] Their clinical diagnosis was mostly performed by dermatologists and podiatrists, and to a lesser extent by other physicians, including orthopedic surgeons and internal medicine specialists. General practitioners were not included in this study. Kuijpers and Tan found a higher clinical accuracy of 93% for dermatologists and 81% for general practitioners.[6] Because only the samples of patients suspected of having onychomycosis were sent for analyses, selection bias could have caused an overestimation of their results. Overall though, our results were comparable to those previously reported and support a substantial risk of overdiagnosis when making a diagnosis of onychomycosis based on history and physical examination alone, i.e., without confirmatory testing.

Methodological limitations

The most important limitation of our study was that patients were included as part of a clinical trial. These patients were already pre-screened and designated as potential candidates, increasing the prevalence of onychomycosis in the study sample. However, at that point, observers were not only focused on distinguishing onychomycosis from other nail-related diseases but also on deciding whether or not a patient could be included in the trial. In case of doubt, the observers may have been inclined to opt for onychomycosis as the most likely diagnosis despite possible doubt. In addition, the observers were only given standardized photographs and, hence, could not take the history or perform the physical examination themselves, which normally provides important context for establishing the most likely diagnosis. Both situations could have led to an underestimation of true positive predictive values. To prevent these types of bias, all patients with any type or form of nail abnormality would need to be included and physically examined by each observer to more accurately evaluate the true diagnostic accuracy of the clinical diagnosis of onychomycosis. Another limitation regarding the differential diagnosis was the fact that we were unable to establish the diagnosis in case of negative confirmatory testing due to the exclusion of these patients from the trial without further diagnostic evaluation. Regarding the confirmatory testing procedure, we used a standardized work-up method combining three confirmatory tests to optimize sensitivity. However, overall sensitivity can never be 100%. The inevitable risk of false negative laboratory test results caused by sampling errors, for example, could have decreased our positive predictive values, potentially underestimating the true positive predictive value of the clinical diagnoses performed by general practitioners as well. However, due to the use of a comprehensive diagnostic work-up and standardized sampling performed by well-trained and instructed staff, we argue that the risk of sampling errors causing false negative test results was limited. Finally,

as mentioned in the introduction, the differential diagnosis of onychomycosis is broad and most likely includes nail trauma, psoriasis, onychogryphosis, and eczema, but also includes less common nail diseases such as lichen planus, paronychia congenita, or yellow nail syndrome, amongst many more.[26] Especially for those cases with a false positive clinical diagnosis and negative confirmatory test results, it would have been very interesting to have known the actual nature and diagnosis of the nail disorder, not being onychomycosis.

RELIABILITY OF THE ONYCHOMYCOSIS SEVERITY INDEX IN DUTCH GENERAL PRACTICE

Summary of findings

Quantifying the severity of onychomycosis was the subject of **Chapter 3**. To quantify onychomycosis severity, Carney et al. developed a classification tool, the Onychomycosis Severity Index (OSI).[9] To establish the reliability of the OSI scores when applied in general practice, we compared OSI scores between the independent observers (interobserver reliability) and the individual observers' repeat scores (intra-observer reliability). The intraclass-correlation coefficient (ICC), in this case expressing interobserver reliability, was calculated for 280 observations and showed poor reliability (ICC 0.578). The intra-observer reliability, based on repeat scores from the same observer for 80 observations, thus representing the reliability of the OSI when used repeatedly by the same observer, was moderate (ICC 0.650). This study showed that the OSI is insufficient for clinical use in general practice, i.e., to base clinical decisions on without further adjustment or simplification of the index that would increase the reliability.

Comparison with previous literature

As mentioned, Carney et al. were the first to propose and validate this quantification tool by letting two groups of dermatologists, including the authors, assess different pictures of onychomycotic toenails. In contrast to our findings, Carney reported high-reliability values with an ICC of 0.95 and 0.93 based on two validations, respectively. This discrepancy could have originated from two important differences in assessment compared with our study. First, the observers were all dermatologists who received additional training and specific instructions from the authors during the scoring process. Secondly, the statistical details on ICC calculations or settings, if you will, were not reported by Carney et al. This is important because these settings highly influence the ICC values calculated. The settings consist of various statistical options regarding the definition of three important components that make up the ICC: the 'model', 'type', and 'definition'.[27,28] The 'model' defines the characteristics of the observers, which affects the generalizability of the ICC results. The 'type' determines whether single measures or means are compared. The 'definition', finally, represents either the absolute agreement or consistency between the observed values. The chosen settings should represent the

clinical use and purpose of the instrument investigated. The standard statistical settings, for example, in SPSS, are usually preprogrammed to compare means and consistency, generating substantially higher ICC values than when single measures and absolute agreement would be selected. Intending to use the OSI as a clinical measuring tool that would influence treatment and follow-up decisions, we argue that the settings applied in our analyses comparing absolute agreement between single measures were necessary to calculate representative ICC results for this purpose. Using standard ICC settings would have substantially increased our ICC results, which could have been the case for the results reported by Carney et al.[28]

Methodological limitations

The most important limitation of our study was that the observers were unable to examine the patients in real-time or have additional photographs in a frontal-oblique orientation to evaluate subungual hyperkeratosis, i.e., nail thickening of >2 mm. This is relevant because the OSI score is based on three aspects: the percentage of the nail involved (0-5 points), the distance of involvement towards the root of the nail (0-5 points), and the existence of more severe involvement as represented by either subungual hyperkeratosis or the accumulation of fungal material called dermatophytomas (0 or 10 points). The score is calculated by multiplying the first two items and, if present, adding 10 points in case of severe involvement, leading to a potential total of 35 points. Hence, the presence of subungual hyperkeratosis can have a relatively large effect on the overall score. Although the observers from Carney et al. did not use direct frontal pictures, they had more detailed, slightly oblique photographs, facilitating the evaluation of nail thickening. We used standardized pictures only from above, making the evaluation of subungual hyperkeratosis more challenging but not impossible (Figure 1). Nonetheless, the most optimal situation would have been to perform an independent and individual physical examination on each participant by each observer, which was not feasible in our study.

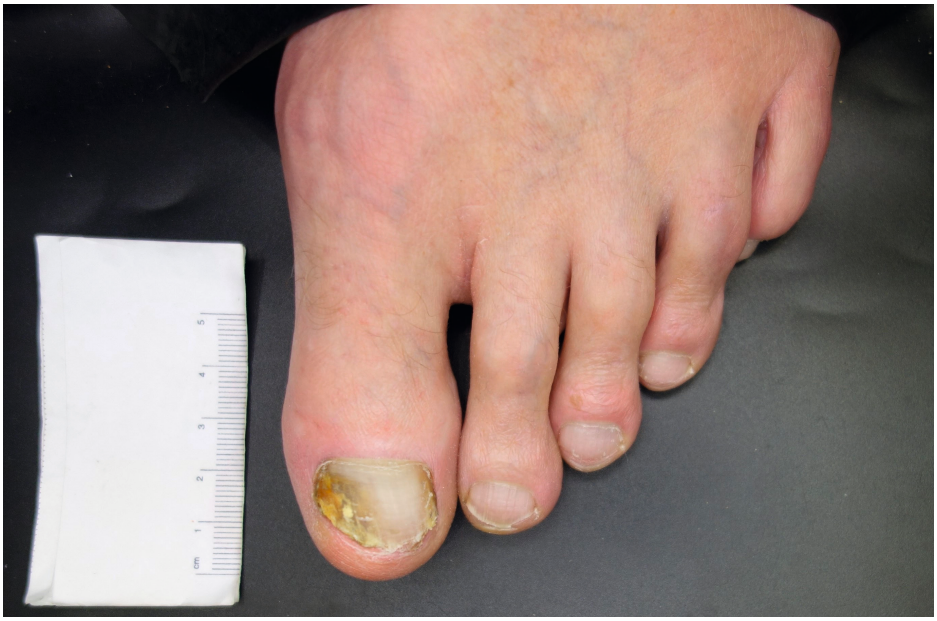

Figure 1 Example of a standardized picture

Furthermore, in contrast to the validation of Carney et al., our observers did not receive additional training, which could have contributed to the lower reliability results found in our study. On the other hand, the OSI was designed to be a simple quantification tool that, according to the developers, should be easily applicable using the simple and clear instructions from the article. More importantly, however, if the OSI were to be introduced in Dutch general practice with over 10.000 active general practitioners diagnosing many more conditions other than onychomycosis on a daily basis, the implementation would likely be limited to written instructions or protocol. Personal training of all practicing GPs on a larger scale would not be feasible in daily practice.

ADVERSE REACTIONS FROM ORAL TERBINAFINE

Summary of findings

In **Chapter 4**, we illustrated that the currently most effective antifungal treatment for onychomycosis, oral terbinafine, can give serious side effects. This report describes a patient with a blank past medical history who was prescribed terbinafine for a mild case of onychomycosis and developed a severe drug eruption in the form of exfoliative dermatitis that warranted the discontinuation of terbinafine, specialist consultation, and additional anti-inflammatory treatment with prednisolone.

Comparison with previous literature and limitations

A post-marketing surveillance study reported an overall incidence rate of adverse reactions from oral terbinafine of 10.5% of which gastrointestinal side effects were the most common (4.9%), followed by adverse skin reactions (2.3%).[29] Only 11 cases (0.04%) were considered serious adverse reactions, including cases of toxicoderma and cholestasis. Other more frequently reported and less severe side effects include headaches, flu-like symptoms, and gastrointestinal symptoms.[10,30] Our case report is an example of a more serious but transient adverse dermatologic reaction. Overall, the scientific literature regarding the more serious adverse reactions from oral terbinafine, of which hepatic failure is the most feared, is limited to case reports and case series where the adverse events primarily occurred in patients with underlying liver disease or comorbidities that increased their susceptibility.[11,31-34] In addition, adverse hepatic reactions are mostly limited to transient elevations of liver function tests that normalize after cessation of treatment, occurring in 3.3 to 7% of patients.[30,35-37]

Inherent to most case reports, ours discussed only one patient and was primarily aimed at describing a potentially serious side effect to illustrate the reason why patients and practitioners might be reluctant towards oral treatment. The case report does not provide information on the likelihood of such adverse events. Therefore, a short literature review was added.

EFFICACY OF TOPICAL MICONAZOLE OR AMOROLFINE FOR ONYCHOMYCOSIS

Summary of findings

The efficacy of topical miconazole and amorolfine was compared with placebo in the Onycho Trial discussed in **Chapter 5**. In total, 111 patients with mild to moderately severe onychomycosis were included and randomly allocated to one of the three double-blinded treatment arms. The outcome after six months of treatment showed that none of the participants in the antifungal groups reached complete cure. Only one patient in the amorolfine group reached clinical cure, and three patients in both treatment arms reached mycological cure, as opposed to 10 patients in the placebo group. There was no significant difference between the treatment groups regarding complete or clinical cure. Interestingly, our placebo was more effective than miconazole and amorolfine in reaching mycological cure and clinical improvement. However, this was not the case in the per-protocol analysis, taking therapy compliance into account. Therefore, we concluded that patients with onychomycosis in Dutch general practice should not be prescribed topical miconazole or amorolfine.

Comparison with previous literature

The efficacy of topical treatments for onychomycosis was previously evaluated in a comprehensive Cochrane review by Foley et al. in 2020.[13] However, amorolfine and

miconazole were not included due to the lack of comparative, placebo-controlled studies. The Onycho Trial was the first randomized, placebo-controlled trial to evaluate miconazole and amorolfine tinctures. Regarding amorolfine, previously reported cure rates were only available from studies that used amorolfine as a comparator to other antifungals. Complete cure rates ranged from 0.9% to 12.6%, clinical cure rates from 1.9% to 16.9%, and mycological cure rates from 15.7% to 33.8%. Hence, overall better than what we found.[16,38] Only the study of Vanderdonckt et al. and Achten et al. previously investigated topical treatment with miconazole 2% tincture, but in non-comparative studies, i.e., without a control group.[39,40] Vanderdonckt et al. reported a complete cure rate of 15 out of 20 nails (75%), but the study of Achten et al. could not calculate cure rates because of missing data due to the loss of follow-up. In addition to these two studies, Haneke et al. compared miconazole cream to oral itraconazole and found a mycological cure rate of 60%.[41] Overall, we were optimistic about the potential effects of amorolfine and miconazole in advance and expected they would potentially be able to cure or at least improve milder cases of onychomycosis.

Methodological limitations

Compared to previous trials included in the Cochrane review and mostly conducted over the course of 48-52 weeks, the Onycho trial had a relatively short treatment period of 24 weeks (6 months). Given the slow growth of toenails, achieving complete cure within this period could be considered a challenge.[42] However, previous studies on topical antifungal treatments showed significant clinical improvement and mycological cure after 6 months.[13] In addition, we argued that most patients in daily practice would likely not adhere to therapy without seeing any improvement, especially after 6 months. A second methodological limitation was that certain selection criteria used, excluded specific patient groups, in particular diabetic patients on metformin, due to the potential interaction of metformin with azoles, although unlikely to occur in daily practice.[43] Since patients with diabetes are at increased risk of developing onychomycosis and complications, the efficacy of topical treatment in this group would have been interesting to evaluate.[20-22,44] The rather surprising finding that our placebo was more effective in reaching mycological cure and clinical improvement than the topical antifungals prompted us to review the literature about possible antifungal effects of the placebo compounds, mainly denatonium benzoate. Again, we did not find literature suggesting substantial antifungal properties of denatonium benzoate.[45-49] Important to note is that clinical improvement and mycological cure were also found in the placebo groups of other previous trials, suggesting the possibility of spontaneous improvement and cure.[13] Furthermore, in contrast to the intention-to-treat analyses, the per-protocol analyses of therapy-compliant patients did not show any significant differences between the groups, implying that compliance could have played a role as suggested by the lower therapy compliance and higher loss to follow-up in the miconazole group compared to the placebo group as treatment incompliance would lower the chances of treatment success.

ASSOCIATION BETWEEN ONYCHOMYCOSIS AND ULCERATIVE COMPLICATIONS IN PATIENTS WITH DIABETES

Summary of findings

Finally, in **Chapter 6**, the association between onychomycosis and ulcerative complications in patients with diabetes in Dutch general practice was studied in a longitudinal retrospective cohort design. The diagnosis of diabetes was defined as the start of the follow-up period. In total, 48.212 of 50.292 available records could be included for analyses with a median follow-up time of 10.3 years (IQR 10.8). During follow-up, 4.1% of all patients in our cohort developed onychomycosis, and 5.7% of all patients developed an ulcer. In our final multivariate Cox proportional hazards model, including all risk factors and confounders available in our dataset, onychomycosis independently and significantly was associated with ulcer development (Hazard Ratio [HR] 1.23, 95% Confidence Interval [CI] 1.01 to 1.49), minor surgeries (HR 1.32, 95% CI 1.16 to 1.51), and bacterial skin infections (HR 1.27, 95% CI 1.10 to 1.48). This study therefore showed that onychomycosis is independently associated with ulcerative- and other clinically important complications in patients with diabetes in Dutch general practice.

Comparison with previous literature

The study by Boyko et al. prospectively showed a higher HR of 1.58 from onychomycosis for developing an ulcer in diabetic veterans after a median of 3.4 years of follow-up.[21] The study of Monteiro et al. showed a comparable HR of 1.22 for patients attending a diabetic foot clinic at a tertiary hospital with a median follow-up of 2.1 years.[50] Both studies were conducted in different populations, likely having a higher a priori risk of developing complications. Also, the follow-up times in both studies were noticeably shorter compared to our median follow-up time of 10.8 years, but this would not have influenced the values of the association measures reported. Despite other studies being conducted in different study populations, the results previously reported were comparable to ours. Our cohort study, therefore, confirmed the independent association between onychomycosis and ulcerative complications, also for patients with diabetes in primary care.

Methodological limitations

The most important methodological limitation of our study was the fact that we used routine care data consisting primarily of ICPC codes and the corresponding dates of registration. These data have limited accuracy, mostly because of registration inconsistencies, since these data are collected as part of the routine care process as opposed to a focused, standardized registration in a prospective cohort design. Using routine care data could have introduced an important reporting bias of patients more prone to developing complications. These patients tend to have a larger burden of disease and more comorbidities, and therefore are more likely to visit their general practitioner. Using routine-care data, therefore, may have led to an overrepresentation

of patients at increased risk of developing complications, thereby overestimating the association. In contrast, patients with onychomycosis with little or no symptoms or comorbidities have a much lower risk of developing complications. Since these patients are less likely to attend to their physician, they are underrepresented in our study. However, as these patients are not likely to have been misclassified as having onychomycosis when in fact they did not, the association between onychomycosis and ulcer development found in our study was probably not affected by this issue.

RECOMMENDATIONS FOR DAILY PRACTICE

Overall, the studies included in this thesis underscore the persisting challenges regarding the diagnosis, the treatment, and the potential consequences of onychomycosis in Dutch general practice.

Firstly, regarding the diagnostic process, onychomycosis has a substantial differential diagnosis, ranging from post-traumatic nail changes and psoriasis to less frequent lichen planus or onychogryphosis. Hence, making a correct diagnosis is not always straightforward, and we have shown that there is a substantial risk of mis- or overdiagnosis without confirmatory testing. This could lead to overtreatment and unnecessary exposure to oral antifungals. This is especially important considering the risk of adverse effects as illustrated by our case report. Therefore, our **first recommendation** would be to consider confirmatory testing early, in particular in case of doubt or if patients are not responding to treatment already started, especially when oral treatment is considered.

Secondly, dismissing onychomycosis as merely a cosmetic concern for everyone affected in general would be short-sighted. Not only did we confirm that onychomycosis is a significant risk factor for ulcerative complications in patients with diabetes, but the majority of the Onycho Trial participants, although a selection of the more affected individuals, reported a substantial burden from having onychomycosis as well. That many patients consider onychomycosis as something they want to get rid of was also reflected by the high response rate during the recruitment phase. Several participants were even willing to travel long distances, even though we were unable to offer any remuneration because of the limited resources. These observations underscore the actual burden patients experience from their onychomycosis and indicate their desire to find an effective treatment. Therefore, our **second** and possibly obvious **recommendation** would be to first and foremost take the patient seriously and inquire about their perceived burden. Even if the focus of concern is primarily cosmetic in nature, this does not mean that onychomycosis does not affect the patient's daily life. One might argue that this in itself could justify an adequate treatment.

As far as treatment modalities are concerned, topical antifungals miconazole and amorolfine should not be recommended in general practice: they were not effective in reaching clinical cure, or mycological cure, nor did they significantly improve symptoms or burden. Although disappointing for our patients, these findings may prevent false hope and unnecessary costs. Other topical antifungals investigated in previous trials might have shown significantly better results compared to placebo, but reported absolute cure rates were still very low (4.1-16.2%) and substantially lower when compared to oral treatment. Therefore, our **third recommendation** would be not to prescribe topical antifungals available in Dutch general practice. If the situation requires and allows, oral antifungal treatment is currently the best option as long as the diagnosis is clear and potential adverse reactions, drug-drug interactions, and contraindications are taken into account and discussed with the patient. It must be emphasized that this is by no means a plea to empirically treat all cases of onychomycosis with oral antifungals. Discussing the necessity of treatment with the patient in the first place is pivotal. In addition, confirmatory testing should be considered in advance, especially in cases where there might be doubt about the diagnosis.

Finally, since we were able to confirm the independent and significant association between onychomycosis and ulcerative complications in general practice, our **fourth recommendation** would be to include the screening for onychomycosis during the routine care for patients with diabetes in general practice, adding this more prominently to the guideline of the Dutch College of General Practitioners for Diabetes Mellitus type 2.

Based on our findings, previous research, and literature we reviewed, and considering these findings in light of the Dutch general practice setting, a flowchart was designed to illustrate and guide the approach to a patient with an abnormal-looking nail suspected of being onychomycosis that would typically present to the general practitioner. It also incorporates the diagnostic, therapeutic, and prognostic considerations laid out in this thesis (Figure 1).

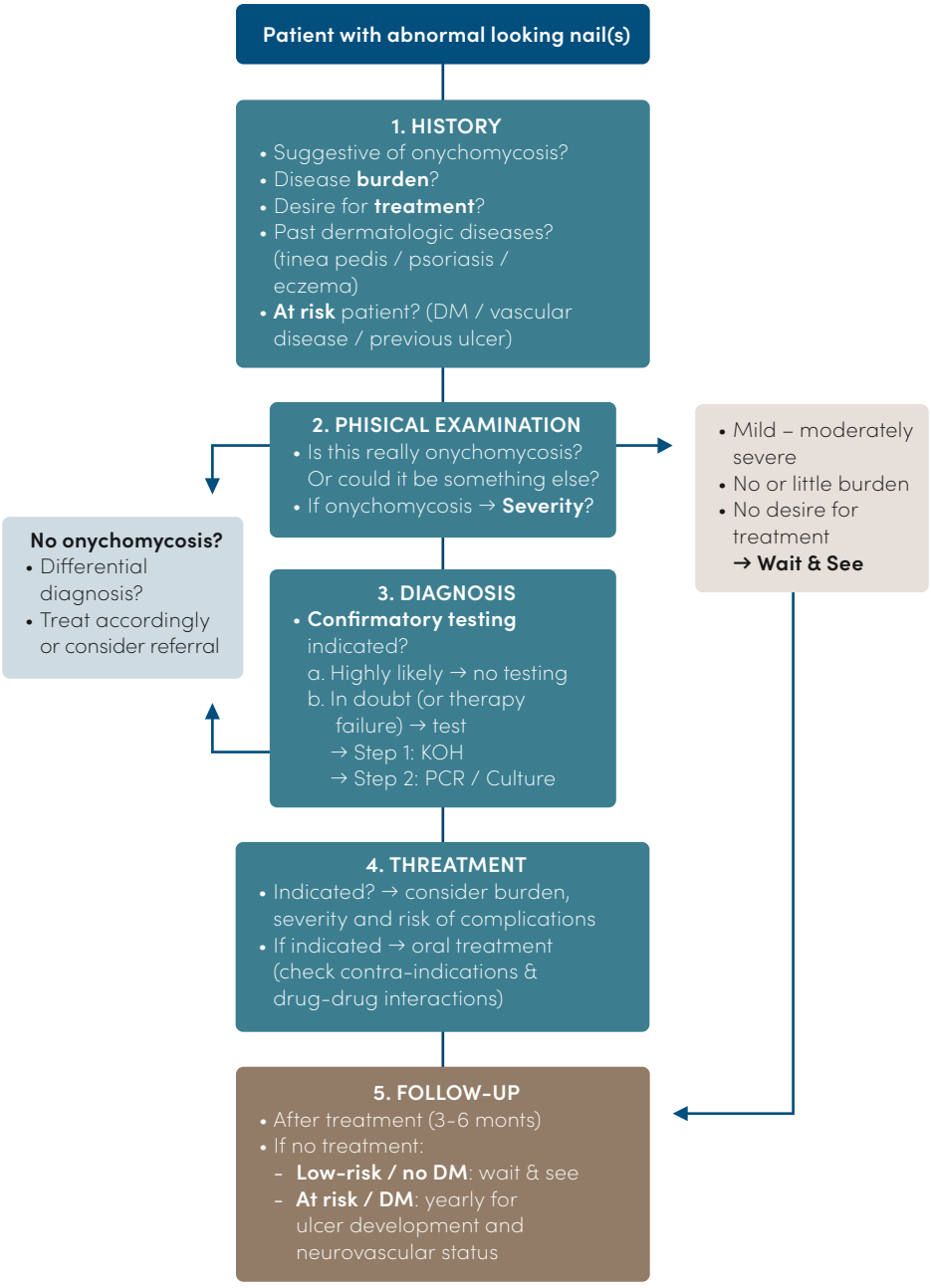

Figure 1 Recommendations for daily practice based on this thesis
The differential diagnosis of onychomycosis (Step 3) includes but is not limited to, nail trauma, nail psoriasis, onychogryphosis, lichen planus, and eczema. DM = diabetes mellitus, KOH = potassium hydroxide microscopy, PCR = polymerase-chain-reaction

FUTURE RESEARCH

Considering the diagnostic challenges identified in **Part I**, future studies aimed to improve the accuracy of the clinical diagnosis should ideally be set up prospectively. To reduce the risk of selection bias and, in addition, provide information about other nail diseases presented in general practice, such diagnostic studies would need to include patients with any type of nail abnormality. The general practitioners would need to be asked about their most likely diagnosis and differential diagnosis based on history and physical examination. The final diagnosis should ideally be confirmed, for example, by additional dermatologic evaluation, especially if not suspected of being onychomycosis. This would give an important insight into the prevalence and specific clinical features of nail disorders other than onychomycosis and would help the general practitioner distinguish onychomycosis from other nail diseases. Regarding the quantification of onychomycosis severity in general practice, a modified severity index for use in general practice could be developed, taking the findings of our study into account, and subsequently tested in a prospective study design. This could potentially increase the accuracy and thereby the clinical relevance of such a modified severity scoring tool.

Regarding the therapeutic challenges addressed in **Part II**, future trials should take the generally poor penetration of antifungal agents in the nail and its deeper layers into account.[51] According to the underlying theory, two pathophysiological aspects are responsible: the biological characteristics of the nail material itself, which is a highly compact and keratinized structure, and the formation of a biofilm produced by the causative fungi, further reducing the susceptibility to topical antifungals.[52] Since the fungicidal potency of topical antimycotics such as miconazole has already been well established, for example, for the treatment of fungal skin infections, newer treatments could be aimed at improving the penetration of the nail and the degradation of the biofilm to improve the delivery of already established effective agents. Treatment modalities such as laser therapy and iontophoresis already tap into this concern by either avoiding the difficult penetration or improving it: laser therapy is aimed at destroying the fungi present in the deeper layers of the nail and nailbed by converting targeted light energy into heat;[53] Iontophoresis uses electrical current provided through an overnight patch to increase the permeability of the nail and to improve penetration of the additional topical antifungal medication applied.[54] However, as one can imagine, both of these examples of device-based treatments are less practical than the simple application of topical agents. In addition, sufficient evidence to either support or oppose these treatments is currently lacking.[13] Since overall treatment efficacy from topical antifungals up to now is modest at best, future research is still needed and should consist of randomized, comparative trials using similar or newer treatment modalities that take the poor penetration of nail tissue well into account. Regarding the many home remedies, such as the application of tea tree oil, mentholated ointment, or vinegar,

sufficient evidence from comparative, randomized study designs is still lacking.[13] The sometimes claimed successes of these remedies could well be the result of spontaneous improvement as suggested by the results found in the placebo groups, not only in our trial but also in previous trials, where mycological cure rates of up to 76% and complete cure rates of up to 9.1% were reported in the placebo groups, respectively.[13]

Finally, considering the implications of onychomycosis in patients with diabetes addressed in **Part III**, future studies would ideally be set up prospectively to prevent the concerns around the potential of reporting and selection bias as discussed in our cohort study. Because the association between onychomycosis and ulcerative complications in patients with diabetes is now also confirmed in primary care, an interesting next step would be to evaluate the effect of the treatment of onychomycosis in patients with diabetes on the risk of developing ulcerative complications over time. A clinical trial would be a suitable study design to compare the development of ulcerative complications between diabetic patients with onychomycosis who receive treatment with patients who do not, i.e., who receive a placebo. Since diabetic patients are currently well monitored through protocolized follow-up in Dutch general practice, conducting a trial in such a setting could be feasible if a sufficiently long follow-up time were possible. In addition, considering the increasing availability of, and access to routine healthcare data through initiatives such as the ELAN data network, not only the association between onychomycosis and the development of diabetic complications, but also similar associations between relevant health outcomes and other common skin and nail conditions in general practice could be studied in the near future.

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Appendices

Nederlandse samenvatting

Bibliography

PhD Portfolio

Curriculum Vitae

Dankwoord

NEDERLANDSE SAMENVATTING

Onderwerp en inhoud van dit proefschrift

Het onderwerp van dit proefschrift is schimmelnagels (onychomycose). Schimmelnagels zijn een probleem waarvoor de huisarts zeer frequent wordt geconsulteerd en eigenlijk is er voor de behandeling in de huisartspraktijk geen door goed wetenschappelijk onderzoek ondersteund advies beschikbaar. Dit proefschrift bestaat uit drie delen waar achtereenvolgens ingegaan wordt op de diagnostiek (**deel I**), de behandeling (**deel II**) en de prognose (**deel III**) van onychomycose in de huisartsenpraktijk. Het doel van dit proefschrift was om enkele praktische uitdagingen rond schimmelnagels op genoemde punten nader te onderzoeken. De context of setting waarin de onderzoeken van dit proefschrift zijn uitgevoerd is hierbij nadrukkelijk de eerstelijnsgezondheidszorg, specifiek de praktijk van de huisarts.

In **hoofdstuk 1** wordt allereerst onychomycose nader toegelicht om de lezer te voorzien van de nodige achtergrond informatie. In **deel I** worden vervolgens twee aspecten van de diagnostiek van onychomycose in de huisartsenpraktijk besproken. Aangezien vaak wordt aangenomen dat onychomycose gemakkelijk vast te stellen is zonder aanvullend laboratorium onderzoek, wordt in **hoofdstuk 2** eerst onderzocht in hoeverre de huisarts in staat is om onychomycose te diagnosticeren op basis van zichtbare nagelafwijkingen alleen, ten opzichte van, met aanvullend laboratorium onderzoek als gouden standaard. Vervolgens wordt in **hoofdstuk 3** geëvalueerd hoe betrouwbaar de Onychomycosis Severity Index (OSI) is wanneer deze gebruikt wordt door de huisarts. De OSI is een eerder ontwikkeld meetinstrument om de ernst van onychomycose vast te kunnen stellen voornamelijk bij onderzoek. Zo'n instrument kan echter ook van waarde zijn voor de praktijk, omdat de mate van aantasting van de nagel invloed heeft op de kans van slagen van een behandeling en op het verdere beloop.

In **deel II** staat vervolgens de behandeling van onychomycose centraal. In **hoofdstuk 4** beschrijven we een hevige huidreactie van een patiënt die een behandeling met tabletten terbinafine kreeg voor een relatief milde vorm van schimmelnagels. Het laat zien dat de behandeling van een kleine kwaal als onychomycose, een serieuze bijwerking kan geven. Dit kan een reden zijn waarom huisartsen en patiënten liever geen tabletten willen proberen maar iets anders, zoals een middel dat op de nagel zelf aangebracht moet worden. Een dergelijk lokaal middel heeft immers minder kans op bijwerkingen. Daarom hebben we in **hoofdstuk 5** de effectiviteit van twee potentiële lokale behandelingen voor schimmelnagels, miconazol (Daktarin®) en amorolfine (Loceryl®), vergeleken met een placebo.

Tot slot hebben we in **deel III**, **hoofdstuk 6**, de invloed van schimmelnagels op het ontwikkelen van een zweer (ulcus) en hieraan gerelateerde complicaties, zoals wondroos, bij patiënten met diabetes mellitus in de huisartsenpraktijk onderzocht.

Achtergrondinformatie over onychomycose

Onychomycose is een nagelaandoening waarbij de nagel geïnfecteerd is geraakt door een schimmel, vaak vanuit de omliggende huid tussen de tenen. Onychomycose wordt dan ook meestal veroorzaakt door schimmels die specifiek de huid en nagels kunnen infecteren, de zogenoemde dermatofyten. De belangrijkste, meest voorkomende dermatofyten die schimmelnagels veroorzaken zijn Trichophyton rubrum en andere Trichophyton soorten. Maar ook andere type schimmels kunnen onychomycose veroorzaken zoals gisten, vooral candida soorten en de zogenoemde non-dermatofyten zoals Aspergillus, zei het in mindere mate. Na de infectie en door de verdere groei en verspreiding van de schimmels, kunnen de aangedane nagels verkleuren, dikker worden en afbrokkelen. Vandaar de veelgebruikte term "kalknagels". Maar nagels kunnen ook om andere redenen verkleuren of veranderen, zoals door (eerdere) beschadiging, onderliggende huidaandoening zoals psoriasis of lichen planus, of bijvoorbeeld door verstoorde groei of een infectie met een bacterie zoals Pseudomonas. Er zijn dus veel verschillende nagelaandoeningen en een kalknagel wordt dus zeker niet altijd veroorzaakt door een schimmel. Anderzijds zijn schimmelnagels wel de meest voorkomende oorzaak van verkleurde nagels. Meer dan de helft van de nagels die er afwijkend uitzien, komt door schimmelnagels. Naar schatting heeft ongeveer 4.3-5.5% van de algemene bevolking in Europa en Amerika één of meerdere schimmelnagels. Bij mensen boven de 60 en mensen met een aandoening die de kans op schimmelnagels vergroot, zoals diabetes mellitus of vaatziekten, is dit percentage logischerwijs hoger.

Hoewel schimmelnagels voor de meeste mensen onschuldig zijn en weinig hinder veroorzaken, laten verschillende onderzoeken zien dat mensen met schimmelnagels wel degelijk meer hinder, d.w.z. klachten als ook een verminderde kwaliteit van leven ervaren dan mensen zonder schimmelnagels. Ook kunnen schimmelnagels vervelende problemen veroorzaken zoals ingegroeide nagels of bacteriële huidinfecties. Schimmelnagels zijn bovendien ook nog eens lastig te behandelen. Want zelfs na een volledige kuur van drie maanden met antischimmel tabletten is nog zeker niet iedereen van de schimmelnagels af, slechts zo'n 60-70%. Daarnaast is er een aanzienlijke kans dat men daarna toch weer een schimmelnagel krijgt van ongeveer 30% binnen drie jaar. Schimmelnagels bij voorbaat afdoen als een cosmetische bijzaak is dan ook iets te kort door de bocht.

Deel I - Diagnostiek

Nauwkeurigheid van de klinische diagnose onychomycose

Onychomycose wordt geacht vrij gemakkelijk vastgesteld te kunnen worden met het blote oog. Daarom adviseert de huidige richtlijn, de NHG-standaard Dermatomycosen, dat aanvullend onderzoek in principe niet nodig is. De richtlijn baseert zich hierbij op eerder onderzoek dat liet zien dat in meer dan 90% van de gevallen de diagnose

correct gesteld werd wanneer dit gecontroleerd werd met aanvullend laboratorium onderzoek naar schimmels. Dit percentage gold echter voor de dermatologen in dit onderzoek; voor huisartsen was dit 81%. Dit onderzoek stamt inmiddels uit de jaren '90. Daarom wilden wij de nauwkeurigheid van de klinische diagnose van onychomycose opnieuw onderzoeken. De resultaten hiervan worden beschreven in **hoofdstuk 2**.

Hiervoor konden wij gegevens van deelnemers aan de Onycho Trial gebruiken omdat bij iedere deelnemer werd vastgesteld of ze al dan niet een schimmelnagel hadden. Dit werd gedaan door gestandaardiseerde foto's, gemaakt met behulp van een mini foto studio Box, te beoordelen en vervolgens een stukje van de betreffende nagel op te sturen voor aanvullende onderzoeken (gouden standaard). Eerst werd op de afdeling Dermatologie van het LUMC een microscopisch onderzoek gedaan middels een zogenoemd KOH-preparaat waarmee schimmeldraden aangetoond kunnen worden. Vervolgens werd op de afdeling Medische Microbiologie een schimmel-DNA onderzoek gedaan (PCR-test) en zo nodig een kweek ingezet. Door de resultaten van deze drie aanvullende tests te vergelijken met het oordeel van de huisarts-onderzoekers aan de hand van de foto's, konden we berekenen in hoeveel van de gevallen de huisarts-onderzoekers het bij het juiste eind hadden. We vergeleken de uitkomsten van 137 deelnemers en berekenden dat in 74.5% van de gevallen de diagnose correct gesteld werd aan de hand van de foto's. In de andere 25.5% van de gevallen werd dus onterecht gedacht dat het een schimmelnagel was aangezien we géén schimmels bij deze groep konden aantonen middels aanvullend onderzoek. Eerder onderzoek door Li et al. toonde een vergelijkbaar resultaat met 75.4% bevestigde diagnosen. Het onderzoek van Kuijper en Tan, waar de NHG richtlijn aan refereert, liet echter betere resultaten zien voor zowel dermatologen (93%) als huisartsen (81%). Dit is mogelijk het gevolg geweest van een selectie van de meer verdachte gevallen, hoewel dit voor ons onderzoek natuurlijk ook het geval was omdat het deelnemers aan de Onycho Trial betrof.

Een belangrijke kanttekening van ons onderzoek was dat we alleen naar deelnemers van de Onycho Trial hebben gekeken. Omdat de onderzoekers misschien geneigd waren om bij twijfel toch de diagnose onychomycose te stellen teneinde de kans op deelname te vergroten, heeft dit mogelijk geleid tot een onderschatting van de daadwerkelijke nauwkeurigheid. Met andere woorden, huisartsen in de praktijk doen het wellicht beter. Daarnaast hadden de arts-onderzoekers alleen de foto's en konden zij de patiënten niet zelf bevragen, noch de nagels onderzoeken. In de praktijk geeft dit uiteraard belangrijke informatie om tot een juiste diagnose te komen. Tot slot en wellicht een gemiste kans, was dat bij de deelnemers die afvielen als er geen schimmels aangetoond konden worden, we niet hebben kunnen onderzoeken wat ze wel hadden. Dat was leerzaam geweest omdat het iets had kunnen vertellen over het voorkomen en de kenmerken van andere nagelaandoeningen in de huisartsenpraktijk.

Desalniettemin konden we met dit onderzoek stellen dat er een aanzienlijke kans bestaat dat iemand met een afwijkende nagel waarvan de huisarts vermoedt dat het om onychomycose gaat, iets anders heeft. Als de huisarts dergelijke patiënt zou behandelen zonder de schimmelinfectie te bevestigen met aanvullend onderzoek, zou dit leiden tot onterechte behandelingen. Daarom moeten we in de praktijk rekening houden met bovenstaande bevindingen en bij gerede twijfel toch aanvullend onderzoek verrichten wanneer behandeling overwogen wordt.

Betrouwbaarheid van de Onychomycosis Severity Index

Het vaststellen van de ernst van onychomycose wordt vooral gedaan in het kader van onderzoek, bijvoorbeeld om het effect van een nieuwe behandeling te meten. Carney et al. ontwikkelden hiervoor een score, de Onychomycosis Severity Index (OSI) om de ernst te bepalen met een getal van 0 (geen schimmelnagel) tot 35 (de hoogste mate van aantasting). Een dergelijk meetinstrument is interessant omdat de ernst van onychomycose van invloed is op de kans van slagen van een behandeling. Daarnaast zou dit in de praktijk gebruikt kunnen worden om het effect van een behandeling en het beloop over de tijd te vervolgen.

De onderzoekers van Carney hadden de betrouwbaarheid van hun score wel onderzocht door meerdere beoordelaars dezelfde foto's voor te leggen en te kijken in hoeverre hun scores overeen kwamen, maar de beoordelaars waren vrijwel allemaal dermatologen. Daarom wilde we de betrouwbaarheid van deze OSI onderzoeken in de huisartspraktijk, waarbij de OSI dus gebruikt zou worden door huisartsen. Dit onderzoek staat beschreven in **hoofdstuk 3**.

Wij vergeleken 280 OSI scores van drie onafhankelijke beoordelaars, twee huisartsen en een huisarts in opleiding, met elkaar om de onderlinge betrouwbaarheid vast te stellen. Daarnaast vergeleken we 80 herhaalde scores van iedere beoordelaar individueel, om zo deze vorm van betrouwbaarheid vast te stellen. De bijbehorende waarden, intraclass-correlation coefficients (ICC) genoemd, van 0.58 en 0.65, respectievelijk, waren echter aanzienlijk minder dan die van Carney et al. die betere resultaten vonden (ICC 0.93 en 0.95). Ter referentie, ICC waarden <0.50 worden gezien als een indicatie voor slechte betrouwbaarheid, 0.50-0.75 als matig, 0.75-0.90 als goed, en >0.90 als uitstekend. Op basis van onze bevindingen zouden we de OSI in de huidige vorm dan ook niet kunnen aanbevelen voor gebruik in de huisartsenpraktijk, ermee rekening houdend dat beslissingen rondom eventuele behandeling hierop gebaseerd zouden worden.

De manier van berekenen van de betrouwbaarheid heeft mogelijk bijgedragen aan het verschil met de resultaten van Carney et al., waarbij wij waarschijnlijk strengere eisen hebben gesteld aan de berekeningen dan Carney et al. De informatie hierover in het artikel van Carney et al. ontbreekt echter, waardoor we dit niet met zekerheid

kunnen vaststellen. De manier waarop in ons onderzoek de betrouwbaarheid van de OSI is berekend, is echter zorgvuldig onderbouwd waarbij we rekening hebben gehouden met de manier waarop de OSI in de dagelijkse praktijk volgens ons gebruikt zou worden: namelijk als instrument waar daadwerkelijke beslissingen rondom behandeling en monitoring op gebaseerd zouden worden. Vandaar de door ons gekozen, waarschijnlijk strengere berekeningen. Verder hadden de beoordelaars in het onderzoek van Carney uitgebreidere uitleg en instructies gekregen dan bij ons onderzoek. Ook hadden ze aanvullende foto's (schuin van voren) waardoor zij wellicht beter in staat waren om bepaalde aspecten van de OSI score, met name de verdikking van de nagel te beoordelen. Met dergelijke aanvullende foto's hadden de beoordelaars in ons onderzoek waarschijnlijk beter de dikte kunnen bepalen met een hogere betrouwbaarheid tot gevolg. Los daarvan zouden onze resultaten waarschijnlijk ook beter zijn geweest als de nagels van de deelnemers direct, d.w.z. in levende lijve, beoordeeld hadden kunnen worden, hetgeen overigens in beiden onderzoeken niet het geval was.

Deel II - Behandeling

Een hevige huidreactie op terbinafine en andere mogelijke bijwerkingen

In **hoofdstuk 4** bespraken we een casus van een 49 jarige patiënt die voor een relatief milde schimmelnagel een behandeling kreeg met terbinafine tabletten. Een kuur met orale antischimmel medicijnen is vooralsnog de meest effectieve behandeling voor schimmelnagels. De patiënt in deze casus had een blanco medische voorgeschiedenis en kreeg ruim een week later een enorme huiduitslag met vervelling over zijn hele lichaam. Vanwege de hevigheid van het beeld werd niet alleen de medicatie gestaakt maar kreeg de patiënt ook een prednison stootkuur en werd hij verwezen naar de dermatoloog. Na drie weken waren de huidafwijkingen verdwenen. Hoewel deze casus een goed voorbeeld is van een vervelende bijwerking van terbinafine, geeft het uiteraard geen inzicht in welke soorten bijwerkingen en hoe vaak ze optreden in de huisartsenpraktijk.

Daarom hebben we als aanvulling op deze casus wetenschappelijke literatuur gescreend naar bijwerkingen van terbinafine. Een recent onderzoek rapporteerde dat zo'n 10% van de mensen last krijgt van bijwerkingen van terbinafine, voornamelijk van maag-darmklachten, hoofdpijn en huidreacties. De meer ernstige bijwerkingen van de huid of lever worden veel minder vaak gezien en zijn meestal alleen beschreven in casuïstiek zoals de onze. Zo werden eerder een aantal gevallen van leverfalen beschreven, waarvan enkele zeer ernstig verliepen. Het ging daarbij meestal wel om mensen die al bepaalde leverproblemen hadden, al dan niet onderkend. Hoewel ze dus zeldzaam zijn, kunnen dergelijke ernstige gevallen voor zowel patiënten als huisartsen wel een aanleiding vormen om terughoudend te zijn met het gebruik van terbinafine. Verder vonden we in een overkoepelend onderzoek dat tussen 3.3 en 7%

van de patiënten te maken krijgt met stoornissen in de leverwaarden, vaak alleen te zien in het bloedonderzoek. Deze afwijkingen herstelden overigens na afronding of eerder staken van de kuur weer spontaan, zonder verdere consequenties voor de patiënt. Al met al vonden we dat de kans op ernstige bijwerkingen van terbinafine bij mensen zonder leverproblemen erg klein was (<0.1%) en dat het in de meeste gevallen dus veilig gebruikt kan worden.

Effectiviteit van behandeling met miconazol of amorolfine versus placebo
Het onderzoek van dit proefschrift dat betrekking heeft op de lokale behandeling van schimmelnagels staat beschreven in **hoofdstuk 5.** Vanwege potentiële bijwerkingen van tabletten voor schimmelnagels, zoals beschreven in onze casus voor terbinafine, bestaat er interesse in andere behandelopties. Het gaat dan vooral om middelen die op de nagels zelf aangebracht of toegepast kunnen worden c.q. lokale middelen zoals crèmes of nagellakken. Eerdere onderzoeken toonden aan dat bepaalde lokale antischimmelmiddelen zoals efinaconazol, tavaborol en ciclopirox, daadwerkelijk beter zijn dan een placebo. De kans dat iemand met een dergelijke behandeling geneest, wisselde echter sterk per middel en over het algemeen is die kans aanzienlijk minder groot dan met tabletten. Desalniettemin lieten deze onderzoeken zien dat een deel van de schimmelnagels dus wel konden genezen of in ieder geval verbeteren: bij 30-95% was de schimmel na behandeling verdwenen op basis van het laboratorium onderzoek en 4-16% had een normale nagel na de behandeling.

Twee van dergelijke middelen die voor Nederland relevant zouden zijn, waren echter nog niet goed onderzocht. Het ging hierbij om miconazol (Daktarin®), een middel dat in Nederland veel gebruikt wordt, en amorolfine (Loceryl®) wat verkrijgbaar is in omringende landen maar praktischer in gebruik is dan miconazol vanwege de wekelijkse toepassing in plaats van dagelijks gebruik. Bij gebrek aan wetenschappelijk bewijs kon de huidige richtlijn geen goede aanbevelingen doen wat betreft deze lokale middelen. In 2018 werd dit punt al opgemerkt en als kennislacune toegevoegd aan de Nationale Onderzoeksagenda Huisartsgeneeskunde. Zodoende hebben we een geneesmiddelenonderzoek opgezet om de effectiviteit van lokaal miconazol of amorolfine te vergelijken met een placebo door middel van een zogenoemde gerandomiseerde, dubbelblinde trial, de gouden standaard voor dergelijk geneesmiddelen onderzoek. Gerandomiseerd wil zeggen dat de deelnemers willekeurig verdeeld worden over de behandelgroepen. Dubbelblind wil zeggen dat zowel de deelnemers als de onderzoekers niet weten wie welk middel krijgt.

Voor ons onderzoek includeerden we 111 deelnemers met milde tot matig-ernstige schimmelnagels en bekeken vervolgens per groep hoeveel mensen na de behandeling van 6 maanden genezen waren, zowel zichtbaar als op de aanwezigheid van schimmels in het aanvullende laboratorium onderzoek. Daarnaast keken we ook naar de verschillen in eventuele verbetering, symptomen, bijwerkingen en de therapietrouw.

Het resultaat was dat niemand die miconazol of amorolfine had gekregen volledig was genezen na 6 maanden. Slechts één patiënt in de amorolfine groep had een volledig normale nagel na de behandeling. Statistisch was er geen verschil in volledige genezing tussen de groepen. Deelnemers in de placebo groep hadden zelfs iets vaker dat er géén schimmels meer gevonden werden in het laboratorium onderzoek en ook vaker zichtbare verbetering na zes maanden dan de deelnemers die één van de antischimmelmiddelen hadden gekregen. De overige uitkomsten verschilden niet tussen de groepen.

Een mogelijke verklaring voor deze gesuggereerde genezing door de placebo, kan zijn dat een deel van deze groep spontaan verbeterde, dus uit zichzelf en niet door de placebo. In eerdere trials werd dit namelijk ook al beschreven met soms aanzienlijke aantallen deelnemers die genazen in de placebo groep, variërend van 6.2% zichtbare genezing tot 29.3% genezing qua schimmels in het laboratorium onderzoek. Dat onze placebo met als belangrijkste bestanddeel de bittere stof denatoniumbenzoaat, daadwerkelijk schimmeldodende werking zou hebben, leek ook niet heel waarschijnlijk op basis van de literatuur die we hierover konden vinden. Daarnaast zagen we dat deze verschillen ook niet meer aanwezig waren wanneer de deelnemers eruit gefilterd werden die minder therapietrouw waren geweest. Mogelijk waren er dus relatief meer mensen in de antischimmel groepen die minder goed hun medicatie hadden gebruikt waardoor hun kans van slagen dus ook lager is geworden. Dit konden we echter niet objectief vaststellen omdat we alleen de door de deelnemers zelf gerapporteerde gegevens hierover hadden. Een andere kanttekening van dit onderzoek was dat onze behandeling van zes maanden relatief kort was ten opzichte van andere onderzoeken die vaak een jaar duurde. Omdat eerdere resultaten van andere lokale middelen al verbetering en genezing na zes maanden lieten zien, en omdat we verwachtten dat mensen toch niet doorgaan met een behandeling als ze na een half jaar nog steeds geen vooruitgang zouden zien, was het wat ons betreft niet zinvol om deze behandelperiode langer te maken. Ook als we naar onze resultaten na zes maanden kijken, lijkt de kans heel klein dat de middelen die wij onderzochten na een jaar wél effectief zouden worden. Ondanks bovenstaande kanttekeningen, kunnen we op basis van de resultaten wel voldoende zeker concluderen dat lokale behandeling met miconazol of amorolfine voor mild tot matig-ernstige schimmelnagels maar beperkt effectief is en zodoende niet aanbevolen zou moeten worden.

Deel III - Prognose

De associatie tussen onychomycose en diabetische complicaties

In het laatste onderzoek, beschreven in **hoofdstuk 6**, wilden we nagaan of schimmelnagels bij patiënten met diabetes in de huisartspraktijk de kans op het ontstaan van een zweer (ulcus) en hieraan gerelateerde complicaties vergroot. Dit hebben we gedaan door middel van het uitvoeren van een cohortonderzoek. In een

dergelijk onderzoek worden groepen patiënten over de tijd vervolgd en wordt gekeken wie een bepaalde blootstelling krijgt, in ons geval aan schimmelnagels, en wie er een bepaalde uitkomst ontwikkelt, in ons geval een ulcus. Op deze manier wordt de associatie tussen een blootstelling en uitkomst onderzocht. Men spreekt hier bewust van de 'associatie' (tussen schimmelnagels en ulcera) omdat een oorzakelijk verband met dit soort onderzoek niet kan worden aangetoond. Dat schimmelnagels en het ontstaan van ulcera bij diabeten met elkaar geassocieerd zijn, werd overigens al eerder al vastgesteld maar meestal in een andere onderzoekspopulatie en niet specifiek voor de huisartsenpraktijk.

Aan de hand van gecodeerde routine zorgdata van 48.212 patiënten met diabetes in onze regio, beschikbaar via het Extramuraal LUMC Academisch Netwerk (ELAN), konden we deze associatie onderzoeken in een voor ons relevante populatie. We keken daarbij terug in de tijd en vervolgden de patiënten over een periode van ruim 10 jaar vanaf het moment dat ze de diagnose diabetes kregen. Vervolgens keken we over deze periode wie van hen schimmelnagels kreeg (4.1% in totaal), al dan niet gevolgd door het ontstaan van een ulcus (5.7% in totaal) of een hieraan verwant problemen zoals een bacteriële huidinfectie (wondroos/cellulitis), de noodzaak tot een chirurgische ingreep in de huisartsenpraktijk of een verwijzing naar het ziekenhuis. Uiteraard namen we in onze analyses ook andere bekende risicofactoren voor het ontwikkelen van schimmelnagels en voetzweren mee zoals onder meer leeftijd, geslacht, roken en perifeer vaatlijden. Hieruit bleek dat schimmelnagels significant en onafhankelijk (van de andere factoren) geassocieerd waren met het ontstaan van een ulcus, uitgedrukt als een Hazard Ratio (HR) van 1,23, ofwel een 1,23 keer hogere kans op het ontwikkelen van een zweer. Voor kleine chirurgische ingrepen was dit 1,32 en voor wondroos/cellulitis was dit 1,27. Voor verwijzingen naar het ziekenhuis was dit 1,17, maar dit was niet statistisch significant. Zoals gezegd waren er eerdere onderzoeken die deze verhoogde associatie tussen onychomycose en diabetische ulcera vonden, zoals het onderzoek van Boyko et al. en Monteiro et al. die respectievelijk een HR van 1,58 en 1,22 vonden. Hoewel deze onderzoeken in een andere populatie waren verricht, konden we de associatie tussen onychomycose en ulceratieve complicaties bij diabeten nu dus ook bevestigen voor patiënten in de huisartsenpraktijk.

De belangrijkste kanttekening bij dit onderzoek is het feit dat we routine zorgdata hebben gebruikt. Inherent aan deze data wordt niet alles altijd even goed gecodeerd. Dit in tegenstelling tot een onderzoek waarbij men vooraf bedenkt om patiënten over de tijd te gaan volgen. Zo kan het zijn dat niet altijd de nagels van de patiënt met diabetes onderzocht worden, bijvoorbeeld als iemand geen last heeft of voor iets anders komt. Er zit dus altijd een bepaalde mate van selectie en misclassificatie in, die niet altijd geregistreerd wordt. Vooral de mensen met milde klachten kunnen onopgemerkt blijven. Aangezien de kans groter is dat patiënten met meer uitgesproken klachten wél geregistreerd worden in tegenstelling tot hen met weinig klachten, kan de

associatie die wij hebben gevonden daarom een overschatting van de werkelijkheid zijn. De vraag is in hoeverre dit relevant is, aangezien de huisarts vooral alert moet zijn op de patiënten met de meer uitgesproken klachten aangezien zij immers het verhoogde risico lopen op het ontwikkelen van complicaties.

Hoewel de zorg voor mensen met diabetes in de Nederlandse huisartsenpraktijk al uitgebreid is beschreven en vastgelegd in goed doordachte richtlijnen waarbij het alert zijn op nagelafwijkingen wel genoemd wordt, zouden wij op basis van onze bevindingen ervoor willen pleiten om het controleren op schimmelnagels een meer prominente plek te geven in de richtlijn voor diabetes mellitus type 2.

Conclusies en aanbevelingen voor de toekomst

Onychomycose is een veelvoorkomende kwaal in de huisartsenpraktijk. Het is niet de enige, maar wel de meest voorkomende oorzaak van verkleurde nagels. Hoewel schimmelnagels bij veel mensen niet of nauwelijks klachten veroorzaken, zijn er ook genoeg mensen bij wie schimmelnagels wel degelijk hinder veroorzaken, zoals schaamte, maar ook klachten van ingegroeide nagels, pijn, of huidinfecties. Vooral voor mensen die hier op voorhand al gevoeliger voor zijn zoals patiënten met diabetes. Schimmelnagels leveren in de praktijk nog steeds een aantal uitdagingen op, zowel bij het stellen van de diagnose, de behandeling als met betrekking tot het ontstaan van complicaties.

Allereerst lieten we zien dat het niet altijd even makkelijk is om de juiste diagnose te stellen, waarbij in ons onderzoek bleek dat ongeveer een kwart van de patiënten iets anders had dan de schimmelnagel waar de onderzoekers in eerste instantie aan dachten. Het gericht inzetten van beschikbaar laboratorium onderzoek, vooral bij twijfel of als de behandeling niet aanslaat, kan dit probleem voor een deel ondervangen. Deze kennis kan gebruikt worden om de huisarts te helpen om beter onderscheid te maken tussen de verschillende aandoeningen.

Aangezien de mate van aantasting van invloed is op de kans van slagen van een behandeling en eventuele complicaties, zou een objectieve score hiervoor zinvol kunnen zijn. De eerder voor dit doel ontwikkelde Onychomycosis Severity Index (OSI) bleek echter niet voldoende betrouwbaar toen wij dit onderzochten onder huisartsen. Oefening in het gebruik en eventuele aanpassing van de score kan de betrouwbaarheid waarschijnlijk vergroten. Omdat het vaststellen van de ernst van onychomycose de huisarts nuttige informatie kan geven, zou het zinvol zijn om een aangepaste, vereenvoudigde score te ontwikkelen t.b.v. de huisartspraktijk.

Een effectieve behandeling van schimmelnagels anders dan met tabletten bleek eveneens niet eenvoudig. Vanwege de potentiële bijwerkingen van een orale kuur zoals beschreven in een casus, bestaat nog steeds de behoefte aan een goed alternatief.

Voor behandeling van schimmelnagels bleken lokale middelen in ons onderzoek in het geheel niet effectief en kunnen we ze dan ook niet aanraden. Vooralsnog blijft orale behandeling dus de meest effectieve optie. Hierbij dient nog altijd goed overwogen te worden of behandeling echt noodzakelijk is en dient rekening gehouden te worden met eventuele contra-indicaties en interacties met andere middelen. Gezien de resultaten van eerder onderzoek zou niet alleen de ernst maar ook de mate van hinder meegewogen moeten worden bij de beslissing om al dan niet te behandelen. Het probleem van de gebrekkige effectiviteit van lokale antimycotica lijkt niet zozeer te zitten in de schimmeldodende eigenschappen van de middelen zelf, maar meer in het onvermogen van deze middelen om voldoende door te dringen tot in de nagel. Fundamenteel onderzoek hiernaar onderschrijft dit probleem. Bij de ontwikkeling en het onderzoek naar nieuwe behandelingen, zou vooral met deze gebrekkige penetratie rekening gehouden moeten worden.

Tot slot onderzochten we de associatie tussen onychomycose en gerelateerde complicaties bij patiënten met diabetes. Ook bij diabeten die in de huisartsenpraktijk onder behandeling en controle zijn, bleek dat patiënten met onychomycose een duidelijk verhoogd risico liepen op het ontwikkelen van zweren en huidinfecties. Dat patiënten met diabetes regelmatig hun voeten en tenen controleren op wondjes is al lang gemeengoed, maar het specifiek controleren op schimmelnagels om dit te kunnen vervolgen en zo nodig te behandelen, hoort hier wat ons betreft in de toekomst ook bij. Om te weten te komen of de antimycotische behandeling van de schimmelnagels daadwerkelijk zweren en andere complicaties kan voorkomen bij mensen met diabetes, zou dit uitgezocht moeten worden.

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PhD PORTFOLIO

Summary PhD training and teaching activities

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Courses and training

2019 Castor cursus: introductie, van CRF naar Castor, van Database naar Dataset
2021 Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK), NFU
2022 Basic Methods and Reasoning in Biostatistics, Boerhaave Nascholing, Leiden
2022 PhD Introductory Meeting, LUMC
2022 EUniWell Summer School "COVID-19: Impact on European health & well-being"

(Inter)national conferences and presentations

Invited speaker

2019 LVH Symposium Rijnland & Holland Midden, Alphen a/d Rijn, The Netherlands. Oral presentation: "Lokale behandeling van schimmelnagels - Introductie van de Onycho Trial"
2019 LOVAH Wetenschapsdag, Utrecht, The Netherlands. Workshop: "Kleine Kwalen"
2021 26th WONCA European Conference, the Netherlands. Poster presentation: "The Onycho Project - Effectiveness of Local Treatment for Onychomycosis - A Double Blind Randomized Controlled Trial"
2022 NHG Wetenschapsdag 2022, The Hague, The Netherlands. Pecha Kucha: "Diagnostische waarde van onychomycose als klinische diagnose in de eerste lijn"
2022 NAPCRG Annual Meeting 2022, Phoenix, Arizona. Poster presentation: "The Accuracy of Clinical Diagnosis of Onychomycosis in Dutch Family Practice"
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Other

2020 LOVAH conference, Rotterdam, The Netherlands
2022 NHG conference, Den Bosch, The Netherlands
2024 NHG conference, Den Bosch, The Netherlands

Grants

2019 Fonds Alledaagse Ziekten, research grants for the Onycho project and the Mollusca survey

Awards

2025 Kees Esser Academiseringsprijs - best scientific article by GP trainee - the Onycho Trial, presented by SBOH on April 3, 2025.
2025 NHG Wetenschapsprijs 2025 for the Onycho Trial, presented by NHG on September 26, 2025.

Teaching activities

2019-2024 LUMC Master program teaching: Introduction course to internships, Faculty of Medicine, Leiden University Medical Center
2019-2024 LUMC Bachelor program teaching: Common trauma of the upper and lower extremity in primary care practice and Dermatology in primary care practice, Faculty of Medicine, Leiden University Medical Center
2023 Boerhaave Nascholing, Leiden, The Netherlands. Vorderingen en praktijk 2023: Onychomycose diagnostiek en behandeling
2024 PAO-H Nascholing, Utrecht, The Netherlands. Kleine Kwalen 2024: Onychomycose – diagnostiek en behandeling in de praktijk

Student supervision

2020 CAT student Cristina Craita – Treatment of molluscum contagiosum in children
2021 Research intern Michiel Blanksma – Reliability of the Onychomycosis Severity Index
2021 Research intern Maikel Arkesteijn – Accuracy of clinical diagnosis of onychomycosis
2021 Research intern Mustafa Hasani – Molluscum contagiosum survey
2021 CAT student Frida van Rosmalen – Combining laser and topical treatment in patients with onychomycosis
2022 Research intern Khisraw Sayed – Effectiveness of topical antimycotics for onychomycosis in primary care
2022 Research intern Kim Heckmans – ELAN database research: Association between onychomycosis and diabetic ulcerative complications in Dutch general practice

CURRICULUM VITAE

Roeland Michiel Watjer was born on 9 January 1984 and raised in Leiden. After attending the Waldorf Primary School and subsequently the Leiden Stedelijk Gymnasium, he studied Medicine at Utrecht University from 2003 to 2009. During his studies, he was active in the faculty's medical student society and joined C.S. Veritas. Upon obtaining his medical degree, he began his residency at the Departments of Surgery and Intensive Care Medicine in Ede and Gouda, respectively. In 2012, he enrolled in a traineeship in Global Health and Tropical Medicine during which period he worked as a medical officer in Lesotho and as a resident in Paediatrics, Surgery, and Obstetrics in The Hague and Apeldoorn. After completing his degree in Global Health and Tropical Medicine at the Royal Tropical Institute in 2015, he worked in the Emergency Department of the Sint Maarten Medical Center until 2017. Upon returning to the Netherlands, he worked in Elderly Care Medicine in the Rotterdam area in 2018. In 2019, he commenced his General Practice specialty training in combination with a PhD research into fungal nail infections at the Department of Public Health and Primary Care of the Leiden University Medical Center. He completed both his research and training programme in late 2024 and is currently practising as general practitioner while also holding a research and teaching position at the Department of Public Health and Primary Care, focusing on the scientific education of GP trainees.

DANKWOORD

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