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Efficacy and safety of capillary stabilising agents for venous insufficiency or haemorrhoidal diseases

Final Report

Ludwig Boltzmann Institut
Health Technology Assessment

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Abbreviations

acc. ..... according
ATC-Code ..... Anatomical Therapeutic Chemical/Defined Daily Dose Classification
CEAP ..... classification for CVI based on clinical signs of venous disease (C), etiology (E), anatomy (A), and the underlying pathophysiology (P)
CI ..... confidence intervall
CVI ..... chronic venous insufficiency
EKO ..... Code of Reimbursement (for pharmaceuticals, in German: Erstattungskodex)
GRADE ..... Grading of Recommendations, Assessment, Development and Evaluation
HCSE ..... horse chestnut seed extract
HD ..... haemorrhoidal disease
HVB ..... Hauptverband der Sozialversicherung (Main Association of Austrian Social Security Institutions)
LBI-HTA ..... Ludwig Boltzmann Institute for Health Technology Assessment
MPFF ..... micronised purified flavonoid fraction
n/a ..... data not available
non-RCT ..... non-randomised controlled trial
N.S. ..... not statistically significant
OTC ..... over-the-counter
OR ..... odds ratio
RCT ..... randomised controlled trial
RR ..... relative risk
S.S. ..... statistically significant
vs. ..... versus

Summary

Background

Chronic venous insufficiency (CVI) and haemorrhoidal diseases (HD) are very common, affecting about 20 to 40% of the Austrian population. Even if CVI and HD are not directly associated with mortality, both diseases severely affect the quality of life.

venöse Insuffizienz und Hämorrhoiden häufige Krankheiten

One frequently chosen approach to reduce symptoms is oral treatment with capillary stabilising agents. However, while roughly € 20 million are spent annually on these drugs, their benefit has never been thoroughly evaluated so far.

häufige Verschreibung kapillarstabilisierender Mittel

The aim of this systematic review was to assess the efficacy and safety of a treatment of CVI and HD with capillary stabilising agents that are listed in the Austrian Code of Reimbursement (EKO).

Ziel: Wirksamkeit und Sicherheit kapillarstabilisierender Mittel

Methods

A total of 681 records were identified through a database search, a hand search and via additional industry requests. Studies were selected according to predefined criteria. In the end, 56 studies met our inclusion criteria.

nach Literatursuche 56 Studien eingeschlossen

The risk of bias and strength of evidence were assessed according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Studienbewertung nach GRADE

Literature selection, data extraction and evidence assessment were done by two review authors (IZ, SF), independently from each other, whereby differences were discussed in order to achieve consensus. A third person was involved in cases of uncertainty.

Auswahl und Extraktion Literatur

Results

Oxerutin-containing agents (Venoruton®)

The studies on oxerutin-containing agents *(Venoruton®)* have shown that compression stockings reduced leg volume (obsolete surrogate parameter for oedema) more than oxerutin-containing agents. Furthermore, if patients took oxerutin-containing agents in addition to wearing compression stockings, some experienced a slight improvement of some CVI signs (oedema) and symptoms (heaviness) compared to compression stockings in combination with placebo. However, improvement in symptoms is marginal and below clinical relevance. In addition, oxerutin-containing agents reduced the severity of signs and symptoms of HD, yet whether this improvement is statistically significant is unknown.

Oxerutin + Kompressionsstrümpfe reduzierten Anzeichen und Symptome marginal

The studies have either an unclear or high risk of bias and the overall strength of evidence is low.

Evidenzstärke gering

Flavonoid fraction-containing agents (Daflon® 500 mg tablets)

Flavonoidfraktion hilft eventuell etwas um Anzeichen der CVI zu verbessern

Flavonoid fraction-containing agents (*Daflon®*) in addition to wearing compression stockings slightly improved ulcer healing compared to wearing compression stockings only and ulcer healing plus oedema compared to compression stockings combined with placebo. Yet, up to 50% of patients did not show improvements. Other signs and symptoms were either not measured or the benefit was below clinical relevance. Whether patients benefit from taking flavonoid fraction-containing agents after surgery compared to no treatment after surgery is unknown, due to incomplete data on outcome and statistical significance.

Behandlung Hämorrhoiden mit Flavonoidfraktion sowie Entzündunghemmer ähnlich (in)effektiv

Treating HD with flavonoid fraction-containing agents does not seem more effective than with anti-inflammatory medication, however data on between-group differences are incomplete. Compared to office-based treatment (e.g., infrared photocoagulation or sclerotherapy), fewer patients who took flavonoid fraction-containing agents had bleedings during medication. Yet, after stopping medication, office-based treatments were eventually slightly more effective in terms of symptoms and recurrence rate. Compared to placebo, a treatment of HD with flavonoid fraction-containing agents slightly improved the signs and symptoms. However many data are incomplete and improvement of symptoms (quality of life, pain etc.) is not clinically relevant. After surgery, flavonoid fraction-containing agents reduced the severity of pain and the recurrence rate slightly more than no treatment, yet pain reduction was not clinically relevant. We are unable to draw a conclusion on whether flavonoid fraction-containing agents have an additional benefit when combined with fibre supplements, compared to no treatment (and fibre supplements).

Evidenzstärke überwiegend gering

The studies have either an unclear or high risk of bias and the overall strength of evidence is moderate to low.

20 mg aescin-containing agents (Reparil® 20 mg dragées)

Wirksamkeit von 20 mg Aescin unbekannt

We could not identify any randomised controlled trials to assess the efficacy of agents containing 20 mg of aescin *(Reparil® 20 mg dragées)* for the treatment of CVI and HD.

50 mg aescin-containing agents (Venosin retard® 50 mg capsules)

50 mg Aescin + Kompressionsstrümpfe eventuell wirksam bei CVI

A treatment with agents containing 50 mg of aescin (*Venosin® retard 50 mg capsules*), in addition to compression stockings, improved some signs (oedema) and symptoms (pain) of CVI, compared to compression stockings with placebo. However, we are unable to draw a conclusion regarding a treatment of HD with 50 mg aescin.

Evidenzstärke gering

The strength of evidence is low.

Calcium dobesilate (Doxium® 500 mg capsules)

Calciumdobesilat + Kompressionsstrümpfe eventuell wirksam bei CVI

When added to compression stockings, calcium dobesilate slightly improved some symptoms of CVI (pain, cramps, restless legs), compared to placebo (and compression therapy). For other symptoms (itching, swelling), this was not the case. We are unable to draw a conclusion on the efficacy of *Doxium®* for HD, since the drug is not explicitly indicated for HD.

moderate Evidenzstärke

The risk of bias in the studies is low and the strength of evidence is moderate.

Comparison between capillary stabilising agents

Oxerutin-containing agents for the treatment of CVI have shown similar results for oedema, pain, itching, heavy legs and swelling as 50 mg aescin containing agents and slightly better (with unknown significance) improvements of general CVI symptoms than flavonoid fraction-containing agents. Moreover, there was no superiority of either calcium dobesilate- or flavonoid fraction-containing agents in terms of reducing HD symptoms and the recurrence rate. We do not know whether one agent is generally superior to others.

nicht klar, welches Medikament am besten wirkt

Furthermore, the strength of evidence is low.

geringe Evidenzstärke

Comparison with further alternatives

We could not identify any evidence where a CVI treatment with capillary stabilising agents was compared with lifestyle changes, medical or surgical treatment. In addition, there was no evidence available to assess capillary stabilising agents for a treatment of HD compared to lifestyle changes and surgical treatment options.

kaum Studien im Vergleich mit anderen Behandlungsoptionen

Safety

A treatment of CVI and HD with capillary stabilising agents does not seem to be associated with a high rate of serious adverse events or side effects.

schwere Nebenwirkungen nicht zu erwarten

Discussion and conlusion

Since the strength of the evidence of nearly all identified studies is low, we cannot draw a final conclusion on the efficacy of capillary stabilising agents for the treatment of CVI and HD.

insgesamt schwache Evidenz

Major limitations of the studies are, firstly, the lack of transparency concerning the study design (e.g., unclear allocation concealment) and, secondly, study designs that introduce a high risk of bias. Examples for the latter are the small number of patients with short durations of treatment or flexibly allowing people to have additional interventions (e.g., wearing compression stockings for CVI treatment), which raises the question of whether any effect measured was due to the drug treatment or to the additional intervention.

viele Studienlimitationen

Moreover, some of the used outcome indicators (leg volume, symptoms measured on scales from 1-3) are obsolete according to today's standards and, therefore, are a very weak outcome to draw a conclusion for efficacy as a whole.

einige Endpunkte veraltet

From the numerous patient-relevant signs and symptoms of CVI and HD presented in the studies, some single parameters showed better improvement in the groups that received capillary stabilising agents than in the control groups. In addition, some of the differences between the groups were statistically significant. However, the clinical relevance of any improvement presented was marginal and, in most cases, even negligible.

zwar Verbesserungen in Behandlungsgruppen, aber nicht klinisch relevant

For *Doxium® 500 mg capsules* (for CVI only), *Venoruton®* (for CVI only), *Daflon® 500 mg tablets* (for CVI and HD) and *Venosin retard® 50 mg capsules* (for CVI only) the evidence shows a weak tendency for a benefit, yet the results are very uncertain.

Doxium, Venoruton, Daflon + Venosin retard wirken eventuell

For *Reparil® 20 mg dragées* we could not identify any efficacy-assessing evidence and, therefore, it is unclear whether the drug is more effective than other alternatives.

kaum Evidenz zu Reparil

stärkere Evidenz unabdingbar, um solidarische Finanzierung kapillarstabilisierender Mittel zu rechtfertigen

Future reimbursement of the drugs should be made conditional upon the generation of robust evidence concerning patients' benefits. This needs to be provided by the manufacturers. Cooperation with public payers in terms of study design (particularly concerning the selection of outcome parameters) is recommended.

Zusammenfassung

Hintergrund

kapillarstabilisierende Mittel gehören zu Vasoprotektoren

Vasoprotektoren sind Medikamente, die auf die Blutgefäße wirken. Zu ihnen zählen auch sogenannte kapillarstabilisierende Mittel, die hauptsächlich bei der Behandlung chronisch venöser Insuffizienz (CVI) sowie Hämorrhoiden eingesetzt werden.

Medikamente oft verschrieben

Wirksamkeit und Sicherheit geprüft

Kapillarstabilisierende Mittel werden in Österreich oft verschrieben, wobei der Nutzen weitgehend unklar ist. Daher soll der vorliegende Bericht die Wirksamkeit und Sicherheit kapillarstabilisierender Mittel, die im Erstattungskodex (EKO) gelistet sind und von der Sozialversicherung erstattet werden, bei der Behandlung von CVI und Hämorrhoiden untersuchen.

CVI entsteht durch inadäquaten Venenabfluss,

Folgen: Schmerzen bis Geschwüre

Die CVI kann vorrangig durch einen inadäquaten Venenabfluss entstehen, meist hervorgerufen durch einen geringen Blutfluss oder schwache Venenklappen, vorrangig in den Beinen. Es gibt kaum Daten zur Prävalenz der CVI in Österreich, es wird aber davon ausgegangen, dass jeder 5.-6. Mensch die Krankheit aufweist. Die Diagnose der CVI erfolgt über deren Symptome, wie Schmerzen, schwere Beine oder Juckreiz bis hin zu typischen Anzeichen wie Hautveränderungen, Ödeme und Geschwüre, mittels einer klinischen Untersuchung und/oder Ultraschall. Die Behandlung der CVI sollte konservativ starten, gefolgt oder unterstützt von Medikamenten. Operative Maßnahmen gelten als letzte Option.

Hämorrhoiden sind vaskuläre Strukturen im Afterbereich, die bei Vergrößerung pathologisch werden

Hämorrhoiden sind vaskuläre Strukturen im Afterbereich, die im Sinne des Hämorrhoidalleidens vergrößert sind. Die genaue Ursache der Erkrankung ist nicht geklärt, möglicherweise ist ein erhöhter Druck im Rektum ausschlaggebend. Auch gibt es kaum Daten zur Prävalenz in Österreich. Schätzungen gehen von ca. 40 % Betroffenen aus. Die Symptome von Hämorrhoiden sind abhängig von der Lokalisation, meist gehen Hämorrhoiden mit Juckreiz und Schmerzen einher. Typische Anzeichen reichen von Prolaps, der auch Nässen kann, bis hin zu fäkaler Inkontinenz. Die Diagnose sollte über eine präzise Anamnese erfolgen. Die Behandlung von Hämorrhoiden setzt an der Symptomverbesserung und Verhinderung der Verschlechterung des Krankheitsgrads an. In frühen Stadien sind Lebensstiländerungen (z. B. Diät) indiziert, gefolgt oder unterstützt von Medikamenten und lokalen ambulanten Maßnahmen (z. B. Sklerotherapie). In späteren Stadien wird oftmals ein operativer Eingriff notwendig.

Auflistung der in Österreich erstatteten Produkte

Kapillarstabilisierende Mittel sind unterteilbar in Bioflavonoide und andere kapillarstabilisierende Mittel. Im Jahr 2013 gab die Sozialversicherung ca. 19,4 Millionen Euro für folgende, im EKO gelistete, kapillarstabilisierende Mittel aus:

- Venoruton® 300 mg Dragées
- Venoruton® 500 mg Tabletten
- Venoruton® 1000 mg Granulat
- Daflon® 500 mg Tabletten
- Reparil® 20 mg Dragées
- Venosin retard® 50 mg Kapseln
- Doxium® 500 mg Kapseln

Fragestellung und Methoden

Forschungsfragen

Die Forschungsfragen des Berichts wurden wie folgt definiert:

- Sind die derzeit im Erstattungskodex gelisteten, kapillarstabilisierenden Mittel zur Behandlung von PatientInnen mit venöser Insuffizienz oder Hämorrhoiden wirksamer und sicherer bezüglich der definierten Outcomeparameter im Vergleich zu Alternativen (z. B. keine aktive Therapie, Placebo, etc.)
- Bestehen innerhalb der kapillarstabilisierenden Mittel Unterschiede in der Wirksamkeit bzw. Sicherheit?

systematische + händische Literatursuche

Zur Identifikation relevanter Literatur wurden eine systematische Literatursuche in vier Datenbanken (Chochrane, Centre for Research and Dissemination, Embase und Medline) und eine zusätzliche Handsuche durchgeführt. Außerdem wurden auch alle österreichischen Vertriebspartner der Medikamente, bzw. die Hersteller, bezüglich weiterer Studien kontaktiert.

56 Studien eingeschlossen

Von insgesamt 681 Treffern wurden letztlich 56 Studien, die den Einschlusskriterien entsprachen, für eine Datenextraktion ausgewählt. Darunter waren zwei systematische Übersichtsarbeiten, eine Meta-Analyse, 40 randomisierte kontrollierte Studien (RCTs), sechs nicht randomisierte kontrollierte Studien und sieben einarmige Studien. Im Falle des Einschlusses von systematischen Übersichtsarbeiten, wurden nur Einzelstudien mit jüngerem Veröffentlichungsdatum zitiert.

Bewertung Bias-Risiko und Evidenzstärke nach GRADE

Das Bias-Risiko sowie die Bewertung der Evidenzstärke wurden nach dem Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Schema vorgenommen.

4-Augenprinzip

Die Datenextraktion, die Bewertung des Bias Risikos und der Evidenzstärke wurde vom Erstautor vorgenommen und von der Zweitautorin kontrolliert.

patientInnen-relevante Endpunkte

Als patientInnen-relevante Endpunkte zur Bewertung der Wirksamkeit und Sicherheit kapillarstabilisierender Mittel bei der Behandlung der CVI wurden Veränderung der Anzeichen der CVI (z. B. Hautveränderungen, Ödeme und Geschwüre) und der Symptome der CVI (z. B. Schmerzen, Krämpfe, ruhelose, schwere Beine, Juckreiz, Schwellungen, Parästhesie), die Lebensqualität sowie unerwünschte Ereignisse herangezogen. Bei der Behandlung von Hämorrhoiden waren die Endpunkte Veränderungen der Anzeichen (z. B. Prolaps, Nässen und Inkontinenz) und Symptome (Schmerzen, Blutungen und Juckreiz) sowie Lebensqualität, Rückfallrate und unerwünschte Ereignisse.

einige Endpunkte nicht klinisch relevant

Die Anzeichen und Symptome wurden oftmals mit Scores auf Skalen von 0-3 oder 0-100 gemessen und Ödeme als Volumen oder Umfang angegeben. Die klinische Relevanz der Indikatoren wurde von ExpertInnen eingeschätzt. So wurde die Angabe von Beinvolumen als wenig relevant, Skalen von 0-3 oder 0-100 als veraltet, eine Umfangreduktion erst von 10 mm und mehr, eine Score-Veränderung von 5 und mehr sowie ein Gruppenunterschied bei Blutungen von 3 Tagen und mehr als klinisch relevant eingestuft.

Ergebnisse

Oxerutin enthaltende Mittel (Venoruton®)

Chronisch venöse Insuffizienz

Für die Bewertung der Wirksamkeit und Sicherheit von Oxerutin enthaltenden Mitteln zur Behandlung der CVI konnten 10 RCTs und 2 non-RCTs mit insgesamt 1.084 PatientInnen identifiziert werden.

10 RCTs und 2 non-RCTs identifiziert

Die Vergleichsgruppen, insofern es welche gab, erhielten entweder Placebo, Kompressionsstrümpfe oder keine Behandlung (non-RCT).

Vergleichsgruppen

Die Scores für Ödeme wurden sowohl in den Oxerutin- als auch in den *Placebo-Gruppen* reduziert. Gemessen als Beinvolumen (ein veralteter Surrogatparameter), und als Knöchelumfang konnten Ödeme statistisch signifikant mehr in den Oxerutin-Gruppen reduziert werden, als mit Placebo. Beingeschwüre traten jedoch sowohl bei mit Oxerutin als auch mit Placebo behandelten PatientInnen erneut auf. Generelle und einzelne CVI-Symptome (z. B. Schmerzen, Krämpfe etc.) wurden in den Oxerutin Gruppen meist stärker reduziert als in den Placebo-Gruppen, der Unterschied ist jedoch marginal und ohne klinische Relevanz. Es gilt zu beachten, dass in einigen Studien die PatientInnen zusätzliche Kompressionsstrümpfe getragen haben.

Oxerutin tendenziell etwas besser als Placebo

Für den Vergleich von Oxerutin mit *Kompressionsstrümpfe*n wurde lediglich das Beinvolumen (Surrogatparameter für Ödeme) erhoben, das jedoch mit Kompressionsstrümpfen stärker reduziert wurde.

Kompressionsstrümpfe eventuell besser als Oxerutin

Insgesamt gab es keine unerwünschten Ereignisse mit Oxerutin.

keine Nebenwirkungen

Die Studien zeigten ein unklares oder hohes Verzerrungspotenzial und die Stärke der Evidenz wurde insgesamt als niedrig bis sehr niedrig eingestuft.

geringe Evidenzstärke

Hämorrhoidalleiden

Für die Bewertung der Wirksamkeit und Sicherheit von Oxerutin enthaltenden Mitteln zur Behandlung von Hämorrhoiden konnte 1 RCT mit insgesamt 97 PatientInnen identifiziert werden. Die Vergleichsgruppe erhielt Placebo.

1 RCT identifiziert

Die generellen Anzeichen und Symptome von Hämorrhoiden konnten in der Oxerutin-Gruppe tendenziell eher verbesserst werden, als in der Placebo-Gruppe allerdings wurden keine Angaben zur statistischen Signifikanz des Unterschieds gemacht.

Oxerutin ggf. etwas besser als Placebo, aber unklar ob Unterschied signifikant

Durch die Behandlung mit Oxerutin bedingte Nebenwirkungen wurden in ca. 6 % der PatientInnen festgestellt.

6 % Nebenwirkungen

Die Studie hat ein unklares Verzerrungspotenzial und die Stärke der Evidenz ist niedrig

geringe Evidenzstärke

Flavonoidfraktion enthaltende Mittel (Daflon® 500 mg Tabletten)

Chronisch venöse Insuffizienz

Für die Bewertung der Wirksamkeit und Sicherheit von Flavonoidfraktion enthaltenden Mitteln zur Behandlung der CVI konnten 1 Meta-Analyse, 8 RCTs, 1 non-RCT und 5 einarmige Studien mit insgesamt 13.613 PatientInnen identifiziert werden.

15 Studien identifiziert

Die Vergleichsgruppen, insofern es welche gab, erhielten entweder Placebo oder keine medikamentöse Behandlung (dies war in 2 Studien der Fall, wo alle PatientInnen einer OP unterzogen wurden).

Vergleich: Placebo oder keine Behandlung

Flavonoidfraktion tendenziell besser als Placebo, aber Vorteil unsicher und nicht bei allen PatientInnen

Hautveränderungen konnten bei mehr PatientInnen der Flavonoidfraktion-Gruppen, als bei PatientInnen die *Placebo* erhielten, verbessert werden. Zu Ödemen, gemessen in ml, gab es widersprüchliche Ergebnisse in den Studien, jedoch stieg das Volumen in den Flavonoidfraktion-Gruppen, während der Knöchelumfang bei den Behandelten minimal (klinisch nicht relevant) sank und geringfügig bessere Ulcus-Heilungsraten beschrieben wurden. Zu keinem dieser Ergebnisse wurde angegeben, ob die Gruppenunterschiede signifikant sind. Generelle Symptome sowie Krämpfe im Speziellen konnten mit Flavonoidfraktion enthaltenden Mitteln in signifikant mehr PatientInnen verbessert werden als mit Placebo – in bis zu 50 % der PatientInnen traten jedoch gar keine Verbesserung. Es gilt zu beachten, dass in einigen Studien die PatientInnen zusätzliche Kompressionsstrümpfe tragen konnten.

Flavonoidfraktion mit Kompressionsstrümpfen unterstützt Heilung von Ulcus bei einigen PatientInnen

Geschwüre wurden bei PatientInnen, die *Flavonoidfraktion enthaltende Mittel mit zusätzlichen Kompressionsstrümpfen* erhielten, statistisch signifikant häufiger geheilt sowie reduziert als bei PatientInnen, die *nur Kompressionsstrümpfe* bekamen. Bei 30 bis 50 % der PatientInnen heilten sie trotz Behandlung nicht. Ebenso konnte das Symptom „schwere Beine" in der Behandlungsgruppe etwas verbessert werden, der Unterschied ist jedoch minimal und klinisch nicht relevant.

nach OP Flavonoidfraktion möglicherweise etwas symptomlindernd, Ergebnis sehr unsicher

Ödeme, Juckreiz, schwere Beine und die Lebensqualität konnten mit Flavonoidfraktion enthaltenen Mitteln und zusätzlicher Operation eher verbessert werden als nur mit einer Operation. Es fehlten jedoch fast überall vollständige Angaben zu den Ergebnissen, sowie Angaben zur statistischen Signifikanz der Unterschiede.

0-8 % Nebenwirkungen

Nebenwirkungen mit Flavonoidfraktion enthaltenden Mitteln traten in 0-8 % der PatientInnen auf.

geringe Evidenzstärke

Die Studien weisen entweder ein unklares (fehlende Angaben) oder hohes Verzerrungspotenzial auf und die Stärke der Evidenz ist niedrig.

Hämorrhoidalleiden

13 RCTS + 1 Ein-Arm-Studie

Für die Bewertung der Wirksamkeit und Sicherheit von Flavonoidfraktion enthaltenden Mitteln zur Behandlung von Hämorrhoiden konnten 13 RCTs und 1 einarmige Studie mit insgesamt 2.031 PatientInnen identifiziert werden. Die Vergleichsgruppen erhielten Placebo, keine Behandlung, ambulante Maßnahmen oder Entzündungshemmer.

mehr Verbesserungen mit Flavonoidfraktion als mit Placebo, aber Ergebnisse sehr unsicher

Sowohl generelle Anzeichen von Hämorrhoiden sowie Prolaps und „Nässen" im Speziellen als auch generelle Symptome sowie Schmerzen und Juckreiz im Speziellen konnten mit Flavonoidfraktion enthaltenden Mitteln eher verbessert werden, als mit *Placebo*. Jedoch ist die endgültige Beurteilung wegen oft fehlender Angaben zu den verwendeten Skalen eingeschränkt und die Veränderungen bei manchen Indikatoren (Lebensqualität, generelle Anzeichen von Hämorrhoiden, Schmerzen) klinisch nicht relevant. Blutungen konnten meist mehr mit Flavonoidfraktion enthaltenden Mitteln reduziert werden als mit Placebo, jedoch waren die Änderungen nicht klinisch relevant. Die Rückfallrate war mit Placebo geringer.

Schmerzreduktion mit Flavonoidfraktion nach OP klinisch nicht relevant, jedoch etwas weniger Rückfälle

Nach einem *operativen Eingriff* konnten Schmerzen mit Flavonoidfraktion enthaltenden Mitteln geringfügig mehr (aber klinisch nicht relevant) reduziert werden, als ohne Behandlung. Die Rückfallrate war bei PatientInnen in der Behandlungsgruppe um 5 %-Punkte geringer, hingegen war die Anzahl der Tage, an denen Blutungen nach der OP auftraten, in beiden Studiengruppen ähnlich.

Schmerzen, Blutungen und auch Juckreiz konnten mit einer Behandlung durch *Entzündunghemmer* tendenziell mehr reduziert werden als bei einer Gabe von Flavonoidfraktion enthaltenden Mitteln, die Unterschiede sind jedoch nicht signifikant bzw. die Angaben zur statistischen Signifikanz fehlen.

Schmerzen, Blutungen + Juckreiz eher reduziert mit Entzündungshemmern

Im Vergleich mit *ambulanten Maßnahmen*, wie z. B. die Sklerotherapie, war eine Behandlung mit Flavonoidfraktion enthaltenden Mitteln bei der Verbesserung genereller Symptome und Rückfallraten gleichauf, allerdings wurden kaum Angaben zur Signifikanz der Gruppenunterschiede gemacht. Bei der Reduktion von Blutungen und der Verbesserung der Lebensqualität konnten langfristig bessere Ergebnisse mit ambulanten Maßnahmen erzielt werden. Es ist zu beachten, dass PatientInnen teilweise zusätzlich eine ballaststoffreiche Ernährung bekamen.

langfristig ambulante Maßnahmen womöglich etwas besser als Flavonoidfraktion

Wenn alle PatientInnen zusätzlich eine ballaststoffreiche Ernährung bekamen, gab es bei Blutungen und bei der Rückfallrate kaum einen Unterschied zwischen einer Behandlung der Hämorrhoiden mit Flavonoidfraktion enthaltenden Mitteln oder keiner Behandlung.

wenn ballaststoffreiche Nahrung, dann kaum Vorteil von Flavonoidfraktion

Nebenwirkungen mit Flavonoidfraktion enthaltenden Mitteln traten in 0-8 % der PatientInnen auf.

0-8 % Nebenwirkungen

Die Studien weisen ein teils unklares, teils hohes Verzerrungspotenzial auf, die Stärke der Evidenz ist moderat bis niedrig

Evidenzstärke moderat bis niedrig

20 mg Aescin enthaltende Mittel (Reparil® 20 mg Dragées)

Chronisch venöse Insuffizienz

Zur Bewertung der Wirksamkeit von 20 mg Aescin enthaltenden Mitteln zur Behandlung der CVI konnten keine Studien identifiziert werden. Lediglich zur Bewertung der Sicherheit konnte ein non-RCT identifiziert werden.

1 non-RCT für Bewertung Sicherheit identifiziert

Nebenwirkungen mit 20 mg Aescin enthaltenden Mitteln traten in ca. 1 % der PatientInnen auf.

1 % Nebenwirkungen

Hämorrhoidalleiden

Es konnten keine Studien zur Bewertung der Wirksamkeit oder Sicherheit von 20 mg Aescin enthaltenden Mitteln bei Hämorrhoiden identifiziert werden.

keine Evidenz

50 mg Aescin enthaltende Mittel (Venosin retard® 50 mg Kapseln)

Chronisch venöse Insuffizienz

Für die Bewertung der Wirksamkeit und Sicherheit von 50 mg Aescin enthaltenden Mitteln zur Behandlung der CVI konnte 1 systematischer Review mit insgesamt 1.292 PatientInnen identifiziert werden.

1 systematischen Review identifiziert

Die Vergleichsgruppen erhielten entweder Placebo und/oder Kompressionsstrümpfe.

Vergleich: Placebo und/oder Strümpfe

Im Vergleich zu *Placebo* konnten Ödeme und Schmerzen statistisch signifikant mehr mit 50 mg Aescin enthaltenden Mitteln reduziert werden.

50 mg Aescin wirksamer als Placebo

Mit zusätzlichen Kompressionsstrümpfen konnten Ödeme und CVI-Anzeichen mit 50 mg Aescin etwas mehr als ohne weitere Behandlung verbessert werden, die Unterschiede sind jedoch nicht signifikant.

50 mg Aescin mit Kompression möglicherweise wirksam

keine Nebenwirkungen

Es traten keine Nebenwirkungen mit 50 mg Aescin enthaltenden Mitteln auf.

Evidenzstärke gering

Der verwendete Review weist ein geringes Verzerrungspotenzial auf, die darin behandelten Studien hingegen ein hohes, weshalb die Stärke der Evidenz insgesamt als niedrig einzustufen ist.

Hämorrhoidalleiden

keine Evidenz

Es konnten keine Studien zur Bewertung der Wirksamkeit oder Sicherheit von 50 mg Aescin enthaltenden Mitteln bei Hämorrhoiden identifiziert werden.

Calciumdobesilat enthaltende Mittel (Doxium® 500 mg Kapseln)

Chronisch venöse Insuffizienz

8 Studien identifiziert

Für die Bewertung der Wirksamkeit und Sicherheit von Calciumdobesilat enthaltenden Mitteln zur Behandlung der CVI konnten 1 systematischer Review, 4 RCTs, 1 non-RCT sowie 2 Ein-Arm-Studien mit insgesamt 2.768 PatientInnen identifiziert werden.

Vergleich: Placebo

Die Vergleichsgruppen des systematischen Reviews und der RCTs erhielten Placebo. Es gilt zu beachten, dass in einigen Studien die PatientInnen zusätzliche Kompressionsstrümpfe tragen konnten.

Ödemreduktion mit Calciumdob. fraglich

Ödeme konnten nicht in allen Studien zum Vorteil von Calciumdobesilat enthaltenden Mitteln im Vergleich zu *Placebo* reduziert werden.

einige Symptomverbesserungen mit Calciumdobesilat

Einige Symptome der CVI (generelle, Schmerzen, Krämpfe und ruhelose Beine) konnten in den Calciumdobesilat erhaltenden Gruppen mehr reduziert werden, als in den *Placebo*-Gruppen. Für andere Symptome (z. B. Juckreiz oder Schwellungen) war dies nicht der Fall.

0-27 % Nebenwirkungen

Nebenwirkungen mit Calciumdobesilat enthaltenden Mitteln traten in ca. 0-27 % der PatientInnen auf.

Evidenzstärke moderat

Das Verzerrungspotenzial in den Studien ist überwiegend gering, die Stärke der Evidenz ist moderat.

Hämorrhoidalleiden

keine Evidenz

Es konnten keine Studien zur Bewertung der Wirksamkeit oder Sicherheit von Calciumdobesilat enthaltenden Mitteln bei Hämorrhoiden identifiziert werden.

Vergleich zwischen kapillarstabilisierenden Mitteln

Chronisch venöse Insuffizienz

4 Studien identifiziert

Für die Bewertung der Wirksamkeit und Sicherheit von kapillarstabilisierenden Mitteln im Vergleich konnten 1 systematischer Review, 2 RCTs und 1 non-RCT identifiziert werden, die Oxerutin enthaltende mit 50 mg Aescin enthaltenden Mitteln oder Flavonoidfraktion enthaltende Mitteln verglichen.

Oxerutin und 50 mg Aescin ähnlich (in)effektiv

Bei den untersuchten Parametern (Ödeme, Schmerzen, Juckreiz, schwere Beine und Schwellungen) erzielten *Oxerutin* und *50 mg Aescin* enthaltenden Mittel ähnliche Ergebnisse.

Nebenwirkungen: 5-16 % vs. 3 %

Nebenwirkungen traten bei 5-16 % der *Oxerutin*-PatientInnen und bei 3 % der *50 mg Aescin*-PatientInnen auf.

Generelle Symptome konnten mit *Oxerutin* enthaltenden Mitteln etwas mehr (Angaben zur statistischen Signifikanz fehlen) reduziert werden als mit *Flavonoidfraktion* enthaltenden Mitteln. Nebenwirkungen traten bei keinem Medikament auf.

generelle Symptome mit Oxerutin etwas mehr reduziert

Die Stärke der Evidenz ist niedrig bis sehr niedrig.

Evidenzstärke gering

Hämorrhoidalleiden

Für die Bewertung der Wirksamkeit und Sicherheit von kapillarstabilisierenden Mitteln im Vergleich zueinander für die Behandlung von Hämorrhoiden konnte 1 RCT identifiziert werden.

1 RCT identifiziert

Einige Symptome konnten mit *Calciumdobesilat* enthaltenden Mitteln zwar geringfügig mehr reduziert werden als mit *Flavonoidfraktion* enthaltenden Mitteln, die Unterschiede waren jedoch entweder nicht signifikant oder Angaben zur Signifikanz fehlten. Nebenwirkungen traten bei keinem Medikament auf. Die Rückfallrate war mit beiden Medikamenten gleich.

keine eindeutige Überlegenheit eines Produktes

Zu Nebenwirkungen wurde nichts in dem RCT berichtet.

Nebenwirkungen unbekannt

Die Stärke der Evidenz ist niedrig.

Evidenzstärke gering

Diskussion

Limitationen der Evidenz

Insgesamt war die Stärke der Evidenz zu gering, um robuste Aussagen über die Wirksamkeit von kapillarstabilisierenden Mitteln zur Behandlung der CVI und von Hämorrhoiden zu treffen.

insgesamt schwache Evidenz

Bezüglich Sicherheit ist davon auszugehen, dass eine Behandlung mit kapillarstabilisierenden Mitteln nicht mit zahlreichen oder schwerwiegenden Nebenwirkungen assoziiert ist.

kaum unerwünschte Ereignisse

Generell waren die identifizierten Studien vorrangig älteren Publikationsdatums, daher ist es schwierig das Bias-Risiko und die Evidenzstärke mit heutigen Kriterien zu bewerten.

vorrangig alte Studien

Problematisch ist, dass PatientInnen in einigen Interventionsgruppen nicht standardisiert weitere Interventionen (Kompressionsstrümpfe bei der CVI-Behandlung, ballaststoffreiche Nahrung bei Hämorrhoiden) erhielten, daher ist es möglich, dass positive Effekte nicht durch die kapillarstabilisierenden Mittel, sondern durch die zusätzlichen Interventionen hervorgerufen wurden.

neben medikamentöser Behandlung auch andere Behandlungen

Einige Parameter, mit denen Endpunkte gemessen wurden, sind veraltet; so werden heutzutage keine Messungen mehr auf Skalen von 0-3 oder 0-100 durchgeführt. Außerdem war die klinische Relevanz einiger Endpunkte nicht gegeben, auch wenn die Studiengruppenunterschiede signifikant waren.

einige Outcome-Parameter veraltet

Zusätzliche Probleme stellen die vorwiegend kleinen Fallzahlen in den Studien und auch die kurzen Studiendauern dar. Die wenigsten Studien hatten eine Nachbetrachtungszeit, nachdem die Medikamente abgesetzt wurden.

kleine Fallzahlen, kurze Studiendauern

Limitationen des Reviews

Schwächen Review:

Die Schwächen der vorliegenden systematischen Übersichtsarbeit liegen in folgenden Punkten:

Surrogatparameter akzeptiert und Scores der Studien adaptiert zu Skala von 0-10

Es wurden Surrogatparameter, wie Beinvolumen oder Knöchelumfang, akzeptiert, um Ödeme zu messen, wenngleich sie wenig Aussagekraft zum patientInnenrelevanten Nutzen haben und teilweise veraltet sind. Außerdem wurden zur besseren Vergleichbarkeit die gemessenen Scores der Studien an eine Skala von 0 bis 10 angepasst. Die Daten basieren jedoch auf Skalen, deren Validität umstritten ist (beispielsweise 0-3) und Primärerhebungen mit der akzeptierten Skala (0-10) würden möglicherweise zu anderen Ergebnissen führen.

einige Studien ausgeschlossen, da Dosis nicht in EKO

Einige Studien wurden nicht in die Synthese eingeschlossen, da die Dosis oder die Darreichungsform nicht im EKO gelistet ist. Insofern gelten die Ergebnisse des vorliegenden Berichts ausschließlich für die sieben eingangs genannten Produkte.

keine getrennte Betrachtung der Oxerutin-Dosen

Weiters erfolgte keine getrennte Betrachtung der einzelnen Dosen und Darreichungsformen der Oxerutin enthaltenden Mittel. Jedoch war die Evidenzstärke der entsprechenden Studien relativ gering, insofern wäre eine individuelle Betrachtung wenig aussagekräftig gewesen.

wirksamstes Mittel nicht zu identifizieren

Außerdem war es auf Basis der vorhandenen Evidenz nicht möglich, das wirksamste kapillarstabilisierende Mittel für eine Behandlung der CVI oder von Hämorrhoiden zu ermitteln.

Fazit

endgültige Wirksamkeit nicht bewiesen

Die endgültige Wirksamkeit oder Unwirksamkeit kapillarstabilisierender Mittel für die Behandlung der CVI oder von Hämorrhoiden konnte nicht bewiesen werden.

Doxium, Venoruton, Daflon + Venosin retard wirken eventuell

Die Evidenz zeigt tendenziell eine Wirksamkeit für *Doxium® 500 mg Kapseln* (nur für CVI), *Venoruton®* (nur für CVI), *Daflon® 500 mg Tabletten* (für CVI und Hämorrhoiden) und *Venosin retard® 50 mg Kapseln (*nur für CVI), auch wenn die Ergebnisse sehr ungewiss sind.

kaum Evidenz zu Reparil

Für *Reparil® 20 mg Dragées* konnten wir keine Evidenz identifizieren, um die Wirksamkeit bei CVI oder Hämorrhoiden zu bewerten.

vor Hintergrund jährlicher Ausgaben von 20 Mio. Euro:

Es ist sicherlich fraglich, ob Studien aus den 1980er Jahren mit heutigen Kriterien bewertet werden können. Zugleich ist es aber auch höchst fragwürdig, weiterhin 20 Millionen Euro öffentlicher Gelder für kapillarstabilisierende Mittel pro Jahr auszugeben, wenn deren Wirksamkeit nicht deutlich belegt werden kann.

stärkere Evidenz unabdingbar

Die künftige Kostenerstattung der Medikamente sollte an die Generierung robuster Evidenz zur Belegung der Wirksamkeit seitens der Hersteller geknüpft werden. Es wird empfohlen, das Studiendesign (z. B. die Definition der Outcomeparameter) in Kooperation mit den öffentlichen Kostenträgern zu erstellen.

1 Background

This report will focus on the drugs of the subcategory C05C "capillary stabilising agents" that are listed in the Code of Reimbursement (Erstattungskodex; EKO), of the Main Association of Austrian Social Security Institutions (Hauptverband der österreichischen Sozialversicherung; HVB). This document contains approved, eligible and secured medicinal products which are available in Austria [1].

Bericht fokussiert auf kapillarstabilisierende Mittel, die von Sozialversicherung erstattet werden

Vasoprotectives are blood vessel-affecting drugs. They constitute a therapeutic subgroup of the group "C-Cardiovascular System" in the Anatomical Therapeutic Chemical/Defined Daily Dose Classification (ATC-Code) with the code "C05" [1, 2]. Capillary stabilising agents are mainly used for the treatment of chronic venous insufficiency (CVI), especially reducing the associated symptoms, and haemorrhoidal diseases (HD).

Vasoprotektoren in ATC-Code zu Gruppe „C05-Blutkreislauf", für Behandlung venöse Insuffizienz + Hämorrhoiden

Capillary stabilising agents are often prescribed by physicians, yet their benefit is uncertain. However, the main principle of the Austrian health care system is that a medical treatment must be sufficient and appropriate, but should not exceed the needs [1]. Therefore, this report will provide a systematic analysis of the literature to prove the efficacy and safety of capillary stabilising agents for the treatment of CVI and haemorrhoidal diseases.

Medikamente oft verschrieben, aber Nutzen unklar

In the following introductory sections, we will highlight some background information regarding the two targeted diseases (CVI and HD) and the various capillary stabilising agents that are listed in the EKO.

im Folgenden Hintergrund zu Krankheiten und Medikamenten

1.1 Targeted diseases

This report will focus on two different diseases (see Chapter 1.2): venous insufficiency (chronic) and haemorrhoidal diseases, which are further described below.

Fokus Bericht auf chronisch venöse Insuffizienz oder Hämorrhoiden

1.1.1 Diseases of the veins

The human circulatory system consists of three sets of vessels: arteries, lymphatics, and veins. Arteries deliver oxygen-rich blood from the heart to the tissues and lymphatic vessels bring this fluid back into circulation. Veins, on the other hand, deliver oxygen-depleted blood from the organs and tissues back to the heart and lungs, where it is re-oxygenated [3].

Kreislaufsystem besteht aus Arterien, Lymphgefäßen und Venen

In general, diseases of the veins can be divided into two major categories: blockage from a blood clot (thrombosis or embolism) and inadequate venous drainage (insufficiency). Haemorrhoids and (chronic) venous insufficiency are a subgroup of the latter; they must be distinguished, however, from other diseases caused by inadequate venous drainage, such as varicose veins [3, 4].

Venenerkrankungen durch Blutpfropf oder inadäquaten Rückfluss

In the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), diseases of the veins are categorised within the group "I80-89 diseases of the veins, lymphatic vessels and lymph nodes". This group is classified in ten subgroups [4]:

Unterteilung von Krankheiten laut ICD-10

- I80 Phlebitis and thrombophlebitis
- I81 Portal vein thrombosis
- I82 Other venous embolism and thrombosis
- I83 Varicose veins of lower extremities
- I84 Haemorrhoids
- I85 Oesophageal varices
- I86 Varicose veins of other sites
- I87 Other disorders of veins
- I88 Nonspecific lymphadenitis
- I89 Other noninfective disorders of lymphatic vessels and lymph nodes

I84 Hämorrhoiden
I87.2 venöse Insuffizienz

Whereas haemorrhoids are summarised in category "I84", chronic venous insufficiency is categorised in the subcategory "I87.2 Venous insufficiency (chronic) (peripheral)"of "I87 Other disorders of veins" [4].

1.1.2 Venous insufficiency (chronic)

chronisch venöse Insuffizienz (CVI) kann durch inadäquaten Venenabfluss entstehen

Venous insufficiency can be a consequence of an inadequate venous drainage. When the disease lasts over a long period of time, it is categorised as "chronic". Chronic venous insufficiency (CVI) is also called chronic venous disease (CVD). Inadequate venous drainage, mostly in the legs, may occur as a result of obstructed blood flow between the limbs and the heart or due to the reflux of blood back into the veins, caused by malfunctioning valves [3, 5, 6]. Venous dysfunction can result from either a congenital or an acquired disorder [7].

kaum Daten zu Prävalenz von CVI in Österreich, dennoch: jeder 5.-6. Mensch weist Krankheit auf

No recent information about the prevalence of CVI in Austria is available. An Austrian study published in 1998 about the prevalence of venous diseases (based on self-reporting) has shown that about 6% of the patients reported to be suffering from venous diseases, such as varicosis, phlebitis or venous thrombosis [8]. For estimating the prevalence of CVI in Germany, the Bonn Vein Study[1] is often cited [8, 9]. The study concluded that every 6th male and every 5th female suffers from chronic venous insufficiency. In addition, CVI is more likely in women and older people. The data show that venous disorders are highly prevalent, but that the severity of CVI has decreased over the past 20 years [9].

Diagnose CVI über Symptome, wie Schmerzen, schwere Beine oder Juckreiz bis hin zu typischen Anzeichen wie Hautveränderungen und Ödeme und Geschwüre

In early stages of chronic CVI, the disease can primarily be diagnosed by the presence of symptoms in the legs, such as pain, cramps (especially during the night), restless legs, itching (a tingling sensation of the skin) and heaviness (or heavy legs). The intensity of the symptoms can cause only a moderate discomfort or even limitations in common daily activities. In further stages the presence of reticular or varicose veins, swellings of the legs (or a sensation of tension) and paraesthesia limit the common activities of patients. The swellings are accentuated while standing and increase during the day. In later stages, CVI will cause typical CVI-related signs like skin changes, particularly pigmentation (e.g., telangiectasia: small red points on the skin caused by per-

[1] The Bonn Vein Study was conducted between 2000 and 2002 to investigate the prevalence and severity of chronic venous disorders in the German urban and rural residential population. A total of 3,072 persons, aged between 18 and 79 years, participated, whereas the overall response rate was 59%.

manently opened tiny blood vessels; and lipodermatosclerosis: hardening of the skin which may gain red or brown pigmentation), oedemas and ulcers or eczemas [5, 6, 8-10].

Diagnosis of CVI can be done by clinical examination (e.g., inspection, palpation, etc.) and using ultrasound (duplex or intravascular). Patients should also be asked for symptoms and a complete history examination is recommended [5, 6, 11]. In addition, CT and MR are used to diagnose CVI [11].

Diagnose durch klinische Examination, Ultraschall, etc.

In German-speaking countries, CVI is usually classified according to Widmer [5, 8, 9], summarised in the following table.

in deutschsprachigen Raum: Klassifikation CVI nach Widmer

Table 1.1-1: Classification of venous insufficiency according to Widmer

Classification	Clinical signs
Grade I	telangiectasias beyond the inner ankle, 'corona phlebectatica'
Grade II	indurated edema, eczema, dermatoliposclerosis, hyperpigmentation
Grade III	active or healed ulcer

Reference: [5]

A different classification system is the CEAP classification that was developed for venous diseases by the American Venous Forum (AVF). The classification is based on clinical signs of venous disease (C), etiology (E), anatomy (A), and the underlying pathophysiology (P), and is widely used [5, 7, 9, 12]. The CEAP classification is shown in the following table.

weiteres Klassifikationssystem: CEAP

Table 1.1-2: CEAP classification of venous diseases/insufficiency

Classification		Clinical signs
Clinical	C0	no visible or palpable signs of venous disease
	C1	teleangiectasias or reticular veins
	C2	varicose veins
	C3	swellings
	C4	a. pigmentation and eczema b. lipodermatosclerosis and atrophie blanche
	C5	healed venous ulcer
	C6	active venous ulcer
Etiologic	Ec	ongenital
	Ep	primary
	Es	secondary (post-thrombotic)
	En	no venous cause identified
Anatomic	As	superficial veins
	Ap	perforator veins
	Ad	deep veins
	An	no venous location identified
Pathophysiologic	Pr	reflux
	Po	obstruction
	Pr,o	reflux and obstruction
	Pn:	no venous pathophysiology identifiable

Reference: [12]

Behandlung von CVI sollte konservativ starten, gefolgt oder unterstützt von Medikamenten, operative Maßnahmen als letzte Option

Treatment of venous insufficiency is aimed at improving the symptoms (e.g., pain, heaviness, restless legs, etc.) and signs (especially edema, trophic alternations and ulcer), as well as avoiding the worsening of the CVI stage. Initial treatment should be conservative, starting with lifestyle changes (e.g., exercising or diet) or local treatment (e.g., compressions or wound cleansing, etc., in case of ulcers). Conservative treatment can be followed or supplemented by medication (e.g., capillary stabilising agents). If conservative or medical treatment is not feasible or is ineffective, specific surgical procedures can be considered (e.g., vein stripping, superficial vein surgery, sclerotherapy, interruption of perforator veins, etc.) [5, 6, 11]. The possible treatment options for CVI are summarised in the following table.

Table 1.1-3: Treatment options for venous diseases

Treatment	Treatment option
Lifestyle changes	❁ Exercising (physical activity, elevate legs, etc.) ❁ Diet
Local	❁ Compression therapy (stockings, bandages or compression pumps) ❁ Dressings (hydrocolloids, foam dressings, etc.); often in combination with compression therapy ❁ Wound cleansing ❁ Debridement ❁ Lymph drainage
Medical	❁ Phlebotonics, like capillary stabilising agents (flavonoid fractions, aescin, etc.) ❁ Antibiotics (only if there is an infection) ❁ Topical agents (antimicrobial agents, moisturisers or local anaesthetic creams)
Surgical	❁ Vein stripping ❁ Superficial vein surgery ❁ Sclerotherapy ❁ Interruption of perforator veins ❁ Ablation (radiofrequency or laser)

References: [5, 6, 11]

1.1.3 Haemorrhoids

Hämorrhoiden sind vaskuläre Strukturen im Afterberiech, die im Sinne des Hämorrhoidalleidens vergrößert sind

Haemorrhoids are vascular structures in the anus and lower rectum. They become pathological (also known as piles) when they are swollen or inflamed. The disease is therefore called haemorrhoidal disease (HD). Haemorrhoids can be located inside the rectum (internal haemorrhoids), or they may develop under the skin around the anus (external haemorrhoids) [13-15].

genaue Ursache nicht geklärt, möglicherweise durch erhöhten Druck im Rektum

The exact pathophysiology of haemorrhoids is not clear. Apparently, the veins around the anus tend to stretch under pressure and may bulge or swell. Swollen veins (haemorrhoids) can develop from an increase in pressure in the lower rectum. Factors that might cause increased pressure include [13-15]:

- Straining during bowel movements
- Sitting for long periods of time on the toilet
- Chronic diarrhoea or constipation
- Obesity
- Pregnancy
- Anal intercourse
- Low-fibre diet

kaum Daten zu Prävalenz, in Österreich ca. 40 % betroffen

Exact data on the prevalence of HD is rare. However, haemorrhoids are a common disease, though more likely in older people. In an Austrian study[2], about 39% of the study population suffered from haemorrhoids, whereby a considerable number of people did not complain about symptoms [13, 14].

in Österreich ca. 4.000 Hämorrhoiden-OPs p.a.

In 2012, haemorrhoid surgery (haemorhoidectomy) was performed 3,942 times in Austria (in public hospitals) [16].

Symptome abhängig von Lokation, meist Juckreiz und Schmerzen

The symptoms of haemorrhoids usually depend on the location, but mostly include pain or discomfort, bleeding (partially without any pain and especially during bowel movements) and itching (or prutitus) [13, 14, 17].

typische Anzeichen: Prolaps, Nässen und Inkontinenz

Typical signs of haemorrhoidal diseases are prolapses (a kind of lumps, which may be sensitive or painful), discharge (also called leakage). Furthermore, haemorrhoids (especially internal) can cause faecal incontinence [13, 14, 17].

Diagnose über präzise Anamnese

The diagnosis of haemorrhoids should include a precise anamnesis and physical examination to exclude other diseases. Internal haemorrhoids, without a prolapse, can only be found by endoscopy [13-15].

Komplikationen selten, aber meist Anämien

Complications associated with haemorrhoids are rare, but could contain [13-15]:

- Chronic blood loss from haemorrhoids that may cause anaemia, resulting in fatigue and weakness.
- Interruption of blood supply to an internal haemorrhoid that can cause extreme pain and lead to tissue death.

zwei Klassifikationssysteme für Hämorrhoiden: nach Banov und Goligher

There are two major classification systems for haemorrhoids (or haemorrhoidal diseases): one is by Banov et al. and the other is by Goligher et al. [13-15]. Both systems classify the disease into four grades, whereby the description for every grade is slightly different. The two classification systems are described in the two tables below.

Table 1.1-4: Classification of haemorrhoidal diseases according to Banov et al.

Classification	Clinical signs
Grade I	Prominent haemorrhoidal vessels, no prolapse
Grade II	Prolapse with straining, spontaneous reduction
Grade III	Prolapse with straining, requires manual reduction
Grade IV	Chronic prolapse, manual reduction is ineffective

Reference: [17]

Table 1.1-5: Classification of haemorrhoidal diseases according to Goligher et al.

Classification	Clinical signs
Grade I	Normal appearance; bleeding but no prolapse
Grade II	Bleeding and prolapse, spontaneous reduction
Grade III	Bleeding and prolapse, must be manually reduced
Grade IV	Bleeding and permanent prolapse

Reference: [13]

[2] Between 2008 and 2009, 976 patients who attended the Austrian nationwide health care program for colorectal cancer screening (people of 50 years or older) at four medical institutions were screened for haemorrhoids.

Behandlungsziel: Symptomverbesserung und Verhinderung der Verschlechterung des Krankheitsgrads, von Lebensstiländerungen bis OP

The treatment of haemorrhoids aims at improving the symptoms and avoiding the worsening of the stage of the disease. Initial treatment should be conservative, starting with lifestyle changes (e.g., diet) and followed or supplemented by medication (e.g., capillary stabilising agents). Office-based procedures are reserved for patients with grades I, II, and III haemorrhoidal diseases and who have failed conservative and medical management. An office-based treatment is performed in outpatient facilities or physician's offices and is less invasive than surgical interventions. A surgical treatment of haemorrhoids is indicated when patients are not responding to or feasible for office-based procedures, as well as for patients with large external haemorrhoids or grade III/IV combined internal/external haemorrhoids. However, a surgical treatment can result in faecal incontinence [13, 15, 17].

Behandlungsoptionen in Tabelle

The possible treatment options for haemorrhoids are summarised in the following table.

Table 1.1-6: Treatment options for haemorrhoidal diseases

Treatment	Treatment option
Lifestyle changes	✿ Diet (grade I-III) ✿ Warm baths ✿ Toilet habit retraining
Medical	✿ Capillary stabilising agents (flavonoid fractions, aescin, etc.) ✿ Topical agents (steroids, hydrocortisone, etc.)
Office-based	✿ Rubber band ligation ✿ Sclerotherapy ✿ Infrared-coagulation
Surgical	✿ Surgical excision ✿ Stapled haemorrhoidopexy ✿ Doppler guided ligation

References: [13, 15, 17]

1.2 Vasoprotectives: Capillary stabilising agents

orale Gabe, vorrangig bei venöser Insuffizienz und Hämorrhoiden

Capillary stabilising agents are mainly used to treat chronic venous insufficiency (particularly the symptoms) and haemorrhoids and can be given orally as tablets, dragées or granulate [1].

kapillarstabilisierende Mittel unterteilbar in Bioflavonoide und andere kapillarstabilisierende Mittel

The capillary stabilising agents listed in the Austrian Code of Reimbursement (EKO) are divided into "bioflavonoids" and "other capillary stabilising agents". The bioflavonoids are further divided into drugs containing only rutisode (Venoruton®) and a combination of diosmin (Daflon®) as a component. Moreover, the other capillary stabilising agents are divided into drugs containing aescin (Reparil® and Venosin® retard) and calcium dobesilate (Doxium®) [1].

There were around 2.4 million prescriptions of capillary stabilising agents per year in the outpatient sector from 2011 to 2013. The annual costs for the social health insurance amounted to between 19.2 and 19.4 million Euros in these years[3]. Both numbers were relatively constant over the past three years. The costs for prescribed capillary stabilising agents in 2013 is equivalent to 0.06% of the Austrian health expenditures of 31,960 million Euros [18]. In addition, some of the agents are over-the-counter (OTC) drugs and therefore will in some cases be paid privately by patients. Hence, the total annual expenditures on capillary stabilising agents in Austria will be higher than the figure stated above.

Sozialversicherung gab 2013 ca. 19,4 Millionen Euro für kapillarstabilisierende Mittel aus

The relatively constant course of the costs for and number of prescriptions of capillary stabilising agents in the years 2011 to 2013 are shown in Figure 1.2-1.

Übersicht über Kosten und Verschreibungen

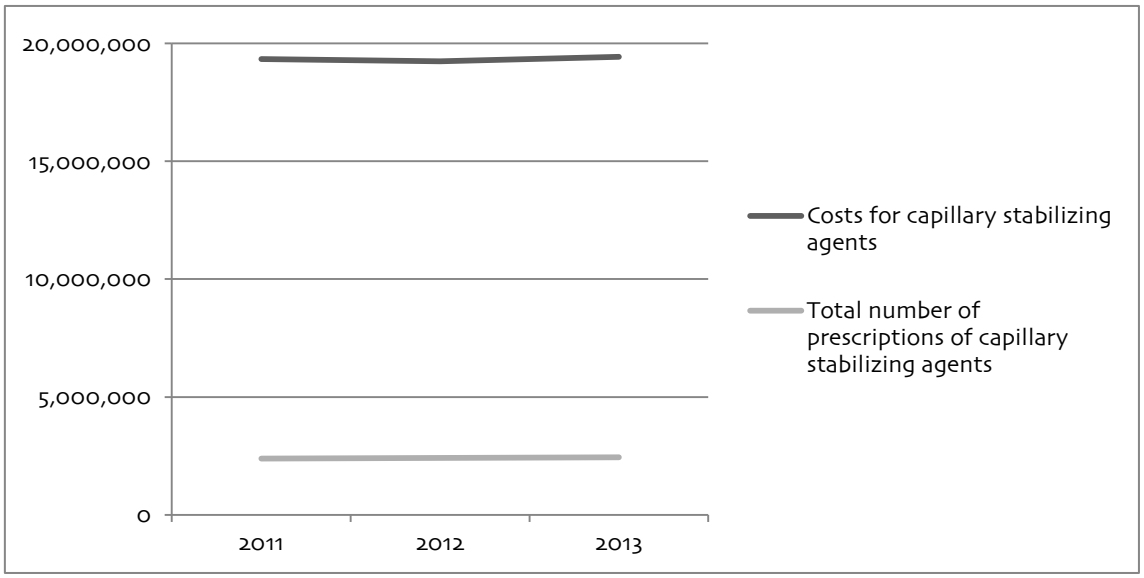

Figure 1.2-1: Development of prescriptions of and costs for capillary stabilising agents in Austria
Reference: From data sent by the Main Association of Austrian Social Security Institutions

[3] The information about the costs and prescriptions of capillary stabilising agents was provided by the Main Association of Austrian Social Security Institutions.

1.2.1 Bioflavonoids

Rutoside: Oxerutin-containing agents (Venoruton®)

Venoruton® ist einziges von Sozialversicherung erstattetes Medikament mit Rutoside bzw. Oxerutin

The only rutoside-containing drug that is listed in the EKO is Venoruton® [1]. The main content of Venoruton® is O-(beta-hydroxyethyl)-rutoside (HR), also known as oxerutin [1, 19]. Furthermore, the drug is available in several dosage forms with different prices – reimbursed by the social insurance – which are summarised in Table 1.2-1.

Indikation: vor allem Symptome venöse Insuffizienz + Hämorrhoiden

The treatment with Venoruton® is indicated for oedema and symptoms associated with CVI, like painful, tired, heavy, swollen legs with cramps and paraesthesia. It can be also used to treat the symptoms of haemorrhoids (pain, pruritus and bleeding) and their complications [19].

rezeptfrei in Apotheken erhältlich

Venoruton® is supposed to act on the capillary wall, increasing its resistance and normalising its permeability. It is an OTC drug, available in pharmacies, whereby the Austrian distributor of the drug is Novartis Consumer Health-Gebro [19]. Moreover, O-(beta-hydroxyethyl)-rutosides are available in other countries under different product names like Paroven (Switzerland) or Relvène (France) [20, 21].

Diosmin, combination: Flavonoid fraction-containing agents (Daflon®)

Daflon® einziges von Sozialversicherung erstattetes Medikament Flavonoidfraktion

The only drug containing a combination of diosmin with another active component listed in the EKO is Daflon® 500 mg tablets (a combination of diosmin and hesperidin) [1]. The main content is a micronised purified flavonoidic fraction of 500 mg, whereby the fraction contains 450 mg diosmin and 50 mg hesperidin (a flavonoid) [22] (see Table 1.2-1).

Indikation: Symptome venöse Insuffizienz + Hämorrhoiden

Daflon® is indicated for the treatment of symptoms related to CVI (heavy legs, pain, cramps, etc.) and symptoms related to haemorrhoidal diseases or acute haemorrhoidal attacks and their frequency, severity and duration [22].

verschreibungspflichtiges Medikament

The drug aims at reducing venous distensibility and stasis, at normalising capillary permeability, and at increasing capillary resistance. Daflon® is only available on prescription of a physician. The Austrian distributor of the drug is Servier Austria GmbH [22]. Moreover, Daflon® is available in other countries under registered product names like Alvenor, Ardium, Arvenum, Capiven, Detralex, Elatec, Flebotropin, Variton or Venitol [23].

Table 1.2-1: Content and prices of bioflavonoids

Product name	Active agent	Number of items per package	Price
Venoruton® 300 mg Dragées	Oxerutin (300 mg)	50	Euro 8.55
Venoruton® 500 mg Tablets	Oxerutin (500 mg)	30	Euro 7.85
Venoruton® 1000 mg Granulate	Oxerutin (1000 mg)	16	Euro 7.85
Daflon® 500 mg Tablets	Flavonoid fraction (500 mg) = 450 mg diosmin + 50 mg hesperidin	30	Euro 7.80

References: [1, 22]

1.2.2 Other capillary stabilising agents

20 mg/0.02 g aescin-containing agents (Reparil®)

Reparil® 20 mg ist ein von Sozialversicherung erstattetes Medikament mit Aescin als Wirkstoff

One of the aescin (or escin)-containing drugs that are listed in the Austrian Code of Reimbursement is Reparil® 20 mg dragées [1]. The main content of Reparil® is a 20 mg dosage of aescin that is a mixture of saponins, found in the horse chestnut (Aesculus hippocastanum) [24, 25]. The drug is available in only one dosage form at a price of 4.40 Euro [1] (see Table 1.2-2).

zahlreiche Indikationsbereiche, hauptsächlich bei CVI

The treatment with Reparil® is mainly indicated for venous diseases, like CVI, varicose veins or leg ulcers. Furthermore, Reparil® can also be used for the treatment of traumatic swellings, tenosynovitis and painful lesions of the vertebral column [24, 25]. The package insert gives no information that the drug is indicated for the treatment of HD.

verschreibungspflichtiges Medikament

Reparil® is supposed to reduce the capillary permeability and to therefore decrease the fluid outflow into the tissue. It is only available on prescription from a physician. The Austrian distributor of the drug is Madaus Ges.m.b.H. in Vienna [24, 25].

50 mg/0.05 g aescin/0.3 g horse chestnut-containing agents (Venosin® retard)

Venosin® retard 50 mg ist ein von Sozialversicherung erstattetes Medikament mit Aescin als Wirkstoff

Another aescin (or escin)-containing drug listed in the Austrian Code of Reimbursement is Venosin® retard 50 mg capsules [1]. The main content is a 50 mg dosage of aescin, made from 240-290 mgs of horse chestnut seed extract (HCSE) [1, 26]. The drug is available only in one dosage form in two different packages sizes at a price of 3.55 and 8.30 Euro [1, 26] (see Table 1.2-2).

Indiziert bei Behandlung von Symptomen der CVI

Venosin® retard is mainly indicated to treat the symptoms of CVI like heavy legs, pain, cramps or itching, but also varicose veins, or phlebitis [26]. The package insert gives no information that the drug is indicated for the treatment of HD.

rezeptfrei in Apotheken erhältlich

The drug is targeting the reduction of venous distensibility and stasis plus the normalisation of capillary permeability and the increase of capillary resistance. Venosin® retard is an OTC drug, available in pharmacies. Astellas Pharma is distributing the drug in Austria [26].

Table 1.2-2: Content and prices of other capillary stabilising agents

Product name	Active agent	Number of items per package	Price
Reparil® 20 mg Dragées	Aescin (20 mg)	60	Euro 4.40
Venosin® retard 50 mg Capsules	Aescin (50 mg) = 240-290 mg horse chestnut extract	20 60	Euro 3.55 Euro 8.30
Doxium® 500 mg Capsules	Calcium dobesilate (500 mg)	60	Euro 19.45

References: [1, 26]

Calcium dobesilate-containing agents (Doxium®)

Doxium® ist einziges Medikament mit Calciumdobesilat

The only drug containing calcium dobesilate, listed in the Austrian Code of Reimbursement, is Doxium® 500 mg capsules [1]. The main content is a 500 mg dosage of calcium dobesilate [27] (see Table 1.2-2).

Indikation: hauptsächlich Symptome CVI

The treatment with Doxium® is indicated for CVI (particularly the symptoms) and the aftereffects, like edema and leg ulcers [27]. Furthermore, the drug can be used for the treatment of dysfunction in the microcirculation and a combination with compression therapy is recommended [27]. The package insert gives no direct information that the drug is indicated for the treatment of HD.

verschreibungspflichtiges Medikament

Doxium® is supposed to reduce the capillary permeability and therefore to decrease the fluid outflow into the tissue. It is only available on prescription from a physician.The Austrian distributor of the drug is Ebewe Pharma (now a part of Sandoz, Novartis) [27].

2 Methods

2.1 Research questions

We have sought to answer the following research questions:

1. Are capillary stabilising agents, listed in the Austrian Code of Reimbursement, more effective and safer for the treatment of patients with venous insufficiency and haemorrhoids with regard to defined outcomes (see PICO scheme) compared to other alternatives (no treatment, placebo, etc.)?
2. Are there any differences between the different capillary stabilising agents according to efficacy and safety?

Forschungsfragen:

kapillarstabilisierende Mittel wirksam und sicher bei Behandlung CVI und Hämorrhoiden?

Unterschiede zwischen Medikamenten?

2.2 Inclusion criteria

The inclusion criteria for relevant studies are summarised in the following table. Since the product names of the capillary stabilising agents listed in the Austrian Code of Reimbursement are different from those in other countries, we also searched for the active components of the individual drugs.

Einschlusskriterien gemäß PIKO-Fragestellung

Table 2.2-1: Inclusion criteria

Population	Patients with: • Venous insufficiency • Haemorrhoids
Intervention, Setting	Oral medication of capillary stabilising agents (ATC-Code C05C): • Oxerutin 0.3 (Venoruton 300 mg) • Oxerutin 0.5 (Venoruton 500 mg) • Oxerutin 1.0 (Venoruton 1000 mg) • Flavonoid fraction 0.5 (Daflon 500 mg) • Aescin 0.02 (Reparil 20 mg) • Aescin 0.05 (Venosin retard 50 mg) • Calcium dobesilate 0.5 (Doxium 500 mg)
Control	Venous insufficiency: • No intervention • Lifestyle changes (exercising, diet, elevate legs, etc.) • Medical treatment (placebo, other capillary stabilising agents mentioned under "intervention", antibiotics, etc.) • Local treatment (compression therapy, etc.; additional wound dressings and debridement if applicable) • Surgical interventions (vein stripping, superficial vein surgery, sclero-therapy, interruption of perforator veins, etc.)

Control *(continuation)*	Haemorrhoids: • No intervention • Lifestyle changes (diet, etc.) • Medical treatment (placebo, other capillary stabilising agents mentioned under "intervention", etc.) • Local/Office-based treatment (rubber band ligation, sclerotherapy, infrared-coagulation, etc.) • Surgical interventions (surgical excision, stapled haemorrhoidopexy, doppler-guided ligation, etc.)

Outcomes	Efficacy:
	• Venous insufficiency:
	  • Change of CVI stage
	  • Improvement of CVI signs (in general, trophic alternations, oedema, etc.)
	  • Improvement of CVI symptoms (pain, swelling, itching, etc.)
	  • Quality of life
	• Haemorrhoids:
	  • Change of HD stage
	  • Improvement of HD signs (in general, discharge, prolapse, etc.)
	  • Improvement of HD symptoms (pain, bleeding, itching, etc.)
	  • Quality of life
	  • Recurrence rate
	Safety:
	• Complications/adverse events (gastrointestinal and neurovegetative disorders, allergic reactions, vomiting, nausea, headache, pain, dizziness, inflammation, tachycardia, etc.)

Types of studies	systematic reviews, meta-analyses, HTA reports, prospective controlled studies with ≥ 10 patients (for efficacy and safety), prospective uncontrolled studies with ≥ 50 patients (for safety only)
Publication period	1900-2014
Language	German/English
Type of publication	(un)published journal articles and research reports

2.3 Exclusion criteria

ausgeschlossene Populationen, Interventionen, Studien und Publikationen

We excluded studies with the following populations and interventions plus the stated types of studies and publications:

- Population:
  - Animals
  - Patients with post-thrombotic syndrome
  - Patients with primary varicose veins (not related to CVI)
- Intervention:
  - Vasoprotectives with ATC-Code C05A "agents for treatment of haemorrhoids and anal fissures for topical use" and C05B "antivaricose therapy"
  - Combination therapies in one of two study groups
  - Capillary stabilising agents and related dosages/dosage forms that are not included in the Austrian Code of Reimbursement

- Types of studies:
  - Dose-response studies
  - Controlled studies with less than 10 patients
  - Uncontrolled studies with less than 50 patients
  - Retrospective studies
  - Case-reports
  - Case-series
  - Editorials, letters to the editor, comments, other correspondence etc.
- Types of publications:
  - Abstracts, posters, comments, letters
  - Books

2.4 Literature search

Literatursuche in vier Datenbanken

The medical literature was searched to identify relevant studies and reviews for the period between 1900 and May 2014. Searches were conducted via the following databases:

- Cochrane
- Centre for Research and Dissemination (CRD)
- Embase
- Medline

detaillierte Suchstrategie im Anhang

The detailed search strategy including the used search terms is described in the appendix. Furthermore, an additional hand search via Scopus and Google was conducted.

außerdem Anfrage Pharmaunternehmen

Furthermore, we contacted the individual Austrian distributors of the several drugs for studies in August 2014.

2.5 Literature selection

Literaturauswahl aus 681 Quellen

A total of 681 records were identified through database, hand search and via additional industry requests. Two review authors (IZ, SF) included and excluded the literature, independently from each other, whereas differences were discussed between the authors. A PRISMA flowchart is shown in Figure 2.5-1, outlining the number of citations considered at each stage of the systematic review.

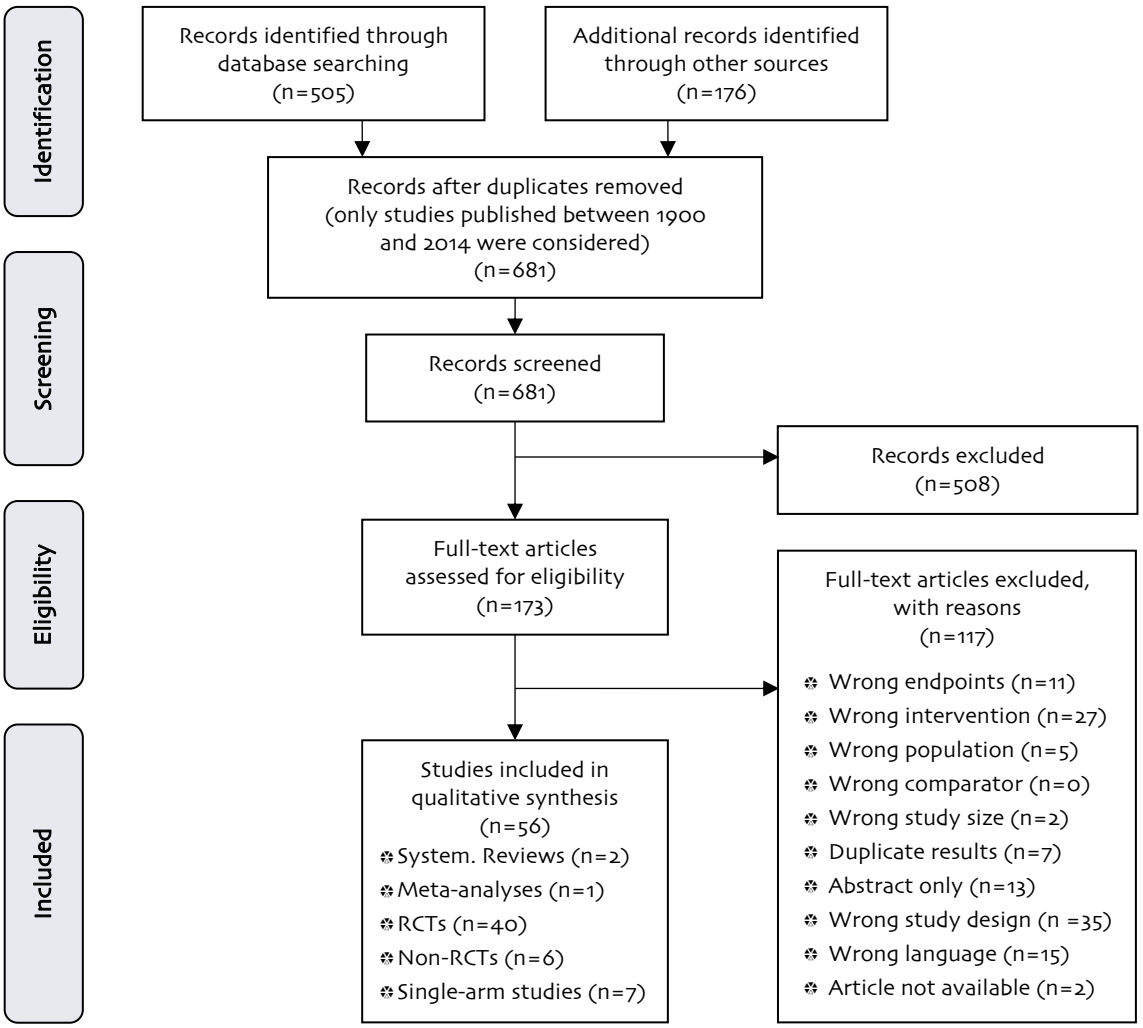

Figure 2.5-1: Summary of the process used to identify and select studies for the review (PRISMA Flow Diagram)

2.6 Data extraction and analysis

Erstautor extrahierte Studiendaten, Zweitautor kontrollierte

One author extracted the data (SF) of the included studies and a second author controlled the extracted data (IZ). If the same data were duplicated in multiple articles, only results from the most comprehensive or most recent article were included.

Ergebnisse getrennt nach Indikation und Wirkstoff

The extracted results of the identified studies are classified by indication (CVI and haemorrhoids) and by the individual agents (flavonoid fractions, oxerutin, aescin, etc.). The studies in the extraction tables are sorted by publication date, starting with the oldest study.

wenn systematischer Review, dann nur neuere Studien

In case a high quality systematic review or meta-analysis was identified for a certain indication and/or intervention, and the reported outcomes matched our criteria, we included only those primary studies that were published after the review.

Meta-Analysen bei Outcomes in mehr als 2 Studien

If homogenous outcome data were available from more than two studies they were quantitatively analysed in a meta-analysis (Software: Comprehensive Meta-Analysis, version 2.2.050), using a random-effects model. The results from the meta-analyses are presented in forest-plots in the respective chapters on the drug-related efficacy and safety. A sensitivity analysis was performed if there were more than 5 studies per outcome (or three studies with minimum a moderate strength of evidence).

Bias-Risiko nach Cochrane in Grafiken dargestellt

For ***all*** studies the methodological quality was assessed using the criteria from the Cochrane risk of bias tool listed in the internal manual of the LBI-HTA [28], by two review authors (SF, IZ), independently from each other. A risk of bias summary is presented in several figures in the relevant chapters. The risk of bias analysis for each individual study is available on author's request.

Bewertung Evidenzstärke von beiden Autoren nach GRADE

The strength of evidence was assessed according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for every defined outcome parameter by two review authors (SF, IZ), independently from each other. Thereby, all relevant study results for each endpoint were summarised and assessed regarding to the strength of evidence. Differences were solved by discussion and consensus or by a third person. A detailed description of the used criteria for assessing the strength of evidence is stated in the internal manual of the LBI-HTA [28] or in the recommendations of GRADE, respectively [29].

GRADE-Kategorien

GRADE uses the following categories to assess the strength of evidence:

- *high*: it is unlikely that new studies will have an important influence on the estimated effect
- *moderate*: new studies will have a potential influence on the estimated effect
- *low*: new studies will have a very likely influence on the estimated effect
- *very low*: an evaluation of the effect is very uncertain

GRADE-Tabellen: nur Veränderungen und Scores angepasst an 0-10 Skala

In some studies, baseline measurements on outcome parameters were not presented, hence changes in outcomes over time could not be calculated. In the GRADE-tables only outcomes that could be presented as reductions or changes from baseline were considered. Furthermore, outcomes measured on different scores were adapted to single scores of 0 to 10 to increase comparability and consistency, i.e., scores of 0-2 were multiplied by 5, scores of 0-3 were multiplied by 3.33 and scores of 0-100 were divided by 10.

vergleichende Wirksamkeitsanalyse nicht möglich

Incidentally, the planned comparative effectiveness analysis (see research question) was not applicable, since we could not identify studies for every agent and indication. Moreover, the quality of evidence did not allow any comparative effectiveness analysis.

2.7 Patient-relevant outcomes

2.7.1 Chronic venous insufficiency

Endpunkte, wie Änderung des Krankheits-Stadiums ...

One of the aims of treating CVI is avoiding the worsening of the disease stage (see Chapter 1.1.2). Therefore, "change of the CVI stage" was chosen as one patient-relevant outcome.

... Anzeichen der CVI (Hauveränderungen, Ödeme, Geschwüre) ...

The disease will also cause typical CVI-related signs, especially in later stages, like skin changes, particularly pigmentation (e.g., telangiectasia: small red points on the skin caused by permanently opened tiny blood vessels; and lipodermatosclerosis: hardening of the skin which may gain red or brown pigmentation); oedemas and ulcers (or eczemas). Therefore, the assessment of these signs was chosen as patient-relevant outcome. Incidentally, skin changes are summarised under the term "trophic alternations" and "oedema" could be measured as volume (in ml, l, cm^3, etc.), circumference (in mm or cm at the calf, ankle or at the leg in general) or assessed on a scale.

... Symptome der CVI (Schmerzen, Krämpfe, ruhelose, schwere Beine, Juckreiz, Schwellungen, Parästhesie) ...

CVI can primarily be diagnosed by the presence of symptoms in the legs (see also Chapter 1.1.2), in early stages especially pain, cramps (mostly during the night), restless legs, itching (a tingling sensation of the skin), a feeling of heaviness (also called heavy legs). The intensity of the symptoms can cause discomfort and limitations in common daily activities. In further stages the presence of swellings of the legs (a sensation of tension) and paraesthesia are limiting common activities of patients. The swellings are accentuated while standing and increase during the day. Hence, the assessment of these symptoms was defined as patient-relevant. In addition, the assessment of general symptoms was selected, e.g., if studies did not report individual symptoms.

... Lebensqualität ...

Furthermore, the quality of life was chosen as an additional patient-relevant outcome.

... sowie unerwünschte Ereignisse

To assess the safety we selected adverse events in general and treatment-related adverse events. If possible, the adverse events were classified by major and minor adverse events.

Zusammenfassung Endpunkte

In summary, the patient-relevant outcomes to assess efficacy and safety of stabilising agents for the treatment of CVI[4] are:

Efficacy[5]:

- Change of the CVI stage
- CVI signs:
  - general
  - trophic alternations (telangieactasia, reticular or varicose veins and lipodermatosclerosis)
  - oedema (also measured as leg volume and leg, ankle or calf circumference)
  - ulcer

[4] Surrogate parameters measuring one of the stated outcomes were NOT extracted (e.g., haemodynamic parameters like blood pressure, etc.).

[5] Outcomes were extracted at 1; 2; 3; 6; 12 months and the study's individual latest point of time of outcome reporting after begin of treatment.

- CVI symptoms:
  - general
  - pain
  - cramps
  - restless legs
  - itching (sometimes described as tingling sensation)
  - heaviness (sometimes described as heavy legs)
  - swelling (sometimes describes as sensation of tension)
  - paraesthesia
- Quality of life (QoL)

Safety:

- General adverse events
  - major
  - minor
- Treatment-related adverse events
  - major
  - minor

2.7.2 Haemorrhoidal disease

One of the aims of treating HD is avoiding the worsening of the disease stage (see Chapter 1.1.3). Therefore, "change of the HD stage" was chosen as one patient-relevant outcome.

Endpunkte, wie Änderung des Krankheits-Stadiums ...

The disease will cause typical HD-related signs, like prolapses (sometimes defined as swellings), discharge (sometimes called leakage) and (faecal) incontinence. Therefore, the assessment of these signs was chosen as patient-relevant outcomes.

... Anzeichen der Hämorrhoiden (Prolaps, Nässen, Inkontinenz) ...

HD is primarily diagnosed by the presence of symptoms (see also Chapter 1.1.3) such as pain, bleeding, and itching (or pruritus). The intensity of the symptoms can cause discomfort and limitations in common daily activities and in bowel movement. Hence, the assessment of these symptoms was defined as patient-relevant. In addition, the assessment of symptoms in general was selected, e.g., if studies did not report individual symptoms.

... Symptome der Hämorrhoiden (Schmerzen, Blutungen, Juckreiz) ...

Furthermore, the quality of life and the recurrence rate were chosen as additional patient-relevant outcomes.

... Lebensqualität, Rückfallrate ...

To assess the safety we selected adverse events in general and treatment-related adverse events. If possible, the adverse events were classified by major and minor adverse events.

... sowie unerwünschte Ereignisse

Zusammenfassung Endpunkte

In summary, the following patient-relevant outcomes have been analysed to assess the efficacy and safety of capillary stabilising agents for the treatment of HD[6]:

Efficacy[7]:

- Change of the HD stage
- HD signs:
  - general
  - prolapse (improvement, change or visibility, sometimes described as swelling)
  - discharge (sometimes described as leakage)
  - incontinence
- HD symptoms:
  - general
  - pain
  - bleeding
  - itching (sometimes described as pruritus)
- Quality of life (QoL)
- Recurrence rate

Safety:

- General adverse events
  - major
  - minor
- Treatment-related adverse events
  - major
  - minor

2.7.3 Clinical relevance of outcome indicators

Anzeichen und Symptome oft mit Scores gemessen, Ödeme als Volumen oder Umfang angegeben

In the individual studies, the reported outcomes were measured with different indicators. For measuring CVI and HD signs and symptoms scores with different scales (0-3, 0-10) have often been used. Oedema has been primarily measured by leg volume (in ml or cm^3) or leg circumference (in mm). Another very frequently used indicator was the percentage of patients with signs/symptoms or with improvement of signs/symptoms.

klinische Relevanz von Indikatoren von ExpertInnen eingestuft

For evaluating the clinical benefit for patients it is important to assess the clinical relevance of the presented measurements, e.g., the change in scores from baseline or the difference between groups. Our definitions of clinical relevance are based on consultations of two clinical experts (both are angiologists).

---

[6] Surrogate parameters measuring one of the stated outcomes were NOT extracted (e.g., biochemical parameters).

[7] Outcomes were extracted at <1, 1; 2; 4; 8; 12; 24; 50 weeks and the study's individual latest point of time of outcome reporting after beginning of treatment.

In terms of leg volume for assessing oedema, this indicator is a surrogate parameter and of little value concerning the assessment of patient-relevant benefits.

Beinvolumen wenig relevant

Outcomes measured with scores on a scale from 0-10 have been defined as clinically relevant, if the score is reduced by 5 or more. A measurement on scales from 0-3, 0-100 or 0-40 – which has often been used in the studies – has been rated as inappropriate according to clinical experts, as the validity of the results measured on such scales is severely limited.

Skalen von 0-3, 0-40 und 0-100 veraltet

In terms of calf and ankle circumference in mm – which has been used for measuring oedema – a reduction of ≥10mm has been defined as clinically relevant, by the consulted clinical experts

erst Reduktion Umfang ≥10 mm relevant (CVI)

Regarding days of bleeding which has been used for assessing HD, a difference between the treatment groups of 3 days and more has been considered as clinically relevant.

Gruppenunterschied Blutungen ≥3 Tage relevant

With respect to presenting the benefit of the treatment in % of patients with (improved) signs/symptoms, it needs to be noted that even in cases where the difference between groups is statistically significant, there may be still a large number of patients who have signs and symptoms or patients without improvement despite treatment. This has additionally been taken into account when rating the overall evidence.

oft signifikanter Gruppenunterschied bei Verbesserung Anzeichen/Symptome, aber Veränderung nur marginal

3 Results

3.1 Chronic venous insufficiency

Overall, 2 systematic reviews, 1 meta-analysis, 24 randomised controlled trials (RCTs), 4 non-randomised controlled trials (2 of them were registry studies) and 6 uncontrolled trials (called single-arm studies),were identified to assess either the efficacy or safety or both of capillary stabilising agents for the treatment of chronic venous insufficiency (CVI).

insgesamt 37 Studien zur Behandlung von CVI identifiziert

3.1.1 Oxerutin-containing agents

Study characteristics

For evaluating the efficacy and safety of oxerutin (0-beta-hydroxyethyl-rutoside, HR) containing capillary stabilising agents, we identified 10 RCTs [20, 21, 30-38] and 2 additional non-randomised controlled registry studies [39, 40] that met our inclusion criteria. The studies are comparing the treatment of CVI using oxerutin-containing agents with either placebo [20, 30-38], compression stockings [21, 39, 40] or no treatment [39]. The dosages of oxerutin varied from 300 mg three times a day [34] over 500 mg two to four times a day [21, 33-36, 38] up to 1,000 mg one to three times a day [20, 32, 37, 40].

10 RCTs und 2 non-RCTs mit 1.084 PatientInnen eingeschlossen

Vergleichsgruppen: Placebo, Kompressionsstrümpfe und keine Behandlung

The study characteristics and results are summarised in Table 3.1-1 for RCTs and in Table 3.1-2 for non-randomised controlled trials.

Studiencharakteristika in Tabellen

There were no studies identified comparing oxerutin-containing agents with other interventions, such as lifestyle changes or further local, medical and surgical treatment, mentioned in Chapter 1.1.2.

keine Studien mit anderen Vergleichsgruppen

Table 3.1-1: Efficacy and safety-related outcomes of randomised controlled trials of oxerutin-containing agents vs. placebo and/or compression stockings for CVI

Author, year, reference number	Capelli 1987 [32]	Wright 1991 [38]	Renton 1994 [35]	Neumann 1995 [21]	Cloarec 1996 [20]	Rehn 1996 (a) [34]	Unkauf 1996 [33] Großmann 1997 [36]	Cesarone 2002 (a) [31]	Cesarone 2002 (b) [30]	Petruzellis 2002 [37]
Country	Italy	UK	UK	Netherlands	France	Germany	Germany	Italy, UK	Italy, UK	Italy
Study design	RCT	RCT[8]	RCT	RCT	RCT	RCT[9]	RCT	RCT[10]	RCT	RCT
Sponsor	n/a	Zyma	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Intervention/ product	3x 1,000 mg HR granulate (Venoruton®) per day	2x 500 mg HR tablets (Paroven®) per day	4x 500 mg HR tablets (Paroven®) per day	2x 500 mg HR tablets (Venoruton®) per day	2x 1,000 mg HR granulate (Relvene®) per day	3x 300 mg | 2x 500 mg HR tablets (Venoruton®) per day	2x 500 mg HR tablets (Venoruton®) per day + compression stockings	3x 500 mg | 3x 1,000 mg HR (Venoruton®/ Paroven®) per day	2x 1,000 mg HR granulate (Venoruton®/ Paroven®) per day + compression stockings	1-3x 1,000 mg HR granulate (Venoruton®) per day[11]
Comparator	Placebo	Placebo	Placebo	Compression stockings	Placebo	Placebo	Placebo + compression stockings	Placebo	Placebo + compression stockings	Placebo
Number of pts.	10 vs. 10	69 vs. 69	19 vs. 21	12 vs. 12	53 vs. 51	20 | 20 vs. 20	64 vs. 56	15 | 16 vs. 15	20 vs. 20	40 vs. 20
Age of patients (yrs.)	19-42	Ø 67 vs. 68	n/a	Ø 49 vs. 45	Ø 48 vs. 54	Ø 58 | 58 vs. 59	Ø 59 vs. 61	Ø 45 | 44 vs. 44	46 vs. 46	52 vs. 53
Sex (% female)	100 vs. 100	56 vs. 64	n/a	73 vs. 83	81 vs. 88	100 | 100 vs. 100	100 vs. 100	47 | 44 vs. 47	30 vs. 35	90 vs. 70
Height (cm)/ weight (kg)/ BMI (kg/m²)	n/a	n/a / n/a / n/a	n/a / n/a / n/a	n/a / n/a / 26 vs. 26	Unclear information	167 | 167 vs. 167/64 | 66 vs. 66 / n/a	165 vs. 163 / 76 vs. 74 / n/a	n/a / n/a / n/a	n/a / n/a / n/a	n/a / n/a / n/a
Clinical classification	n/a	n/a[12]	n/a	Grade I + II acc. to Widmer	Grade II acc. to Widmer	Grade II acc. to Widmer	Grade II acc. to Widmer	n/a	n/a	Grade I + II acc. to Widmer
Primary endpoint	Increase of venous distensibility	Recurrence rate of ulcer	n/a	n/a	Leg circumference at calf + ankle	Change of leg volume	Change of oedema and associated symptoms	Capillary filtration rate (CFR)	Improvement of plasma free radicals (PFRs)	Venous capacity

[8] All patients were wearing compression stockings.

[9] Study contained of five study groups, whereas data of three groups were extracted only: for patients who received 300 mg tablets, 500 mg tablets and placebo as treatment. Treatment in the other groups met not inclusion criteria and was therefore not extracted.

[10] Study contained of two groups receiving 0-beta-hydroxyethyl-rutosides (it is not clear if patients received Paroven and/or Venoruton), a placebo-group and a group of healthy subjects, whereas the results for the group of healthy subjects were not extracted.

[11] Patients with grade I (acc. to Widmer) CVI received 2 x 1,000 mg HR per day in the first two weeks and 1 x 1,000 mg HR per day in the last two weeks of the treatment phase. Patients with grade II (acc. to Widmer) CVI received 3 x 1,000 mg HR per day in the first two weeks and 2 x 1,000 mg HR per day in the last two weeks of the treatment phase.

[12] All patients had recently healed venous ulcers.

Author, year, reference number	Capelli 1987 [32]	Wright 1991 [38]	Renton 1994 [35]	Neumann 1995 [21]	Cloarec 1996 [20]	Rehn 1996 (a) [34]	Unkauf 1996 [33] Großmann 1997 [36]	Cesarone 2002 (a) [31]	Cesarone 2002 (b) [30]	Petruzellis 2002 [37]
Inclusion criteria	Female patients, taking oral contraceptives, with symptoms and plethysmo-graphic signs of moderate CVI	n/a	Patients with ankle oedema due to mild to moderste venous hypertension due to deep or superficial incompetence	Patients with uni- or bilateral CVI grade I or II (Widmer), with no previous surgical or sclerosing therapy, aged 20-75 years, venous refill time <20 seconds, Transcutaneo us oxygen ≤55 mm Hg	Patients of both sexes, aged 20-70 years, with uni- or bilateral CVI grade II (Widmer), with pitting oedema in minimum one leg and minimum two symptoms of CVI	Female patients, postmeno-pausal, with CVI grade II (Widmer), generally rejected compression therapy	Female patients, aged 18-75 with CVI grade II (Widmer) with uni- or bilateral clinical leg oedema	Patients with venous hyper-tension (evalu-ated by colour duplex scanning and AVP measurement with intrave-nous needle), selected on ba-sis of severe superficial venous incom-petence with normal deep venous system, on waiting list for surgery	Patients with severe venous hypertension (ambulatory venous pressure >55 mm Hg, refilling time <8 seconds) with ankle swelling and lipodermatosc lerosis	Patients with grade I or II CVI, aged 18-65 years.
Duration of Treatment (months)	1	18	1	4	2[13]	3[14]	3[15]	1	1[16]	1
Follow-up (months)	0	0	0	0	0	0	1.5	0	0	0
Drop-outs, n (%)	n/a	n/a	4 (21) vs. 5 (24)	1 (8) vs. 0 (0)	5 (5)[17]	n/a	11 (9)[18]	n/a	n/a	n/a
Efficacy-related outcomes										
Change of CVI stage	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
CVI signs (general)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Trophic alterations	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

[13] The study started with a placebo-run-in-phase of four weeks, followed by an 8-week treatment phase.

[14] The study started with a placebo-run-in-phase of two weeks, followed by a 12-week treatment phase.

[15] The study started with a placebo-run-in-phase of one week, followed by a 12-week treatment phase and a 6-week follow-up phase without treatment.

[16] The study started with a wash-out phase of 2 weeks.

[17] Of the 109 patients who entered study, a total of 5 patients withdrew from study, but these patients were not considered for any results of the study.

[18] Of the 133 patients who entered the study, a total of 13 patients withdrew from study.

Author, year, reference number	Capelli 1987 [32]	Wright 1991 [38]	Renton 1994 [35]	Neumann 1995 [21]	Cloarec 1996 [20]	Rehn 1996 (a) [34]	Unkauf 1996 [33] Großmann 1997 [36]	Cesarone 2002 (a) [31]	Cesarone 2002 (b) [30]	Petruzellis 2002 [37]
Oedema (or leg volume or circumference)	n/a	n/a	*Oedema score (0-10)*[19]*:* *Foot:* Baseline: 1.5 vs. 2.7; p=n/a After 1 month: 0.5 vs. 1; p=n/a After 2; 3; 6; 12 months: n/a *Ankle:* Baseline: 1.2 vs. 2.8; p=n/a After 1 month: 1 vs. 1.5; p=n/a After 2; 3; 6; 12 months: n/a	*Leg volume (ml)*[20]*:* Baseline: 3,233 vs. 3,430; p=n/a After 1 month: 3,204 vs. 3,176; **p<0.001 (in favour of stockings)** After 2, 3 months: n/a After 4 months: 3,143 vs.3,200; **p=0.005 (in favour of stockings)** After 6; 12 months: n/a	*Oedema*[21]*:* Baseline: 51 vs. 50; p=n/a After 1 month: 49 vs. 50; p=n/a After 2 months: 38 vs. 49; p=n/a After 3; 6; 12 months: n/a *Calf circum-ference (mm):* Baseline: 347 vs. 339; p=n/a After 1 month: 344 vs. 339; **p<0.01** After 2 months: 340 vs. 339; **p<0.01** After 3; 6; 12 months: n/a *Ankle circum-ference (mm):* Baseline: 227 vs. 223; p=n/a After 1 month: 225 vs. 223; **p<0.01** After 2 months: 221 vs. 225; **p<0.01** After 3; 6; 12 months: n/a	*Leg volume change (ml)*[22]*:* Baseline: 0 | 0 vs. 0 After 1 month: -4.6 | -7.4 vs. 6.5; **p=0.008 | p<0.0001** After 2 months: -23.0 | -23.9 vs. -2.6; **p<0.001 | p<0.001** After 3 months: -29.8 | -29.2 vs. 2.1; **p<0.001 | p<0.001** After 6; 12 months: n/a	*Leg volume (ml):* Baseline: 2,165 vs. 2,167; **p=N.S.** After 1 month: 2,111 vs. 2,142; **p=0.028** After 2 months: 2,116 vs. 2,138; **p=N.S.** After 3 months: 2,101 vs. 2,134; **p=0.033** After 4.5 months: 2,133 vs. 2,159; **p=N.S.** After 6; 12 months: n/a *Leg volume change (ml):* Baseline: 0 vs. 0 After 1 month: --53.9 vs. -24.9; **p=0.028** After 2 months: -48.9 vs. -28.7; **p=N.S.** After 3 months: -63.9 vs.+8.6; **p=0.004** After 4.5 months: -32.2 vs.-8.3; **p=N.S.** After 6; 12 months: n/a	n/a	n/a	*Oedema score (0-3)*[23]*:* Baseline: 1.73 vs. 1.9; p=n/a After 1 month: 0.65 vs. 1.55; **p<0.01** After 2; 3; 6; 12 months: n/a

[19] Oedema was measured with an analogue scale (0-10) by asking the patients.

[20] Oedema/leg volume was measured with an opto-electronic volometer in ml.

[21] Oedema was measured as the presence of pitting oedema in number of legs.

[22] Oedema/leg volume was measured with a rectangular glass container, filled with water. Results were only given as volume reduction from baseline (in ml).

[23] Oedema was measured with a composite analogue scale (0-3).

Author, year, reference number	Capelli 1987 [32]	Wright 1991 [38]	Renton 1994 [35]	Neumann 1995 [21]	Cloarec 1996 [20]	Rehn 1996 (a) [34]	Unkauf 1996 [33] Großmann 1997 [36]	Cesarone 2002 (a) [31]	Cesarone 2002 (b) [30]	Petruzellis 2002 [37]
Ulcer	n/a	*Recurrence rate (%):* Baseline: - After 1; 2; 3; 6 months: n/a After 12 months: 23 vs. 22; **p=N.S.** After 18 months: 34 vs. 32; **p=N.S.**	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
CVI symptoms (general)	*Improvement (%)*[24]*:* Baseline: - After 1 month: 97 vs. 60; **p<0.002** After 2; 3; 6; 12 months: n/a	n/a	n/a[25]	n/a[26]	*Score (0-15)*[27]*:* Baseline: 10.0 vs. 10.6; p=n/a After 1 month: 7.0 vs. 9.6; **p<0.001** After 2 months: 4.3 vs. 9.5; **p<0.001** After 3;6; 12 months: n/a.	n/a[28]	n/a[29]	*Score (0-10)*[30]*:* Baseline: 7.8 | 7.9 vs. 7.9; p=n/a After 1 month: 4.0 | 3.1 vs.6; p=n/a After 2; 3; 6; 12 months: n/a	*Score (0-10)*[31]*:* Baseline: 8.5 vs8.3; p=n/a After 1 month: 3.1 vs. 8.5; p=n/a After 2; 3; 6; 12 months: n/a	n/a[32]

[24] Subjective symptoms were measured by the following score: 0=absent, 1= light, 2=mild, 3=severe, 4= very severe; whereas only the improved number of legs after 1 month was shown.

[25] Subjective symptoms were measured with an analogue scale (scaling was not described) for pain, cramps, restless legs and paraesthesia.

[26] Only a general statement for subjective symptoms was given, without presenting any data.

[27] Subjective symptoms were measured with an arbitrary scale (0-3) for pain, cramps, restless legs, heaviness and swelling. Maximum score for general symptoms is 15.

[28] Subjective symptoms were measured with a visual analogue scale (0-10 cm) for heaviness, swelling and itching. The results for 300 and 500 mg treatment were pooled in the study.

[29] Subjective symptoms were measured with a visual analogue scale (0-10 cm) for restless legs, itching and heaviness.

[30] Subjective symptoms were measured with a visual analogue scale (0-10 cm), based on pain, cramps, restless legs, swelling and heaviness.

[31] Subjective symptoms were measured with a composite analogue scale (0-10), based on pain, restless legs, swelling and skin alternations.

[32] Subjective signs and symptoms were measured with a 4-point rating scale (0-3) for oedema, cramps, heaviness and paraesthesia.

Author, year, reference number	Capelli 1987 [32]	Wright 1991 [38]	Renton 1994 [35]	Neumann 1995 [21]	Cloarec 1996 [20]	Rehn 1996 (a) [34]	Unkauf 1996 [33] Großmann 1997 [36]	Cesarone 2002 (a) [31]	Cesarone 2002 (b) [30]	Petruzellis 2002 [37]
Pain	*Improvement (%):* Baseline: - After 1 month: 100 vs. 100; **p=N.S.** After 2; 3; 6; 12 months: n/a	n/a	*Score (0-10):* Baseline: 4.5 vs. 2.3; p=n/a After 1 month: 3.2 vs. 1.9; p=n/a After 2; 3; 6; 12 months: n/a	n/a	*Score (0-3):* Baseline: 1.7 vs. 1.9; p=n/a After 1 month: 1.4 vs. 1.8; p=n/a After 2 months: 0.9 vs. 1.8; p=n/a After 3 months: n/a	n/a	n/a	n/a	n/a	n/a
Cramps	*Improvement (%):* Baseline: - After 1 month: 100 vs. 25; **p=N.S.** After 2; 3; 6; 12 months: n/a	n/a	*Score (0-10):* Baseline: 2.5 vs. 3.1; p=n/a After 1 month: 0.7 vs. 1; p=n/a After 2; 3; 6; 12 months: n/a	n/a	*Score (0-3):* Baseline: 1.7 vs. 2.1; p=n/a After 1 month: 1.2 vs. 1.9; p=n/a After 2 months: 0.6 vs. 1.6; p=n/a After 3;6; 12 months: n/a	n/a	n/a	n/a	n/a	*Score (0-3):* Baseline: 1.5 vs. 1.35; p=n/a After 1 month: 0.28 vs. 0.3; **p=N.S.** After 2; 3; 6; 12 months: n/a
Restless legs	*Improvement (%):* Baseline: - After 1 month: 100 vs. 80; p=n/a After 2; 3; 6; 12 months: n/a	n/a	*Score (0-10):* Baseline: 4 vs. 3; p=n/a After 1 month: 3.2 vs. 2.5; p=n/a After 2; 3; 6; 12 months: n/a	n/a	*Score (0-3):* Baseline: 2.0 vs. 2.2; p=n/a After 1 month: 1.2 vs. 1.9; p=n/a After 2 months: 0.6 vs. 1.9; p=n/a After 3; 6; 12 months: n/a	n/a	n/a	n/a	n/a	n/a

Author, year, reference number	Capelli 1987 [32]	Wright 1991 [38]	Renton 1994 [35]	Neumann 1995 [21]	Cloarec 1996 [20]	Rehn 1996 (a) [34]	Unkauf 1996 [33] Großmann 1997 [36]	Cesarone 2002 (a) [31]	Cesarone 2002 (b) [30]	Petruzellis 2002 [37]
Itching (= tingling sensation)	*Improvement (%):* Baseline: - After 1 month: 100 vs.100; **p=N.S.** After 2; 3; 6; 12 months: n/a	n/a	n/a	n/a	n/a	*Score (0-10):* Baseline: 2.3 vs. n/a; p=n/a After 1 month: n/a After 2 months: n/a After 3 months: 0.1 vs. n/a; p=n/a After 6; 12 months: n/a	*Score (0-10):* Baseline: 2.5 vs. 2.8; p=n/a After 1 month: 1.6 vs. 2.4; p=n/a After 2 months: 1.7 vs. 2.1; p=n/a After 3 months: 1.6 vs. 1.4; p=n/a After 4.5 months: 1.9 vs. 1.8; p=n/a After 6; 12 months: n/a	n/a	n/a	n/a
Heaviness (= heavy legs)	*Improvement (%):* Baseline: - After 1 month: 89 vs. 67; p=n/a After 2; 3; 6; 12 months: n/a	n/a	n/a	n/a	*Score (0-3):* Baseline: 2.3 vs. 2.3; p=n/a After 1 month: 1.7 vs. 2.0; p=n/a After 2 months: 1.2 vs. 2.2; p=n/a After 3; 6; 12 months: n/a	*Score (0-10):* Baseline: 5.2 vs. 4.9; p=n/a After 1 month: n/a After 2 months: n/a After 3 months: 1.1 vs. 4.1; p=n/a After 6; 12 months: n/a	*Score (0-10):* Baseline: 3.7 vs. 4.0; p=n/a After 1 month: 2.2 vs. 3.2; p=n/a After 2 months: 2.7 vs. 2.6; p=n/a After 3 months: 2.7 vs. 2.2; p=n/a After 4.5 months:2.8 vs. 2.2; p=n/a After 6; 12 months: n/a	n/a	n/a	*Score (0-3):* Baseline: 2.18 vs. 2.15; p=n/a After 1 month: 1.03 vs. 1.0; **p<0.01** After 2; 3; 6; 12 months: n/a

Author, year, reference number	Capelli 1987 [32]	Wright 1991 [38]	Renton 1994 [35]	Neumann 1995 [21]	Cloarec 1996 [20]	Rehn 1996 (a) [34]	Unkauf 1996 [33] Großmann 1997 [36]	Cesarone 2002 (a) [31]	Cesarone 2002 (b) [30]	Petruzellis 2002 [37]
Swelling (= sensation of tension)	*Improvement (%):* Baseline: - After 1 month: 100 vs. 100; **p=N.S.** After 2; 3; 6; 12 months: n/a	n/a	n/a	n/a	*Score (0-3):* Baseline: 2.2 vs. 2.3; p=n/a After 1 month: 1.5 vs. 2.0; p=n/a After 2 months: 1.0 vs. 2.0; p=n/a After 3; 6; 12 months: n/a	*Score (0-10):* Baseline: 4.7 vs. n/a; p=n/a After 1 month: n/a After 2 months: n/a After 3 months: 0.7 vs. n/a; p=n/a After 6; 12 months: n/a	*Score (0-10):* Baseline: 3.5 vs. 3.7; p=n/a After 1 month: 2.3 vs. 2.7; p=n/a After 2 months: 2.5 vs. 2.4; p=n/a After 3 months: 2.3 vs. 2.0; p=n/a After 4.5 months: 2.8 vs. 2.2, p=n/a After 6; 12 months: n/a	n/a	n/a	n/a
Paraesthesias	n/a	n/a	*Score (0-10):* Baseline: 4.1 vs. 2.7; p=n/a After 1 month: 2 vs. 0.7; p=n/a After 2; 3; 6; 12 months: n/a	n/a	n/a	n/a	n/a	n/a	n/a	*Score (0-3):* Baseline: 1.48 vs. 1.05; **p=N.S.** After 1 month: 0.35 vs. 0.45; p=n/a After 2; 3; 6; 12 months: n/a
QoL	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Safety-related outcomes										
Adverse events, general in % (n) pts.	0 vs. 0	n/a	n/a	n/a	21 (11) vs. 14 (7); p=n/a (flatulence, abdominal pain, nausea, diarrhoea, etc. in both groups)[33]	n/a[34]	6 (4) vs. 4 (3)[35]; p=n/a (muscle cramps for stockings, gastrointestinal complaints, etc. in both groups)[33]	n/a	0 vs. 0	0 vs. 0

[33] Adverse events were described only in general terms.

[34] In total 7 patients reported abdominal pain or vomiting.

[35] Originally, 133 patients were enrolled in the study, whereas 13 were excluded from efficacy analysis but all 133 patients were included in the safety analysis.

Author, year, reference number	Capelli 1987 [32]	Wright 1991 [38]	Renton 1994 [35]	Neumann 1995 [21]	Cloarec 1996 [20]	Rehn 1996 (a) [34]	Unkauf 1996 [33] Großmann 1997 [36]	Cesarone 2002 (a) [31]	Cesarone 2002 (b) [30]	Petruzellis 2002 [37]
Major adverse events	o vs. o	n/a	n/a	n/a	n/a	n/a	n/a	n/a	o vs. o	o vs. o
Minor adverse events	o vs. o	n/a	n/a	n/a	n/a	n/a	n/a	n/a	o vs. o	o vs. o
Adverse events, treatment-related in % (n) pts.	o vs. o	n/a	o vs. o	o vs. o	n/a	n/a	n/a	n/a	o vs. o	o vs. o
Major adverse events	o vs. o	n/a	o vs. o	o vs. o	n/a	n/a	n/a	n/a	o vs. o	o vs. o
Minor adverse events	o vs. o	n/a	o vs. o	o vs. o	n/a	n/a	n/a	n/a	o vs. o	o vs. o

Abbreviations: acc. = according; CVI = chronic venous insufficiency; HR = 0(beta-hydroxyethyl)-rutosides (also called oxerutin);n = number (of patients); n/a = data not available; N.S. = not statistically significant; pts. = patients; QoL = quality of life; RCT = randomised controlled trial;vs. = versus; yrs. = years

Table 3.1-2: Safety-related outcomes of non-randomised trials of oxerutin-containing agents for CVI

Author, year, reference number	Belcaro 2008 (a) [39]	Belcaro 2008 (b) [40]
Country	Italy	Italy
Study design	Registry study	Registry study
Sponsor	None	None
Intervention/Product	3x 500 mg HR tablets (Venoruton®) | 2x 1,000 mg HR granulate (Venoruton®) per day	2x 1,000 mg HR granulate (Venoruton®) per day[36]
Comparator	No treatment | compression stockings	Compression stockings
Number of pts.	98 | 87 vs. 90 |113	24 vs. 20
Age of patients (yrs.)	Ø 46 | 45 vs. 46 vs. 46	46 vs. 45
Sex (% female)	n/a	63 vs. 60
Height (cm)/Weight (kg)/BMI (kg/m²)	n/a / n/a / n/a	n/a / n/a / n/a
Clinical classification	n/a	n/a
Primary endpoint	n/a	n/a
Inclusion criteria	Patients with severe CVI (ambulatory venous pressure >56 mm Hg, refilling time <10 seconds, deep venous incompetence shown by duplex scanning)	Patients with severe CVI (ambulatory venous pressure >56 mm Hg, refilling time <10 seconds and deep venous incompetence shown by duplex scanning)
Duration of treatment (months)	60	2
Follow-up (months)	0	0
Drop-outs, n (%)	4 (4) | 4 (5) vs. 7 (8) | 8 (7)	n/a
Safety-related outcomes		
Adverse events, general in % (n) pts.	0 | 0 vs. 0 | 0	0 vs. 0
Major adverse events	0 | 0 vs. 0 | 0	0 vs. 0
Minor adverse events	0 | 0 vs. 0 | 0	0 vs. 0
Adverse events, treatment-related in % (n) pts.	0 | 0 vs. 0 | 0	0 vs. 0
Major adverse events	0 | 0 vs. 0 | 0	0 vs. 0
Minor adverse events	0 | 0 vs. 0 | 0	0 vs. 0

Abbreviations: CVI = chronic venous insufficiency, HR = 0(beta-hydroxyethyl)-rutosides (also called Oxerutin), n = number (of patients); n/a = data not available; pts. = patients; yrs. = years

[36] The study included an additional treatment group that received oral HR and additional topical HR as a gel. The results of this group were not extracted, since the treatment with gel is not meeting the inclusion criteria. The results of another group with healthy subjects were also not extracted. Furthermore, all groups received topical treatment with a gel, whereas the gel was placebo.

Efficacy

10 RCTs:
9 Placebo-kontrolliert und 1 vergleicht mit Kompressionsstrümpfen

For evaluating the efficacy of oxerutin (0-beta-hydroxyethyl-rutoside, HR) containing capillary stabilising agents, we identified a total of 10 RCTs [20, 21, 30-38] that met our inclusion criteria (one study was published twice [33, 36]). Of these, 9 were placebo-controlled [20, 30-38] and 1 compared HR against compression therapy [21]. Furthermore, in 2 of the identified studies, patients have additionally worn compression stockings in both study groups [30, 33, 36].

652 PatientInnen in Studien: durchschnittlich 44-68 Jahre alt, 30-100 % Frauen, Krankheitsgrad I-II nach Widmer

Overall, there were 652 patients in the studies, of whom 139 were treated with 1,000 mg oxerutin granulate, 199 received the 500 mg and 20 the 300 mg tablets. A total of 282 patients in the control groups received placebo and 12 were treated with compression stockings only [20, 21, 30-38]. The patients were on average between 45 and 67 years in the treatment groups and between 44 and 68 years in the control groups. The majority of the patients – except in two studies [30, 31] -were females: 30-100% in the oxerutin groups and 35-100% in the control groups [20, 21, 32, 33, 36-38]. Furthermore, the patients had CVI grade I and II according to Widmer [20, 21, 33, 34, 36, 37]. In addition, the duration of treatment was 1-18 months, whereby there was mostly no follow-up without treatment [20, 21, 30-32, 34, 35, 37, 38], except in one study (follow-up was 1.5 months) [33, 36].The drop-out rate differed between 4 and 23% [20, 21, 33, 35,36].

Zusammenfassung in GRADE-Tabellen

A summary of the effect sizes for the individual outcome indicators is presented in Tables 3.1-3 to 3.1-4.

Oxerutin-containing agents (+ compression stockings) versus placebo (+ compression stockings)

einige nicht berichtete Endpunkte

None of the identified studies assessed the change of the CVI stage, the CVI signs in general, trophic alternations (a sign for CVI) and the quality of life of a treatment with oxerutin versus placebo.

Scores für Ödeme gleichermaßen in Gruppen reduziert

Regarding individual signs of CVI, oedema was assessed in 6 studies and measured by several parameters: in two studies the change of the score (0-10) was reduced slightly in the oxerutin groups and in the placebo groups with -1; -0.2 and -3.3 vs. -1.7; -1.3 and -1.3 for oedema at the foot, ankle and in general respectively. Whether the difference is statistically significant is unknown [35, 37].

Ödem als Beinvolumen zusammengefasst: signifikant mehr reduziert in Oxerutin-Gruppen

Furthermore, in two other studies, oedema was measured by leg volume (in ml) and in both studies the volume was more reduced during 3 months of treatment in the treatment than in the control groups. The difference between the study groups was statistically significant [33, 36, 41]. However, one of these studies measured the leg volume 1.5 months after treatment and the values did not show a statistically significant difference anymore [33, 36].

Meta-Analysen zeigen zunehmende Reduktion Beinvolumen mit Oxerutin

The results from the meta-analysis on leg volume change after 1, 2 and 3 months of treatment are displayed in the Figures 3.1-1, 3.1-2 and 3.1-3. The individual forest plots are showing that the reduction of the leg volume is increasing with every month with a mean difference in the first month of -13.1 ml, of -20.8 ml in second month and of -31.5 ml in the third month. The difference is statistically significant in favour of a treatment with oxerutin-containing agents compared to placebo in every month (the shown p-values are related to the overall effect and not to I^2). Furthermore, the forest plot shows that the study with more patients [33, 36] does not provide more precise estimated effect, due to a low weight of the study (small square) and a wide confidence interval (long horizontal line).

Umfänge am Bein etwas mehr in Oxerutin-Gruppen reduziert

In addition, another study assessed oedema by measuring the ankle and calf circumference (in mm) and by stating the number of legs with pitting oedema, whereby all values were reduced slightly more in the treatment groups than in the placebo groups during 2 months of treatment (in mm: -7 to -6 vs. ±0 to +2; number of legs: -13 vs. -1) [20].

Beingeschwüre kamen wieder

Ulcer, another consequence of CVI, was measured as the recurrence rate which was slightly, but not statistically significantly, higher after 18 months of treatment in the oxerutin group compared to the placebo group (34 vs. 32%) [38].

Study name	Statistics for each study			Sample size		Mean difference, 95% CI
	Difference in means	Lower limit	Upper limit	Oxerutin	Placebo	
Rehn 1996 (a) (300 mg HR)	-11.10	-18.50	-3.70	20	10	
Rehn 1996 (a) (500 mg HR)	-13.90	-20.78	-7.02	20	10	
Unkauf 1996/Großmann 1997	-29.00	-58.46	0.46	64	56	
Total (95% CI)	**-13.07**	**-18.03**	**-8.10**	**104**	**76**	
						-60 -30 0 30 60
Random effects meta-analysis; I^2: 0.0%; p<0.001						Favours oxerutin Favours placebo

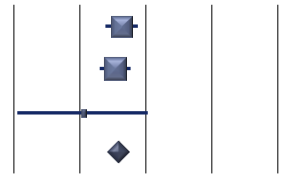

Figure 3.1-1: Leg volume change (in ml) after 1 month for oxerutin-containing agents (+ compression stockings) vs. placebo (+ compression stockings)

Study name	Statistics for each study			Sample size		Mean difference, 95% CI
	Difference in means	Lower limit	Upper limit	Oxerutin	Placebo	
Rehn 1996 (a) (300 mg HR)	-20.40	-27.40	-13.40	20	10	
Rehn 1996 (a) (500 mg HR)	-21.30	-29.17	-13.43	20	10	
Unkauf 1996/Großmann 1997	-20.20	-54.70	14.30	64	56	
Total (95% CI)	**-20.78**	**-25.95**	**-15.61**	**104**	**76**	
						-60 -30 0 30 60
Random effects meta-analysis; I^2: 0.0%; p<0.001						Favours oxerutin Favours placebo

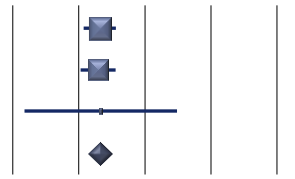

Figure 3.1-2: Leg volume change (in ml) after 2 months for oxerutin-containing agents (+ compression stockings) vs. placebo (+ compression stockings)

Study name	Statistics for each study			Sample size		Mean difference, 95% CI
	Difference in means	Lower limit	Upper limit	Oxerutin	Placebo	
Rehn 1996 (a) (300 mg HR)	-31.90	-40.49	-23.31	20	10	
Rehn 1996 (a) (500 mg HR)	-31.30	-38.87	-23.73	20	10	
Unkauf 1996/Großmann 1997	-31.00	-68.72	1.72	64	56	
Total (95% CI)	**-31.55**	**-37.14**	**-25.95**	**104**	**76**	
						-65 -32,5 0 32,5 65
Random effects meta-analysis; I^2: 0.0%; p<0.0001						Favours oxerutin Favours placebo

Figure 3.1-3: Leg volume change (in ml) after 3 months for oxerutin-containing agents (+ compression stockings) vs. placebo (+ compression stockings)

generelle CVI-Symptome in Oxerutin Gruppen stärker reduziert, zeigt auch Forest-Plot

The symptoms of CVI, in general, were more reduced (on a score of 0-10) and improved (in %) in the oxerutin groups than in the placebo groups during the first month of treatment (score: -5.4 to -2 vs. -1.9 to +0.2; percentage: 97 vs. 60%) [20, 30-32]. The reduction or improvement was described as statistically significant [20, 32]. The meta-analysis of the symptom score reduction after 1 month is displayed in Figure 3.1-4. The forest plot is showing that the reduction of the symptom score and the difference is statistically significant in favour of a treatment with oxerutin-containing agents compared to placebo. However, the meta-analyses shows also a high heterogeneity with I^2>80%. That means the studies are measuring different effects due to e.g., differences in subject population or intervention. In addition, the reduction of the general symptom score in one study was higher in the treatment group after 2 months of treatment (-3.8 vs. -0.8). The difference between groups was statistically significant [20].

einzelne CVI-Symptome (Schmerzen Krämpfe, etc.) konnten in Oxerutin-Gruppen meist etwas stärker reduziert werden

The individual symptoms of CVI (score 0-10) could mostly be more reduced (was not stated if statistically significant) after 2 months (and also after 1 month) of treatment in the oxerutin groups than in the placebo groups for pain (-2.7 vs. -0.3.), cramps (-3.7 vs. 1.7) and restless legs (-4.7 vs. -1) [20]. The scores (0-10) for itching, heaviness and swelling were improved slightly more (was not stated if statistically significant) after 3 months of treatment in the oxerutin groups compared to the placebo groups (itching: -2.2 to -0.9 vs. -1.4; heaviness: -4.1 to -1 vs. -1.8 to -0.8; swelling: -4 to -1.2 vs. -1.7) [33, 35, 36]. However, the reduction of scores for itching, heaviness and swelling after 1.5 months of treatment were slightly lower in the oxerutin groups than in the placebo groups (itching: -0.6 vs. -1; heaviness: -0.9 vs. -1.8; swelling: -0.7 vs. -1.5) [33, 36]. The percentage of patients with improvement after 1 month of treatment was in both study groups similar (and therefore not statistically significantly higher of lower in one group) for pain, cramps, itching and swelling (respective 100 vs. 100%) and slightly higher in the treatment groups than in the placebo groups for restless legs (100 vs. 80%) and heaviness (89 vs. 67%) [32].The score after 1 month for paraesthesias could be reduced slightly more (was not stated if statistically significant) in the oxerutin groups compared to placebo (-3.8 to -2.1 vs. -2) [35, 37].

Study name	Statistics for each study			Sample size		Mean difference, 95% CI
	Difference in means	Lower limit	Upper limit	Oxerutin	Placebo	
Cloarec 1996	-1.73	-2.58	-0.88	53	51	
Cesarone 2002(a) (500 mg HR)	-2	-3.24	-0.76	15	7	
Cesarone 2002(a) (1,000 mg HR)	-2.90	-4.17	-1.63	16	8	
Cesarone 2002(b)	-5.40	-6.64	-4.16	20	20	
Total (95% CI)	**-2.98**	**-4.60**	**-1.36**	**104**	**86**	
						-8 -4 0 4 8
Random effects meta-analysis; I^2: 87.8%; p<0.001						Favours oxerutin Favours placebo

Figure 3.1-4: Symptom change (score 0-10) after 1 month for oxerutin-containing agents (+ compression stockings) vs. placebo (+ compression stockings)

Oxerutin-containing agents versus compression stockings only

die meisten Endpunkte nicht berichtet

There was no evidence available assessing the change of the CVI stage, the CVI signs in general, trophic alternations and ulcer, CVI-related symptoms and quality of life for a treatment with oxerutin-containing agents compared to compression stockings.

Beinvolumen (Ödeme) mit Kompressionsstrümpfe mehr reduziert

The only reported efficacy-related outcome was the leg volume (in ml). After 4 months of treatment, leg volume was statistically significantly more reduced in the group that was wearing compression stockings (-230 ml) than in the group that received oxerutin-containing agents (-90 ml) [21].

Safety

zusätzlich zwei non-RCTs für Sicherheit

For evaluating the safety of oxerutin-containing capillary stabilising agents, we identified, besides 7 out of the 10 previously described RCTs, 2 additional non-randomised controlled registry studies (non-RCTs) [39, 40] that met our inclusion criteria. The study characteristics and results of the non-RCTs are summarised in the Table 3.1-2.

in non-RCTs 432 PatientInnen, 45-46 Jahre alt, 60 % Frauen

In the non-RCTs, a total of 432 patients were included in the studies, of whom 98 received 500 mg of oxerutin-containing agents three times a day and 111 received 1,000 mg of oxerutin-containing agents twice a day. In the control groups 133 of the patients were wearing compression stockings and 90 did not receive any treatment [39, 40]. The mean ages of the patients were 45 to 46 years in the treatment and in the control groups [39, 40]. Around 60% of the patients in both groups were females [39]. The duration of treatment ranged from 2-60 months, whereas there was no follow-up after treatment [39, 40]. Furthermore, the drop-out rate in the oxerutin groups was 4-5% and in the control groups 7-8% [40].

Zusammenfassung in GRADE-Tabellen

A summary of the effect sizes for the individual outcome indicators is presented in Tables 3.1-3 to 3.1-5.

Oxerutin-containing agents (+ compression stockings) versus placebo (+ compression stockings)

allgemeine unerwünschte Ereignisse: 6-21 % vs. 4-14 %

If reported, the general adverse events differed between 6 and 21% in the oxerutin groups and between 4 and 14% in the control groups. The most common adverse events in both groups were pain, gastrointestinal complaints and nausea, plus muscle cramps for patients who were wearing stockings [20, 33, 36].

keine Nebenwirkungen

There were no treatment-related adverse events in any of the study groups [30, 32, 35, 37].

Oxerutin-containing agents versus compression stockingsonly

keine unerwünschten Ereignisse oder Nebenwirkungen

There were no general or treatment-related adverse events in neither the oxerutin group nor the group that was wearing compression stockings [21, 39, 40].

Oxerutin-containing agents versus no treatment

unerwünschte Ereignisse unberichtet

There was no available evidence that analysed adverse events in general of a treatment with oxerutin-containing agents compared to no treatment.

keine Nebenwirkungen

However, there were no treatment-related adverse events in the oxerutin group or the group that did not receive a treatment [39].

Risk of bias

Bias-Risiko für RCTs insgesamt unklar

The majority of the identified RCTs for a treatment of CVI with oxerutin-containing agents have an unclear risk of bias for several types of biases (see Figure 3.1-5). Half of the studies show a high risk of reporting bias due to not reported baseline values, no reported scaling of outcome measurement or no detailed description of outcomes. In summary, the risk of bias is unclear.

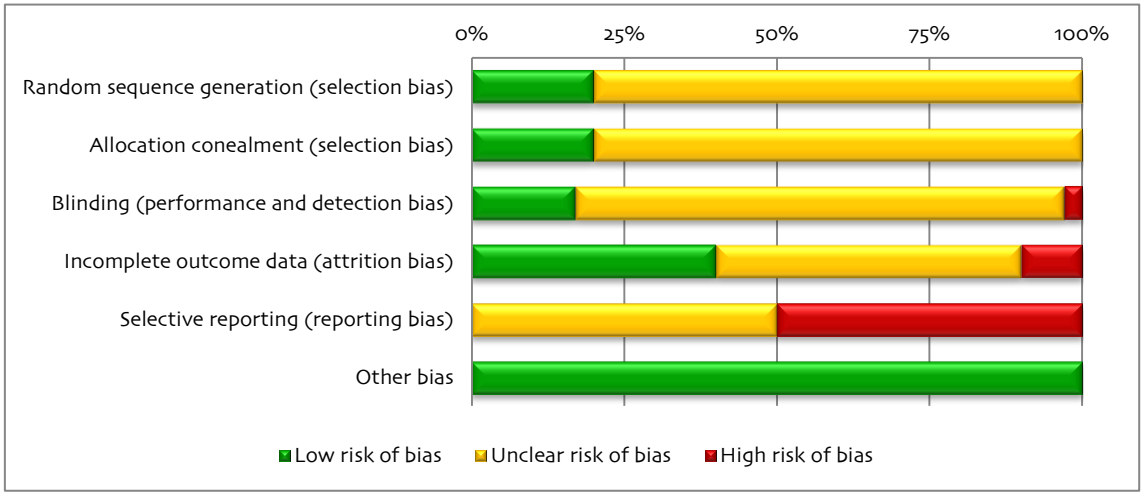

Figure 3.1-5: Risk of bias of RCTs for treatment of CVI with oxerutin-containing agents

Bias-Risiko für non-RCTs insgesamt mittel bis hoch

Partly, the non-RCTs have a high risk of selection bias due to a missing description of the allocated prognostic factors. Furthermore there is a high risk of performance and detection bias due to no blinding of the studies. There is also an existing risk of reporting bias due to a missing analysis of confounding (see Figure 3.1-6).

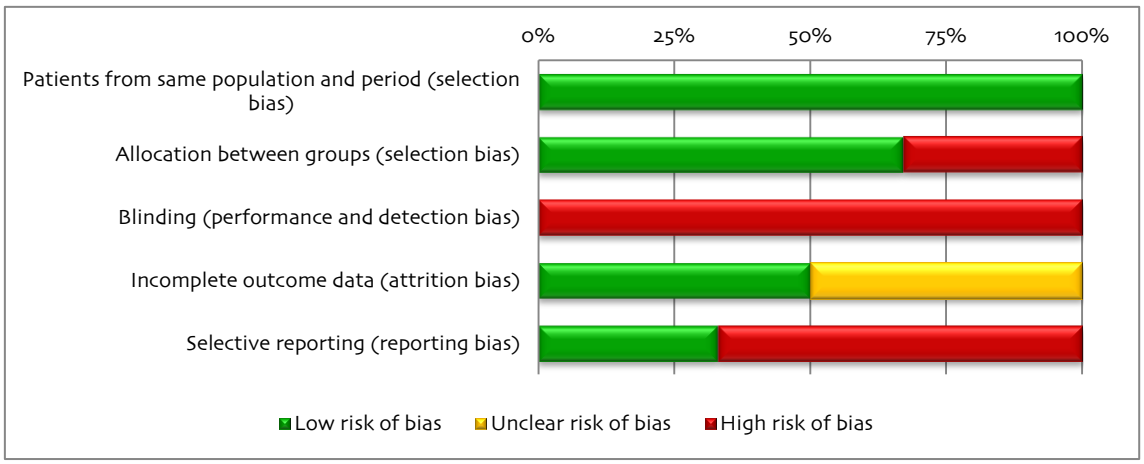

Figure 3.1-6: Risk of bias of non-randomised controlled studies for treatment of CVI with oxerutin-containing agents

Strength of evidence

Evidenzstärke niedrig bis sehr niedrig

Overall, the strength of evidence of the efficacy and safety of a treatment of CVI with oxerutin-containing agents compared to placebo, compression therapy and no treatment (only safety) is low to very low. Although the majority of studies were RCTs, due to several study limitations and a low number of patients in the studies, the strength of evidence was downgraded. The strength of evidence is summarised in the Tables 3.1-3, 3.1.-4 and 3.1-5.

keine Evidenz zu Vergleich mit anderen Behandlungen

There was no evidence available to compare a treatment of CVI with oxerutin-containing agents with other interventions, such as lifestyle changes or further local, medical and surgical treatment, mentioned in Chapter 1.1.2.

Table 3.1-3: Evidence profile: Efficacy and safety of oxerutin-containing agents for treatment of CVI compared to placebo

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Efficacy: oxerutin-containing agents (+ compression stockings) versus placebo (+ compression stockings)							
Change of CVI stage: no evidence							
CVI signs (general): no evidence							
CVI signs (trophic alternations): no evidence							
CVI signs (oedema): change at foot from baseline (score 0-10)							
1/40	RCT	1 mo: -1 vs.-1.7; p=n/a	Serious limitations (-1)[37]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI signs (oedema): change at ankle from baseline (score 0-10)							
1/40	RCT	1 mo: -0.2 vs. -1.3; p=n/a	Serious limitations (-1)[37]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI signs (oedema): general change from baseline (score 0-10)							
1/60	RCT	1 mo: -3.33 vs. -1.33; p=n/a	Serious limitations (-1)[39]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI signs (oedema): leg volume change from baseline (in ml)							
2/180	RCTs	1 mo: -4.6 to -53.9 vs. -24.9 to +6.5; p=S.S.	Serious limitations (-1)[40]	Important inconsistency (-1)[41]	Direct	Imprecise data (-1)[38]	Very low
2/180	RCTs	2 mo: -48.9 to -23 vs. -2.6 to -28.7; p=S.S.	Serious limitations (-1)[40]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
2/180	RCTs	3 mo: -63.9 to -29.8 vs. +2.1 to +8.6; p=S.S.	Serious limitations (-1)[40]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
1/120	RCT	4.5 mo: -32.2 vs. -8.3; p=N.S.	Serious limitations (-1)[40]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI signs (oedema): number of legs change from baseline							
1/104	RCT	1 mo: -2 vs. ±0; p=n/a 2 mo: -13 vs. -1; p=n/a	Serious limitations (-1)[42]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI signs (oedema): calf/ankle circumference change from baseline (in mm)							
1/104	RCT	1 mo: -3/-2 vs. ±0/±0; p=S.S./p=S.S. 2 mo: -7/-6 vs. ±0/+2; p=S.S./p=S.S.	Serious limitations (-1)[42]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low

[37] Unclear random sequence generation and blinding of outcome assessors (patients were asked to evaluate signs and symptoms).

[38] Low incidence, study/studies not powered to detect difference.

[39] Unclear blinding of participants, personnel and outcome assessor, plus random sequence generation.

[40] Unclear random sequence generation in one trial, the other study was conducted as single-blind and unclear blinding of outcome assessment in both studies.

[41] Values of control group increased in one study and decreased in the other study.

[42] Unclear random sequence generation and blinding of outcome assessors.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
CVI signs (ulcer): recurrence rate (in %)							
1/138	RCT	12 mo: 23 vs. 22; p=N.S. 18 mo: 34 vs. 32; p=N.S.	Serious limitations (-1)[42]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI symptoms (general): improvement (in %)							
1/20	RCT	1 mo: 97 vs. 60; p=S.S.	Serious limitations (-1)[43]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI symptoms (general): change from baseline (score 0-10)							
3/190 1/104	RCT RCT	1 mo: -5.4 to -2 vs. -1.9 to +0.2; p=S.S.[44] 2 mo: -3.8 vs. -0.8; p=S.S.[44]	Serious limitations (-1)[45] Serious limitations (-1)[42]	Important inconsistency (-1)[41] n/a (only 1 trial)	Direct Direct	Imprecise data (-1)[38] Imprecise data (-1)[38]	Very low Low
CVI symptoms (pain): improvement (in %)							
1/20	RCT	1 mo: 100 vs. 100; p=N.S.	Serious limitations (-1)[43]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI symptoms (pain): change from baseline (score 0-10)							
2/144 1/104	RCT RCT	1 mo: -1.3 to -1 vs. -0.4 to -0.3; p=n/a[46] 2 mo: -2.7 vs. -0.3; p=n/a[46]	Serious limitations (-1)[47] Serious limitations (-1)[42]	No important inconsistency n/a (only 1 trial)	Direct Direct	Imprecise data (-1)[38] Imprecise data (-1)[38]	Low Low
CVI symptoms (cramps): improvement (in %)							
1/20	RCT	1 mo: 100 vs. 25; p=N.S.	Serious limitations (-1)[43]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI symptoms (cramps): change from baseline (score 0-10)							
3/204 1/104	RCT RCT	1 mo: -4 to -1.7 vs. -3.5 to -0.7; p=N.S. in one study[48] 2 mo: -3.7 vs. 1.7; p=n/a[46]	Serious limitations (-1)[49] Serious limitations (-1)[42]	No important inconsistency n/a (only 1 trial)	Direct Direct	Imprecise data (-1)[38] Imprecise data (-1)[38]	Low Low
CVI symptoms (restless legs): improvement (in %)							
1/20	RCT	1 mo: 100 vs. 80; p=n/a	Serious limitations (-1)[43]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI symptoms (restless legs): change from baseline (score 0-10)							

[43] Unclear blinding of outcome assessor.

[44] The score in one study was 0-15; the values were multiplied with 0.67 to adopt them to a score of 0-10.

[45] Unclear random sequence generation in all 3 studies and unclear blinding of outcome assessor in 1 study.

[46] The scores of studies on a scale of 0-3 were multiplied with 3.33 to adopt them to a score of 0-10.

[47] Unclear random sequence generation in both studies and unclear blinding of outcome assessor in 1 study.

[48] The score in two studies was 0-3, the values were multiplied with 3.33 to adopt them to a score of 0-10.

[49] Unclear random sequence generation in and unclear blinding of outcome assessor all 3 studies.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
2/144	RCT	1 mo: -2.7 to -0.8 vs. -1 to -0.5; p=n/a[46]	Serious limitations (-1)[47]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
1/104	RCT	2 mo: -4.7 vs. -1; p=n/a[46]	Serious limitations (-1)[42]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI symptoms (itching): improvement (in %)							
1/20	RCT	1 mo: 100 vs. 100; p=N.S.	Serious limitations (-1)[43]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI symptoms (itching): change from baseline (score 0-10)							
1/120	RCT	1 mo: -0.9 vs. -0.4; p=n/a	Serious limitations (-1)[50]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
1/120	RCT	2 mo: -0.8 vs. -0.7; p=n/a	Serious limitations (-1)[50]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
2/180	RCT	3 mo: -2.2 to -0.9 vs. -1.4; p=n/a	Serious limitations (-1)[51]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
1/120	RCT	4.5 mo: -0.6 vs. -1; p=n/a	Serious limitations (-1)[50]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI symptoms (heaviness): improvement (in %)							
1/20	RCT	1 mo: 89 vs. 67; p=n/a	Serious limitations (-1)[43]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI symptoms (heaviness): change from baseline (score 0-10)							
3/284	RCT	1 mo: -3.8 to -1.5 vs. -3.8 to -0.8; p=s.s in one study[46]	Serious limitations (-1)[52]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
2/224	RCT	2 mo: -3.7 to -1 vs. -1.4 to -0.3; p=n/a[46]	Serious limitations (-1)[53]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
2/180	RCT	3 mo: -4.1 to -1 vs. -1.8 to -0.8; p=n/a	Serious limitations (-1)[54]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
1/120	RCT	4.5 mo: -0.9 vs. -1.8; p=n/a	Serious limitations (-1)[50]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI symptoms (swelling): improvement (in %)							
1/20	RCT	1 mo: 100 vs. 100; p=N.S.	Serious limitations (-1)[43]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI symptoms (swelling): change from baseline (score 0-10)							
2/224	RCT	1 mo: -2.3 to -1.2 vs. -1; p=n/a[46]	Serious limitations (-1)[53]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
2/224	RCT	2 mo: -4 to -1 vs. -1.3 to -1; p=n/a[46]	Serious limitations (-1)[53]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
2/180	RCT	3 mo: -4 to -1.2vs. -1.7; p=n/a	Serious limitations (-1)[54]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
1/120	RCT	4.5 mo: -0.7 vs. -1.5; p=n/a	Serious limitations (-1)[50]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low

[50] Unclear random sequence generation and blinding of outcome assessor.

[51] Unclear random sequence generation in one study, one study was conducted as single-blinded and unclear blinding of outcome assessor in one study.

[52] Unclear random sequence generation in all 3 studies and unclear blinding of outcome assessor in 2 studies.

[53] Unclear random sequence generation and unclear blinding of outcome assessor in 1 study.

[54] Unclear random sequence generation in one study, one study was conducted as single-blinded and unclear blinding of outcome assessor in both studies.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
CVI symptoms (paraesthesias): change from baseline (score 0-10)							
2/100	RCT	1 mo: -3.8 to -2.1 vs. -2; p=n/a	Serious limitations (-1)[55]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
Quality of life: no evidence							
Safety: oxerutin-containing agents (+ compression stockings) versus placebo (+ compression stockings)							
Adverse events (general): in %							
2/224	RCT	6 to 21 vs. 4 to 14; p=n/a	Serious limitations (-1)[55]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low
Adverse events (treatment-related): in %							
4/160	RCT	0 vs. 0; p=N.S.	Serious limitations (-1)[56]	No important inconsistency	Direct	Imprecise data (-1)[38]	Low

Abbreviations: n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

[55] Unclear random sequence generation and unclear blinding of outcome assessor in both studies.

[56] Unclear random sequence generation in 3 studies and unclear blinding of outcome assessor in all studies.

Table 3.1-4: Evidence profile: Efficacy and safety of oxerutin-containing agents for treatment of CVI compared to compression stockings

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Efficacy: oxerutin-containing agents versus compression stockings alone							
Change of CVI stage: no evidence							
CVI signs (general): no evidence							
CVI signs (trophic alternations): no evidence							
CVI signs (oedema): leg volume change from baseline (in ml)							
1/24	RCT	1 mo: -29 vs. -254; p=S.S. (in favour of stockings) 4 mo: -90 vs. -230; p=S.S. (in favour of stockings	Serious limitations (-1)[57]	n/a (only 1 trial)	Direct	Imprecise data (-1)[38]	Low
CVI signs (ulcer): no evidence							
CVI symptoms: no evidence							
Quality of life: no evidence							
Safety: oxerutin-containing agents versus compression stockings alone							
Adverse events (general): in %							
2/342[58]	CT	0 vs. 0; p=N.S.	Serious limitations (-1)[59]	No important inconsistency	Direct	Imprecise data (-1)[38]	Very low
Adverse events (treatment-related): in %							
1/24 3/342[58]	RCT CT	0 vs. 0; p=N.S. 0 vs. 0; p=N.S.	Serious limitations (-1)[57] Serious limitations (-1)[59]	n/a (only 1 trial) No important inconsistency	Direct Direct	Imprecise data (-1)[38] Imprecise data (-1)[38]	Low Very low

Abbreviations: CT = controlled trial; n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

[57] Unclear random sequence generation and unclear blinding of outcome assessor.

[58] One study consisted of four study groups, whereas one group (90 patients) did not receive a treatment and was therefore excluded from this analysis.

[59] Studies were conducted as not blinded (and not randomised).

Table 3.1-5: Evidence profile: Safety of oxerutin-containing agents for treatment of CVI compared to no treatment

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Safety: oxerutin-containing agents versus no treatment							
Adverse events (general): in %							
1/185[60]	CT	o vs. o; p=N.S.	Serious limitations (-1)[61]	No important inconsistency	Direct	Imprecise data (-1)[38]	Very low
Adverse events (treatment-related): in %							
1/185[60]	CT	o vs. o; p=N.S.	Serious limitations (-1)[61]	No important inconsistency	Direct	Imprecise data (-1)[38]	Very low

Abbreviations: CT = controlled trial; n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

[60]Study consisted of four study groups, whereas one group (113 patients) received a treatment with compression stockings and was therefore excluded from this analysis.

[61]Study was conducted as not blinded (and not randomised).

3.1.2 Flavonoid fraction-containing agents

Study characteristics

For evaluating the efficacy and safety of flavonoid fraction-containing capillary stabilising agents for a treatment of CVI, we identified 1 meta-analysis [42], 8 RCTs [43-49], 1 additional non-randomised controlled study [50] and 5 single-arms studies [51-55] that met our inclusion criteria.

1 Meta-Analyse, 8 RCTs, 1 non-RCT, 5 Ein-Arm-Studien mit 13.613 PatientInnen eingeschlossen

Two of these RCTs are summarised in one study [45]. Furthermore, two extracted RCTs [43, 49] are already included in the meta-analysis, thus the outcomes that are included in the meta-analysis and the RCTS will not be mentioned twice (marked grey in the extraction Table 3.1-6). Two single-arm studies reported the results of the same study with different information and were therefore merged [51, 53].

zwei RCTs bereits in Meta-Analyse

The included studies are comparing flavonoid fraction-containing agents with either placebo or no treatment [42-50] for the treatment of CVI.

Vergleich: Placebo oder keine Behandlung

The dosage of drugs was similar in every study: 500 mg two times a day [42-55].

Dosis: 500 mg 2x täglich

The study characteristics and results are summarised in Table 3.1-6 for RCTs and in Table 3.1-7 for non-randomised controlled trials and single-arm studies.

Studienergebnisse in Extraktionstabellen

There were no studies identified comparing flavonoid fraction-containing agents with other interventions, such as lifestyle changes or further local, medical and surgical treatment, mentioned in Chapter 1.1.2.

keine Studien mit anderen Vergleichsgruppen

Table 3.1-6: Efficacy and safety-related outcomes of a meta-analysis and randomised controlled trials of flavonoid fraction-containing agents vs. placebo or compression stockingsor surgery for CVI

Author, year, reference number	Boineau-Geniaux 1988 [47]	Laurent 1988 [45]	Burnand 1989 [46]	Guilhou 1997 [43]	Danielsson 2002 [44]	Roztocil 2003 [49]	Coleridge-Smith 2005 [42]	Veverková 2006 [48]
Country	France	France	UK	France	Sweden	Czech Republic, Slovakia	UK, France, Switzerland	Czech Republic
Study design	RCT	2 RCTs[62]	RCT	RCT	RCT	RCT	Meta-Analysis[63]	RCT
Sponsor	n/a	n/a	n/a	n/a	IRIS	n/a	Servier	n/a
Intervention/ Product	2x 500 mg MPFF (Daflon®) per day	2x 500 mg MPFF (Daflon®) per day	2x 500 mg MPFF (Daflon®) per day	2x 500 mg MPFF (Daflon®) per day[64]	2x 500 mg MPFF (Daflon®) per day	2x 500 mg MPFF (Daflon®) per day + compression stockings	2x 500 mg MPFF (Daflon®) per day + compression stockings	2x 500 mg MPFF (Daflon®) per day + surgery[65]
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo	Compression stockings	2 RCTs: Placebo + compression stockings 3 RCTs: no treatment + compression stockings	No treatment + surgery
Number of pts	16 vs. 20	100 vs. 100	24 vs. 25	52 vs. 55	51 vs. 50	82 vs. 68	723	92 vs. 89
Age of patients (yrs.)	Ø 59	Ø 49	Ø 53	Ø 71 vs. 71	Ø 48 vs. 48	Ø 64 vs. 65	Ø 65	n/a
Sex (% female)	78	87	58 vs. 68	62 vs. 76	76 vs. 68	77 vs. 57	58[66]	n/a
Height (cm)/ Weight (kg)/ BMI (kg/m²)	n/a / n/a / n/a	n/a / n/a / n/a	n/a / n/a / n/a	n/a / n/a / n/a	n/a / n/a / n/a	168 vs. 170 / 88 vs. 87 / 31 vs. 30	n/a / n/a / n/a	n/a / n/a / n/a
Clinical classification	n/a	n/a	n/a	Grade III acc. to Widmer	C1-6 (CEAP classification)	n/a	C6 (CEAP classification)	n/a
Primary endpoint	n/a	n/a	n/a	Complete healing of the reference ulcer	n/a	Fully healed ulcers after 6 months and time to complete healing	Complete ulcer healing after 6 months	n/a

[62] Study summarised the results of two RCTs, published in 1987 in French (Frileux, C. and Gilly, R.).

[63] Meta-analysis of five RCTs. two never published and three published RCTS (Guilhou et al. 1997 [43], Glinski et al. 1999 and Roztocil et al. 2003 [49]). Since not all outcomes of Guilhou et al. and Roztocil et al. were reported in the meta-analysis, the two studies were extracted separately in this report.

[64] Wearing compression stockings was allowed.

[65] All patients of this study were undergoing varicose vein stripping. The intervention group was treated with MPFF und the control group did not receive MPFF. Medical treatment started 2 weeks before surgery and ended 2 weeks after surgery.

[66] Rate was only stated for all studies together.

Author, year, reference number	Boineau-Geniaux 1988 [47]	Laurent 1988 [45]	Burnand 1989 [46]	Guilhou 1997 [43]	Danielsson 2002 [44]	Roztocil 2003 [49]	Coleridge-Smith 2005 [42]	Veverková 2006 [48]
Inclusion criteria	n/a	Trials with one single aetiology, precise definition of each symptom, stable patients for at least the 6 previous months, informed consent	Patients with abnormal half-volume refilling time on foot volumetry + ankle to arm arterial Doppler pressure ratio <1	Patients of both sexes, aged 18-85 years, agree to wear compression stockings with ulcer of chronic venous origin	Patients, aged 18-65 years, symptoms of CVI in the lower leg	Ambulatory male and female patients, aged ≥18 years, with primary or secondary varicose ulcer(s) with diameter 2-10 cm for ≥3 months	Patients with clinical signs of venous leg ulceration (e.g., hyperpigmentation, lipodermato-sclerosis and ulcer located in gaiter region), previous history of varicose veins or post-thrombotic syndrome, duration of ulcer at least 3 months	Patients, aged 18-60 yrs., scheduled to undergo stripping of the great saphenous vein (due to CVI)
Duration of Treatment (months)	2	2	1	2 (or less)	2	6[67]	2-6	1
Follow-up (months)	0	0	0	0	0	0	n/a	0
Drop-outs, n (%)	0 (0) vs. 1 (5)	1 (1) vs. 2 (2)	n/a	2 (4) vs. 4 (7)	3 (6) vs. 1 (2)	2 (2) vs. 16 (24)	n/a	n/a
Efficacy-related outcomes								
Change of CVI stage	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
CVI signs (general)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Trophic alterations	*Improved pts. (%)[68]:* Baseline: - After 1 month: n/a After 2 months: 88 vs. 21; p=n/a After 3; 6; 12 months: n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

[67] The study started with a run-in-phase of two weeks where patients had to stop any unauthorized treatment, followed by a 6 month treatment phase.

[68] Measurement for trophic alternations was given as percentage of patients (in %) with improvement (for ulcer, dermitis and hypodermitis).

Author, year, reference number	Boineau-Geniaux 1988 [47]	Laurent 1988 [45]	Burnand 1989 [46]	Guilhou 1997 [43]	Danielsson 2002 [44]	Roztocil 2003 [49]	Coleridge-Smith 2005 [42]	Veverková 2006 [48]
Oedema (or leg volume or circumference)	*Ankle circumference:* Baseline: n/a After 1 month: n/a After 2 months: n/a; **p<0.05**[69] After 3; 6; 12 months: n/a	*Ankle circumference (mm)*[70]*:* Baseline: n/a After 1 month: -4.1 vs. -0.7; p=n/a After 2 months:-6.5 vs. -0.8; p=n/a After 3; 6; 12 months: n/a	*Leg volume (ml)*[71]*:* Baseline: 1,088 vs. 1,206; p=n/a After 1 month: 1,098 vs. 1,200; p=n/a After 2; 3; 6; 12 months: n/a	n/a	*Leg volume (ml)*[72]*:* Baseline: n/a After 1 month: n/a After 2 months: +11.9 vs. +4.4: **p=N.S.** After 3; 6; 12 months: n/a	n/a	n/a	*Oedema decrease (%):* Baseline: - After 1 month: 84 vs. n/a; **p<0.001** After2; 3; 6; 12 months: n/a
Ulcer	n/a	n/a	n/a	*Healing rate (%)*[73]*:* Baseline: - After 1 month: n/a After 2 months: 32 vs. 13; **p=0.028** After 3; 6; 12 months: n/a	n/a	*Healing rate (%)*[74]*:* Baseline: - After 1 month: n/a After 2 months: 27 vs. 13; **p<0.05** After 3 months: 44 vs. 28; **p<0.05** After 6 months: 65 vs. 41; **p<0.01** After 12 months: n/a *Reduction ulcer size (%):* After 1; 2; 3 months: n/a After 6 months: 77 vs. 69; **p=0.012** After 12 months: n/a	*Healing rate (%)*[75]*:* Baseline: - After 1; 2; 3 months: n/a After 6 months: 61 vs. 48 (RR 32%; CI 3-70%); **p=0.014** After 12 months: n/a	n/a

[69] Measurement for oedema was given only as p-value of variation between the study groups for ankle circumference.

[70] Measurement for oedema was given as reduction in ankle circumferences from baseline (in mm).

[71] Measurement for oedema was given as foot volume (in ml), measured by water displacement.

[72] Measurement for oedema was given as reduction in leg volume from baseline (in ml).

[73] Measurement for ulcer was given in % of patients with complete healing.

[74] Measurement for ulcer was given in % of patients with complete healing. Reduction of the ulcer size after 6 months was 77% vs. 69% (p=0.012).

[75] Measurement for ulcer was given in % of patients with complete healing. Only four RCTs were considered for this outcome.

Author, year, reference number	Boineau-Geniaux 1988 [47]	Laurent 1988 [45]	Burnand 1989 [46]	Guilhou 1997 [43]	Danielsson 2002 [44]	Roztocil 2003 [49]	Coleridge-Smith 2005 [42]	Veverková 2006 [48]
CVI symptoms (general)	*Improved pts. (%)*[76]*:* Baseline: - After 1 month: 48 vs. 31; p=n/a After 2 months: 35 vs. 67; p=n/a After 3; 6; 12 months: n/a	*Improvement (%)*[77]*:* Baseline:- After 1 month: 49 vs. 24; p=n/a After 2 months: 69 vs. 37; **p=S.S.** After 3; 6; 12 months: n/a	n/a	n/a	*Improved pts. (%)*[78]*:* Baseline:- After 1 month: n/a After 2 months: 44 vs. 33; **p=N.S.** After 3; 6; 12 months: n/a	n/a	n/a	n/a[79]
Pain	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a[80]
Cramps	n/a	n/a	n/a	n/a	*Improved pts. (%):* Baseline: - After 1 month: n/a After 2 months: n/a **p=S.S.** After 3; 6; 12 months: n/a	n/a	n/a	n/a
Restless legs	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Itching (= tingling sensation)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	*Improvement (%)*[81]*:* Baseline: - After 1 month: 92 vs. n/a; **p<0.001** After 3; 6; 12 months: n/a

[76] Symptoms were measured on a score (0-3), but only the percentage of patients (in %) with regressed symptoms was stated.

[77] Symptoms were measured on a score (0-3) for discomfort, heaviness, pain, cramps, paraesthesia, oedema and skin redness, whereas only the overall symptom reduction (in %) was stated.

[78] Symptoms were measured with a scale (0-3), whereas only the percentage of patients (in %) with reduced score for general symptoms were reported.

[79] Symptoms were measured on a 10-cm visual analogue scale (VAS) at baseline and after 1 month of treatment.

[80] Pain was measured, whereas only the values one day and 8 days after surgery were stated.

[81] Measured as decrease in percent (%) from baseline.

Author, year, reference number	Boineau-Geniaux 1988 [47]	Laurent 1988 [45]	Burnand 1989 [46]	Guilhou 1997 [43]	Danielsson 2002 [44]	Roztocil 2003 [49]	Coleridge-Smith 2005 [42]	Veverková 2006 [48]
Heaviness (=heavy legs)	n/a	n/a	n/a	*Patients (%)*[82]*:* Baseline: n/a After 1 month: n/a After 2 months: 4 vs. 17; **p=0.03** After 3; 6; 12 months: n/a	n/a	*Score (0-3)*[83]*:* Baseline: 2.3 vs. 2.0: **p<0.001** After 1 month: 1.7 vs. 1.8; **p<0.05** After 2; 3 months: n/a After 6 months: 1.5 vs. 1.7; **p<0.01** After 12 months: n/a	n/a	*Improvement (%)*[81]*:* Baseline: - After 1 month: 89 vs. n/a; **p<0.001** After 3; 6; 12 months: n/a
Swelling (=sensation of tension)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Paraesthesias	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
QoL	n/a	n/a	n/a	n/a	n/a	n/a	n/a	*Improved pts.(%):* Baseline[84]: - After 1 month: 21 vs. 3; p=n/a After 3; 6; 12 months: n/a
Safety-related outcomes								
Adverse events, general in % (n) pts.	6 (1) vs. 5 (1); p=n/a (headache vs. nausea)	9 (9) vs. 13 (13); p=n/a (nausea, headache, pain, insomnia, hypotension in both groups)	n/a	12 (6) vs. 9 (5); p=n/a (venous thrombosis, skin changes around ulcer, asthenia, headache, exacerbation of chronic colopathy vs. eczema, urticaria, pruritus of the scalp, pain)	n/a	n/a	n/a	n/a

[82] Results for heaviness includes also atonic aspect of the ulcer. Only the percentage of patients (in %) with heaviness and atonic aspect at the end of the treatment phase was given.

[83] Heaviness was measured on a 4-item scale (0-3).

[84] QoL was measured with a 20-question quality of life questionnaire (CIVIQ), results are given in percentage of patients (in %) with better QoL than before treatment.

Author, year, reference number	Boineau-Geniaux 1988 [47]	Laurent 1988 [45]	Burnand 1989 [46]	Guilhou 1997 [43]	Danielsson 2002 [44]	Roztocil 2003 [49]	Coleridge-Smith 2005 [42]	Veverková 2006 [48]
Major adverse events	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Minor adverse events	n/a	n/a	n/a	n/a	12 (6) vs. 4 (2); p=n/a (types of events not stated)	n/a	n/a	n/a
Adverse events, treatment-related in % (n) pts.	n/a	n/a	n/a	8 (4) vs. 9 (5); p=n/a (skin changes around ulcer, asthenia, headache, exacerbation of chronic colopathy vs. eczema, urticaria, pruritus of the scalp, pain)	n/a	0 vs. n/a; p=n/a	n/a	n/a
Major adverse events	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Minor adverse events	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Abbreviations: acc. = according; CVI = chronic venous insufficiency; MPFF = micronised purified flavonoid fraction; n = number (of patients); n/a = data not available; N.S. = not statistically significant; pts. = patients; QoL = quality of life; RCT = randomised controlled trial; SLT = standard local therapy (mostly wound cleaning and application of saline); vs. = versus; yrs. = years

Table 3.1-7: Safety-related outcomes of non-randomised trials of flavonoid fraction-containing agents for CVI

Author, year, reference number	Guillot 1989 [51] Pointel 1988 [53]	Roux 1990 [55]	Pinjala 2004 [52]	Saveljev 2008 [50]	Navrátilová 2010 [54]
Country	France	France	India	Russia	Czech Republic
Study design	Single-arm study	Single-arm study	Single-arm study	Non-randomised controlled study	Single-arm study
Sponsor	n/a	n/a	Serdia Pharmaceuticals	n/a	n/a
Intervention/Product	2x 500 mg MPFF (Daflon®) per day	2x 500 mg MPFF (Daflon®) per day	2x 500 mg MPFF (Daflon®) per day	2x 500 mg MPFF (Daflon®) per day + surgery[85]	2x 500 mg MPFF (Daflon®) per day
Comparator	none	none	none	No treatment + surgery	none
Number of pts	215	11,342	308	200 vs. 45	213
Age of patients (yrs.)	Ø 47	Ø 50	Ø 43	Ø 42 vs. 43	Ø 48
Sex (% female)	87	87	58	100	92
Height (cm)/Weight (kg)/ BMI (kg/m²)	164 / 62 / n/a	164 / 65 / n/a	n/a / n/a / n/a	n/a / n/a / 24.5 vs. 24.9	169 / 77 / 27
Clinical classification	n/a	n/a	CEAP classification 0-4	CEAP classification C 2	CEAP classification C3
Primary endpoint	n/a	n/a	n/a	n/a	Ankle and calf circumferences
Inclusion criteria	Patients of both sexes, aged 19-81 years, suffering from functional symptoms of venous insufficiency.	n/a	Outpatients with at least one symptom with or without signs of CVI corresponding to CEAP classification 0-4, untreated for at least 15 days.	Female patients, aged 25-60 yrs., CEAP classification C2, ultrasound angiological features of reflux and unilateral lesion in the great saphenous vein, clinical symptoms	Patients of both sexes, aged ≥18 yrs., with venous oedema without skin changes
Duration of treatment (months)	12	2	6	1.5	6[86]
Follow-up (months)	0	0	0	0	0
Drop-outs, n (%)	45 (36)	n/a	20 (6.5)	n/a	17 (8)

[85] All patients of this study were undergoing varicose vein stripping. The intervention group was treated with MPFF und the control group did not receive MPFF. Medical treatment started 2 weeks before surgery and ended 4 weeks after surgery. All patients had to wear compression stockings.

[86] Study started with a run-in phase without treatment of 2 weeks.

Author, year, reference number	Guillot 1989 [51] Pointel 1988 [53]	Roux 1990 [55]	Pinjala 2004 [52]	Saveljev 2008 [50]	Navrátilová 2010 [54]
Safety-related outcomes					
Adverse events, general in % (n) pts.	9 (20) (gastralgia, dizziness, gynaecological signs, cutaneous eruption)	n/a	6 (12) (dyspepsia, nausea, giddiness, ankle oedema, breathlessness, low pulse rate, headache)	0 (0) vs. 0(0)	n/a
Major adverse events	n/a	n/a	n/a	0 (0) vs. 0(0)	n/a
Minor adverse events	n/a	n/a	n/a	0 (0) vs. 0(0)	n/a
Adverse events, treatment-related in % (n) pts.	n/a	3.3 (374) (types of events not stated)	n/a	2 (4) vs. n/a, p=n/a (gastric irritation vs. n/a)	0 (0)
Major adverse events	n/a	n/a	n/a	0 (0) vs. 0(0)	0 (0)
Minor adverse events	n/a	n/a	n/a	n/a	0 (0)

Abbreviations: CVI = chronic venous insufficiency, MPFF = micronised purified flavonoid fraction;n = number (of patients); n/a = data not available; pts. = patients; yrs. = years

Efficacy

1 Meta-Analyse + 8 RCTs

For evaluating the efficacy of flavonoid fraction-containing capillary stabilising agents, we identified 1 meta-analysis [42]and 8 RCTs [43-48, 56] that met our inclusion criteria.

In Studien: 1.290 PatientInnen, 48-71 Jahre alt, 58-78 % Frauen, Vergleichsgruppen erhielten Placebo, Kompressionsstrümpfe oder keine Behandlung

Overall, there were 1,290 patients in the studies (without the two studies already included in the meta-analysis). All patients in the treatment groups received 500 mg MPFF (Daflon®) per day [42, 44-48]. Patients in the control groups received either placebo [42, 44-47], were treated with compression stockings alone [42] or did not receive a treatment [48]. Furthermore, one study was conducted before and after surgery [48]. The patients were on average between 48 and 71 years in the treatment groups and in the control groups, respectively [42-49]. The majority of the patients were females: 58-87% [42-49]. Furthermore, the CVI grade was stated in the meta-analysis (C6 after the CEAP classification, see Chapter 1.1.2) [42] and in one additional RCT (C1 to 6 after the CEAP classification) [44]. The duration of treatment was 1-6 months. No study had a follow-up without treatment [42-49] and the drop-out rate differed between 0 and 6% in the treatment groups and 2 and 24% in the control groups [43-45, 47, 49].

Zusammenfassung in GRADE-Tabellen

A summary of the effect sizes for the individual outcome indicators is presented in Tables 3.1-8 to 3.1-10.

Flavonoid fraction-containing agents (+ compression stockings) versus placebo (+ compression stockings)

einige nicht berichtete Endpunkte

None of the identified studies assessed the change of the CVI stage, the CVI signs in general, several symptoms of CVI: pain, restless legs, itching, swelling plus paraesthesia, and the quality of life of a treatment with flavonoid fraction-containing agents versus placebo.

Hautveränderungen in beiden Studiengruppen verbessert

Trophic alternations, a typical sign of CVI, were measured in 1 study as improved patients (in %) after 2 months, whereby 88% patients in the treatment group and 21% in the control group had an improvement [47]. It was not stated whether the difference was statistically significant or not.

widersprüchliche Ergebnisse zu Ödemen, gemessen in ml

Regarding the other signs of CVI, oedema was assessed in 4 studies and measured by two different parameters. In two studies oedema was measured by leg volume (in ml), whereby in one study the volume increased during 1 month of treatment in the flavonoid group and decreased in the placebo groups (+10 vs. -6 ml) [46] and in the other study, leg volume increased during 2 months of treatment in both study groups (+12 vs. +4 ml) [44]. It was not stated whether the differences of the volume changes were statistically significant.

Knöchelumfang mit Flavonoidfraktion etwas mehr reduziert

In addition, two other studies assessed oedema by measuring the ankle circumference (in mm) [45, 47]. However, only 1 study allowed the appraisal of the change from baseline until 1 month of treatment: The reduction of the ankle circumference was slightly higher in the treatment group than in the placebo group (-4 vs. -1 mm) [45]. However, it was not stated whether the difference between the groups was statistically significant.

Geschwüre heilten etwas mehr in Behandlungsgruppen

Ulcer, another consequence of CVI, was reported in the meta-analysis (based on the results of 2 RCTs) in terms of the healing rate (in %) which was higher after 2 months of treatment in the flavonoid fraction group compared to the control group in one study (25.5 vs. 11.5%) and lower in the treatment compared to the control group in the other study (20.4 vs. 25.3%) [42]. It was

not possible to identify whether the differences between the study groups were statistically significant or not, since the systematic review summarised the results across studies with different comparators.

generelle CVI-Symptome in Behandlungsgruppen etwas mehr verbessert

The symptoms of CVI, in general, were measured in 3 studies after 1 and 2 months of treatment. The improvement of the general symptoms after 2 months (reported in one study) was statistically significantly higher in the flavonoid fraction group than in the placebo group (69 vs. 37%) [45]. Furthermore, the percentage of improved patients after 2 months of treatment was higher in the treatment group than in the placebo group (44 vs. 33%) in one study (but not statistically significant) [44], though, in another study there were less improved patients in the treatment group than in the placebo group (35 vs. 67%) [47].

Krämpfe wurden in Behandlungsgruppe signifikant verbessert

The only reported symptom of CVI – cramps – could statistically significantly be more improved after 2 months of treatment in the flavonoid fraction groups than in the placebo groups, however detailed data were not presented [44]. For heaviness no change from baseline could be calculated and therefore this outcome was excluded (see Table 3.1-6).

Flavonoid fraction-containing agents + compression stockings versus compression stockings alone

mehrere nicht berichtete Endpunkte

There was no evidence available assessing the change of the CVI stage, the CVI signs in general, trophic alternations and oedema, CVI-related symptoms in general, the change in pain, cramps, restless legs, itching, swelling or paraesthesias and the quality of life after treatment with flavonoid fraction-containing agents and compression stockings versus compression stockings alone.

Geschwüre signifikant mehr in Behandlungsgruppen reduziert, nach 2 Monaten ...

The only outcome reported was ulcer. It was analysed in the meta-analysis (based on the results of 3 RCTs) by the healing rate which was higher after 2 months of treatment in the flavonoid fraction group compared to the control group (14.1 to 40.3% vs. 8.7 to 21%) [42]. The meta-analysis of the ulcer healing rate after 2 months of treatment (Figure 3.1-7) is showing that the difference is statistically significant in favour of a treatment with flavonoid fraction-containing agents supplemented by compression stockings versus compression stockings alone. The risk ratio is 1.90 for the probability of ulcer healing with flavonoid fraction and compression stockings compared to compression stockings alone.

... sowie 3 und 6 Monaten

After 3 and 6 months of treatment (measured in one RCT; also included in meta-analysis [42]),the healing rate was at both measured points of time statistically significantly higher in the treatment group than in the control group (3 months: 44 vs. 28%; 6 months: 65 vs. 41%) [49].

Study name	Statistics for each study			Sample size		Risk ratio, 95% CI
	Risk ratio	Lower limit	Upper limit	Flavonoid fraction	No treatment	
Coleridge-Smith 2005 (from Glinski 1999)	1.62	0.62	4.21	10/71	6/69	
Coleridge-Smith 2005 (from Roztocil 2003)	2.03	1.00	4.11	22/82	9/68	
Coleridge-Smith 2005 (from Saveliev[87])	1.92	1.09	3.40	25/62	13/62	
Total (95% CI)	**1.90**	**1.27**	**2.84**	**57/215**	**28/199**	
						0,1 0,2 0,5 1 2 5 10
Random effects meta-analysis; I^2: 0.0%; p=0.002						Favours compr. alone / Favours MPFF+compr.

Figure 3.1-7: Ulcer healing rate (dichotomous) after 2 months for flavonoid fraction-containing agents + compression stockings vs. compression stockings alone

Größe Beingeschwüre in Behandlungsgruppe signifikant mehr reduziert

The reduction of the ulcer size was reported in one study (also included in the previously mentioned meta-analysis [42]).The ulcer size was statistically significantly more reduced in the treatment than in the control group after 6 months (77 vs. 69%) [49].

„schwere Beine" in Behandlungsgruppe mehr reduziert

In addition, the score (0-10) of heaviness (a symptom of CVI) was statistically significantly more reduced in the treatment group than in the control group after 6 months of treatment (-2.7 vs. -1) [49].

Flavonoid fraction-containing agents + surgery versus surgery only

meherere nicht berichtete Endpunkte

There was no evidence available assessing the change of the CVI stage, the CVI signs in general, trophic alternations and ulcer, CVI-related symptoms in general, the change in pain, cramps, restless legs, swelling and paraesthesias after treatment with flavonoid fraction-containing agents and surgery versus surgery only.

Behandlungsgruppe mehr reduziert: Ödeme, ...

The only reported CVI sign was oedema, which decreased statistically significantly more in the treatment group than in the control group (84% versus no stated value for the control group) [48].

... Juckreiz + schwere Beine

In terms of CVI symptoms, itching and heaviness were statistically significantly more improved in the treatment groups compared to the control groups, yet the values for the control groups were not stated [48].

Lebensqualität in Behandlungsgruppen mehr verbessert

Quality of life improved in more patients in the treatment group than in the control group (21 vs. 3%) [48]. It was not stated whether the difference was statistically significant or not.

[87] The original study from Saveliev was not published and has therefore no publication date.

Safety

For evaluating the safety of flavonoid fraction-containing capillary stabilising agents, we identified, besides 5 out of the 8 previously described studies, 1 additional non-randomised controlled registry studies (non-RCT) [50] and 4 single-arm studies [51-55] (two studies reported the results of the same study with different information and were therefore merged [51, 53]) that met our inclusion criteria and described adverse events. The study characteristics and results of the non-RCT and single-arm studies are summarised in Table 3.1-7.

neben RCTs auch 1 non-RCTS und 4 Ein-Arm-Studien eingeschlossen

In the non-RCT all patients received surgery and the treatment group was additionally treated with flavonoid fraction-containing agents.

OP für alle PatientInnen in non-RCT

In the non-RCT and the 4 single-arm studies, a total of 12,323 patients were included, of whom 12,278 were in the treatment groups and received 500 mg of flavonoid fraction-containing agents (Daflon®) two times a day. The remaining 45 patients were in the control group and received surgery only [50]. The mean ages of the patients were 42 to 50 years in the treatment groups and 43 years in the control group. Between 58 and 100% of the patients in the studies were females. The duration of treatment differed from 1.5 to 12 months. There was no follow-up after treatment. Furthermore, the drop-out rates in the studies were 6.5-36% [51-54].

in non-RCTS und Ein-Arm-Studien: 12.323 PatientInnen, im Alter von Mitte 40 und 58 Jahren, 100 % Frauen

A summary of the effect sizes for the individual outcome indicators is presented in Tables 3.1-8 to 3.1-11.

Zusammenfassung in GRADE-Tabellen

Flavonoid fraction-containing agents (+ compression stockings) versus placebo (+ compression stockings)

If reported, the general adverse events differed between 6 and 12% in the flavonoid fraction groups and between 5 and 13% in the control groups. It was not stated wheter the difference was statistically significant or not. The most common adverse events in both groups were headache, pain and nausea [43, 45, 47].

6-12 % vs. 5-13 % generelle unerwünschte Ereignisse und ...

The forest plot of the meta-analysis of the general adverse events is displayed in Figure 3.1-8. The forest plot shows that there is no statistically significant difference between adverse events that occurred in the treatment and those in the placebo group.

... Gruppenunterschied nicht signifikant

Study name	Statistics for each study			Sample size		Risk ratio, 95% CI
	Risk ratio	Lower limit	Upper limit	Flavonoid fraction	No treatment	
Boineau-Geniaux 1988	1.25	0.08	18.46	1/16	1/20	
Laurent 1988	0.69	0.31	1.55	9/100	13/100	
Guilhou 1997	1.27	0.41	3.91	6/52	5/55	
Total (95% CI)	**0.87**	**0.46**	**1.64**	**16/168**	**19/175**	
Random effects meta-analysis; I^2: 0.0%; p=0.66						0,01 0,1 1 10 100 Favours MPFF Favours placebo

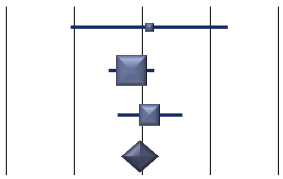

Figure 3.1-8: Adverse events (dichotomous) for flavonoid fraction-containing agents (+ compression stockings) vs. placebo (+ compression stockings)

Nebenwirkungen bei 8 % der PatientInnen in Behandlungsgruppe

Treatment-related adverse events, reported in one study, occurred in 8% of the patients in the treatment and 9% of the patients in the control group. The most common events in the treatment group were skin changes, asthenia and headache [43].

Flavonoid fraction-containing agents + compression stockings versus compression stockings alone

generelle unerwünschte Ereignisse nicht berichtet

There was no available evidence that analysed adverse events in general of a treatment with flavonoid fraction-containing agents combined with compression stockings compared to compression stockings alone.

keine Nebenwirkungen

There were no treatment-related adverse events in the treatment group [49]. However, it was not stated whether treatment-related adverse events occurred in the control group.

Flavonoid fraction-containing agents + surgery versus surgery alone

keine generellen unerwünschten Ereignisse

There were no general adverse events in neither the flavonoid fraction group supplemented by surgery nor in the group that was receiving surgery alone [50].

Nebenwirkungen bei 2 % der PatientInnen

However, there were 2% of treatment-related adverse events (gastric irritation) in the treatment group. It was not stated whether treatment-related adverse events occurred in the control group [50].

Flavonoid fraction agents

6-9 % generelle, 0-3,3 % behandlungsbezogene unerwünschte Ereignisse

There were 6 to 9% of general [51-53]and 0 to 3.3% of treatment-related adverse events [54, 55] after a treatment with flavonoid fraction-containing agents in the single-arm studies. The most common adverse events were gastralgia, nausea, dizziness and headache [51-53].

Risk of bias

ingesamt geringes Bias-Risiko der Meta-Analyse

The identified meta-analysis shows an overall low risk of bias (figure 3.1-9), however, there is partially a high risk of selection bias due to an unclear research question. Furthermore, a high risk of performance and detection bias exists due to no critical appraisal of the quality of the included studies and it is not clear if the studies were assessed by two persons.

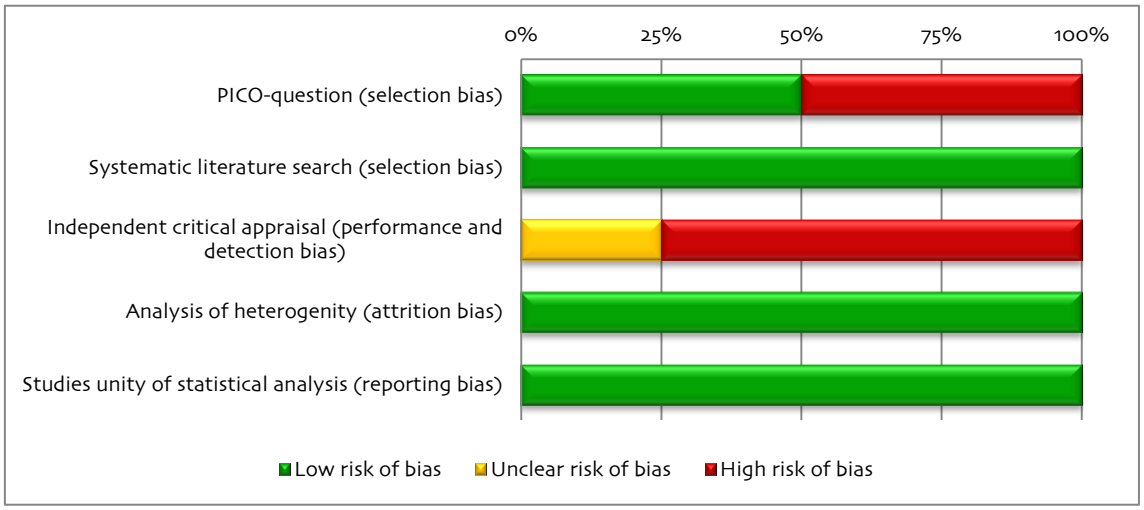

Figure 3.1-9: Risk of bias of meta-analysis for treatment of CVI with flavonoid fraction-containing agents

insgesamt unklares Bias-Risiko der RCTs

The majority of the identified RCTs for a treatment of CVI with flavonoid fraction-containing agents have an unclear risk of bias for several types of biases (see Figure 3.1-10). Nearly half of the studies show a high risk of reporting bias due to not reported baseline values, not reported scaling of outcome assessment or missing description of outcome indicators. In summary, the risk of bias is unclear.

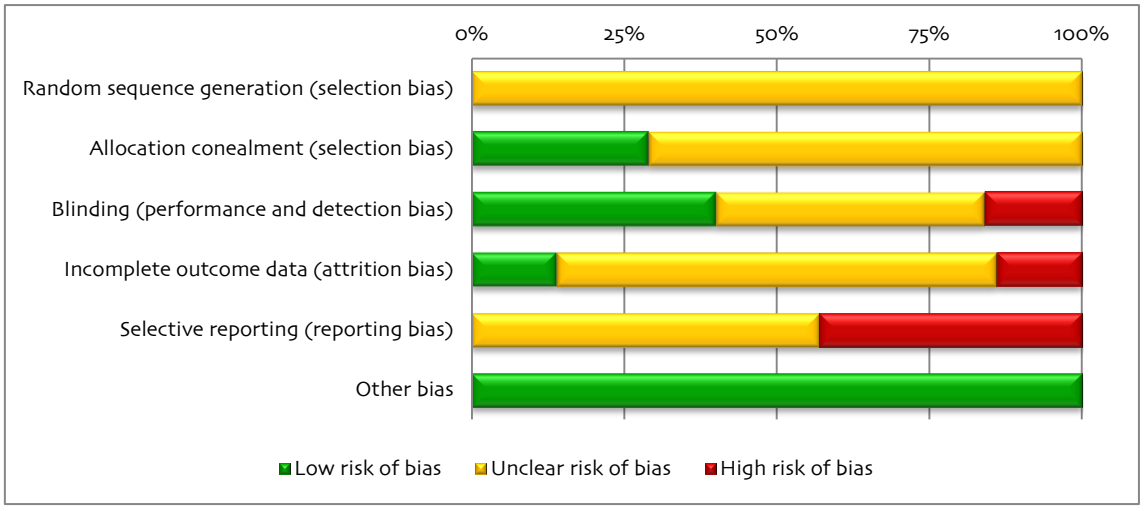

Figure 3.1-10: Risk of bias of RCTs for treatment of CVI with flavonoid fraction-containing agents

Bias-Risiko Ein-Arm-Studien: hoch

Due to the study design of the single-arm studies, several of the individual biases are not relevant (grey-coloured), since there was no control group. The risk of performance and detection bias is high, due to no blinding of the outcome assessor and half of the studies show a high risk of reporting bias due to no confounder adjustment (see Figure 3.1-11). In summary, the risk of bias is high.

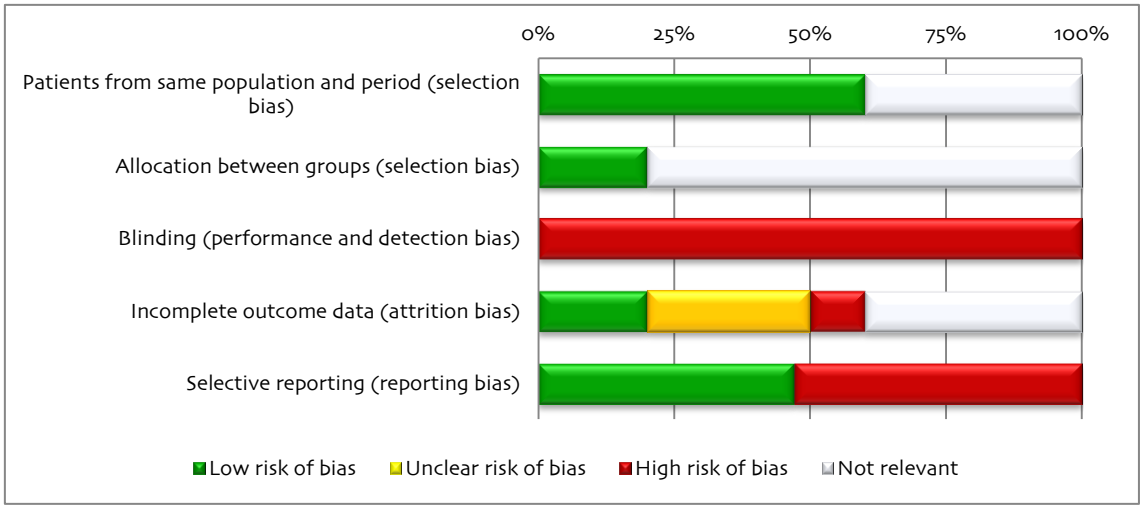

Figure 3.1-11: Risk of bias of (un)controlled studies fortreatment of CVI with flavonoid fraction-containing agents

Strength of evidence

Evidenzstärke: insgesamt gering bis sehr gering

Overall, the strength of evidence of the efficacy and safety of a treatment of CVI with flavonoid fraction-containing agents, supplemented by compression stockings or surgery compared to placebo, compression therapy alone or surgery alone is low to very low. Although the majority of studies were RCTs, due to several study limitations and a low number of patients in the studies, the strength of evidence was downgraded. The strength of evidence is summarised in the Tables 3.1-8 to 3.1-11.

keine Evidenz zu Vergleich mit anderen Behandlungen

There was no evidence to compare a treatment of CVI with flavonoid fraction-containing agents with other interventions, such as lifestyle changes or further local, medical and surgical treatment, mentioned in Chapter 1.1.2.

Table 3.1-8: Evidence profile: Efficacy and safety of flavonoid fraction-containing agents for treatment of CVI compared to placebo

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Efficacy: flavonoid fraction-containing agents (+ compression stockings) versus placebo (+ compression stockings)							
Change of CVI stage: no evidence							
CVI signs (general): no evidence							
CVI signs (trophic alternations): improved patients (in %)							
1/36	RCT	2 mo: 88 vs. 21; p=n/a	Serious limitations (-1)[88]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low
CVI signs (oedema): leg volume change from baseline (in ml)							
1/49 1/101	RCT	1 mo: +10 vs. -6; p=n/a 2 mo: +12 vs. +4; p=n/a	Serious limitations (-1)[90]	n/a (only 1 trial) n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low Low
CVI signs (oedema): ankle circumference change from baseline (in mm)							
1/200	RCT	1 mo: -4 vs. -1; p=n/a	Serious limitations (-1)[88]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low
CVI signs (ulcer): healing rate (in %)							
1/309[91]	Sytem. Review	2 mo: 20.4 to 25.5 vs. 11.5 to 25.3; p=S.S.	Serious limitations (-1)[92]	Important inconsistency[93] (-1)	Direct	Imprecise data (-1)[89]	Very low
CVI symptoms (general): improvement (in %)							
1/200	RCT	1 mo: 49 vs. 24; p=n/a 2 mo: 69 vs. 37; p=S.S.	Serious limitations (-1)[88]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low
CVI symptoms (general): improved patients (in %)							
1/36 1/137	RCT RCTs	1 mo: 48 vs. 31; p=n/a 2 mo: 35 to 44 vs. 33 to 67; p=N.S. in one study	Serious limitations (-1)[88] Serious limitations (-1)[94]	n/a (only 1 trial) Important inconsistency (-1)[95]	Direct Direct	Imprecise data (-1)[89] Imprecise data (-1)[89]	Low Very low
CVI symptoms (pain): no evidence							

[88] Unclear random sequence generation and blinding of outcome assessor.

[89] Low incidence, study/studies not powered to detect difference.

[90] Unclear random sequence generation in one trial and unclear blinding of outcome assessor in each study.

[91] The systematic summarised five studies with 723 patients, since there were only two of these studies with a placebo receiving control group, only this two studies were extracted.

[92] Systematic review was not based on research question and it is unclear if extracted data were reviewed by a second person.

[93] Review included studies comparing flavonoid fraction-containing agents (+ compression stockings) with placebo or nothing (+ compression stockings). In this table we only used the data from studies with a placebo receiving control group, thus it was not possible to use the risk ratio and confidence interval of the systematic review.

[94] Unclear random sequence generation in both studies an unclear blinding of outcomes assessor in one study.

[95] In one study there were more improved patients in the control group than in the treatment group and in the second study the values were the other way round.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
CVI symptoms (cramps): improved patients (in %)							
1/101	RCT	2 mo: n/a; p=S.S.	Serious limitations (-1)[94]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low
CVI symptoms (restless legs): no evidence							
CVI symptoms (itching): no evidence							
CVI symptoms (heaviness): no evidence							
CVI symptoms (swelling): no evidence							
CVI symptoms (paraesthesias): no evidence							
Quality of life: no evidence							
Safety: flavonoid fraction-containing agents (+ compression stockings) versus placebo (+ compression stockings)							
Adverse events (general): in %							
3/343	RCTs	6 to 12 vs. 5 to 13; p=N.S.	Serious limitations (-1)[96]	No important inconsistency	Direct	Imprecise data (-1)[89]	Low
Adverse events (treatment-related): in %							
1/107	RCT	8 vs. 9; p=n/a	Serious limitations (-1)[88]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low

Abbreviations: n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

Table 3.1-9: Evidence profile: Efficacy and safety of flavonoid fraction-containing agents + compression stockings for treatment of CVI compared to compression stockings alone

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Efficacy: flavonoid fraction-containing agents + compression stockings versus compression stockings alone							
Change of CVI stage: no evidence							
CVI signs (general): no evidence							
CVI signs (trophic alternations): no evidence							
CVI signs (oedema): no evidence							

[96] Unclear random sequence generation in all 3 studies and unclear blinding of outcome assessor in 2 studies.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
CVI signs (ulcer): healing rate (in %)							
1/414[97] 1/150 1/150	Sytem. Review RCT RCT	2 mo: 14.1 to 40.3 vs. 8.7 to 21; p=n/a 3 mo: 44 vs. 28; p=S.S. 6 mo: 65 vs. 41; p=S.S.	Serious limitations (-1)[98] Serious limitations (-1)[88] Serious limitations (-1)[88]	Important inconsistency[99] (-1) n/a (only 1 trial) n/a (only 1 trial)	Direct Direct Direct	None Imprecise data (-1)[89] Imprecise data (-1)[89]	Low Low Low
CVI signs (ulcer): reduction of size (in %)							
1/150	RCT	6 mo: 77 vs. 69; p=S.S.	Serious limitations (-1)[88]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low
CVI symptoms (general): no evidence							
CVI symptoms (pain): no evidence							
CVI symptoms (cramps): no evidence							
CVI symptoms (restless legs): no evidence							
CVI symptoms (itching): no evidence							
CVI symptoms (heaviness): score (0-10)							
1/150	RCT	1 mo: -2 vs. -0.7; p=S.S.[100] 6 mo: -2.7 vs. -1; p=S.S.[100]	Serious limitations (-1)[88]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low
CVI symptoms (swelling): no evidence							
CVI symptoms (paraesthesias): no evidence							
Quality of life: no evidence							
Safety: flavonoid fraction-containing agents + compression stockings versus compression stockings alone							
Adverse events (general): no evidence							
Adverse events (treatment-related): in %							
1/150	RCT	0 vs. n/a; p=n/a	Serious limitations (-1)[88]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low

Abbreviations: n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

[97] The systematic review summarised five studies with 723 patients, since there were only three of these studies with a control group only receiving compression stockings, only these three studies were extracted.

[98] Systematic review was not based on research question and it is unclear if extracted data were reviewed by a second person.

[99] Review included studies comparing flavonoid fraction-containing agents (+ compression stockings) with placebo or nothing (+ compression stockings). In this table we only used the data from studies with a compression stocking (and nothing else) receiving control group, thus it was not possible to use the risk ratio and confidence interval of the systematic review.

[100] The score in this study was originally 0-3; the values were multiplied with 3.33 to adopt them to a score of 0-10.

Table 3.1-10: Evidence profile: Efficacy and safety of flavonoid fraction-containing agents + surgery for treatment of CVI compared to surgery alone

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Efficacy: flavonoid fraction-containing agents + surgery versus surgery alone							
Change of CVI stage: no evidence							
CVI signs (general): no evidence							
CVI signs (trophic alternations): no evidence							
CVI signs (oedema): decrease (in %)							
1/181	RCT	1 mo: 84 vs. n/a; p=S.S.	Serious limitations (-1)[101]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low
CVI signs (ulcer): no evidence							
CVI symptoms (general): no evidence							
CVI symptoms (pain): no evidence							
CVI symptoms (cramps): no evidence							
CVI symptoms (restless legs): no evidence							
CVI symptoms (itching): improvement (in %)							
1/181	RCT	1 mo: 92 vs. n/a; p=s.s	Serious limitations (-1)[88]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low
CVI symptoms (heaviness): improvement (in %)							
1/181	RCT	1 mo: 89 vs. n/a; p=s.s	Serious limitations (-1)[88]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low
CVI symptoms (swelling): no evidence							
CVI symptoms (paraesthesias): no evidence							
Quality of life: Improved patients (in %)							
1/181	RCT	1 mo: 21 vs. 3; p=n/a	Serious limitations (-1)[88]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Low
Safety: flavonoid fraction-containing agents + surgery versus surgery alone							
Adverse events (general): in %							
1/245	CT	0 vs. 0; p=N.S.	Serious limitations (-1)[102]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Very low
Adverse events (treatment-related): in %							
1/245	CT	2 vs. n/a; p=n/a	Serious limitations (-1)[233]	n/a (only 1 trial)	Direct	Imprecise data (-1)[89]	Very low

Abbreviations: CT = controlled trial; n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

[101] Unclear random sequence generation.

[102] No blinding of outcome assessor.

Table 3.1-11: Evidence profile: Safety of flavonoid fraction-containing agents for treatment of CVI (results from single-arm studies)

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Safety: flavonoid fraction-containing agents (results from single-arm studies)							
Adverse events (general): in %							
2/523	Single-arm studies	6 to 9	Serious limitations (-1)[103]	No important inconsistency	Direct	Imprecise data (-1)[89]	Very low
Adverse events (treatment-related): in %							
2/11,555	Single-arm studies	0 to 3.3	Serious limitations (-1)[103]	No important inconsistency	Direct	None	Very low

Abbreviations: n/a = data not available; N.S. = not statistically significant; S.S. = statistically significant; vs. = versus

[103] No blinding of outcome assessor in both studies.

3.1.3 20 mg aescin-containing agents

Study characteristics

keine Studien zu Wirksamkeit gefunden

There were no studies to assess the efficacy of capillary stabilising agents containing 20 mg of aescin for the treatment of CVI. Furthermore, there were no studies identified comparing agents containing 20 mg of aescin with other interventions, such as lifestyle changes or further local, medical and surgical treatment, mentioned in Chapter 1.1.2.

Sicherheit: 1 non-RCT eingeschlossen

Dosis: 20 mg 6x täglich

For evaluating the safety of capillary stabilising agents containing 20 mg of aescin, we identified 1 non-randomised controlled study [57] that met our inclusion criteria. The studies compared agents containing 20 mg of aescin taken six times a day with placebo for the treatment of CVI [57]. The study characteristics and results are summarised in Table 3.1-12.

Table 3.1-12: Safety-related outcomes of non-randomised controlled trials of 20 mg aescin-containing agents vs. placebo for CVI

Author, year, reference number	Shah 1997 [57]
Country	Germany, Switzerland
Study design	Non-randomised controlled trial
Sponsor	n/a
Intervention/product	6x 20 mg aescin (HCSE) tablets per day
Comparator	Placebo
Number of pts.	30 vs. 30
Age of patients (yrs.)	54 vs. 56
Sex (% female)	93
Height (cm)/weight (kg)/BMI (kg/m²)	166 vs. 166 / 75 vs. 75 / n/a
Clinical classification	Grade I + II acc. to Widmer
Primary endpoint	Ankle circumference and symptoms
Inclusion criteria	Patients >18 yrs. with CVI grade I + II (acc. to Widmer) with certain scores for signs and symptoms
Duration of Treatment (months)	1.5
Follow-up (months)	0
Drop-outs, n (%)	9 (15)[104]
Safety-related outcomes	
Adverse events, general in % (n) pts.	10(3) vs. 10 (3); p=n/a (gastrointestinal disorders, pain, urinary tract infection vs. gastrointestinal disorders, thrombophlebitis)
Major adverse events	n/a
Minor adverse events	n/a
Adverse events, treatment-related in % (n) pts.	3 (1) vs. 7 (2); p=n/a (pain vs. gastrointestinal disorders)
Major adverse events	n/a
Minor adverse events	n/a

Abbreviations: acc. = according; CVI = chronic venous insufficiency, HCSE = horse chestnut seed extract; n = number (of patients); n/a = data not available; pts. = patients; yrs. = years

[104] A total of 9 patients withdraw from study, whereas one patient was replaced.

Efficacy

As stated above, we could not identify any studies assessing the efficacy of capillary stabilising agents containing 20 mg of aescin for the treatment of CVI.

keine Studien zu Wirksamkeit

Safety

In the only relevant trial identified, 30 patients received agents containing 20 mg of aescin six times a day (treatment group) and the 30 patients in the control group received placebo. The mean age of the patients was 54 years in the treatment and 56 years in the control groups and 93% of the patients were females. The duration of treatment was 1.5 months and there was no follow-up after treatment. The drop-out rate was 15% [57].

1 non-RCT mit 60 PatientInnen, ca. 55 Jahre als, 93 % Frauen eingeschlossen

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.1-14.

Zusammenfassung in GRADE-Tabelle

20 mg aescin-containing agents versus placebo

General adverse events occurred in 10% of the patients in the treatment and in the control group, respectively. The most common adverse events were gastrointestinal disorders, pain and urinary tract infections in the group that received 20 mg aescin versus gastrointestinal disorders and thrombophlebitis in the group that received placebo [57].

generelle unerwünschte Ereignisse in 10 % der PatientInnen beider Studiengruppen

Additionally, there occurred treatment-related adverse events in 1% of the patients in the treatment group (pain) and 2% of the patients in the control group (gastrointestinal disorders) [57].

Nebenwirkungen in 1 vs. 2 % der PatientInnen

Risk of bias

The identified non-RCT has a high risk of reporting bias due to a missing analysis of confounder (see Figure 3.1-12). The risks for other types of biases are low. Thus, the overall risk of bias is low.

generelles Bias-Risiko gering

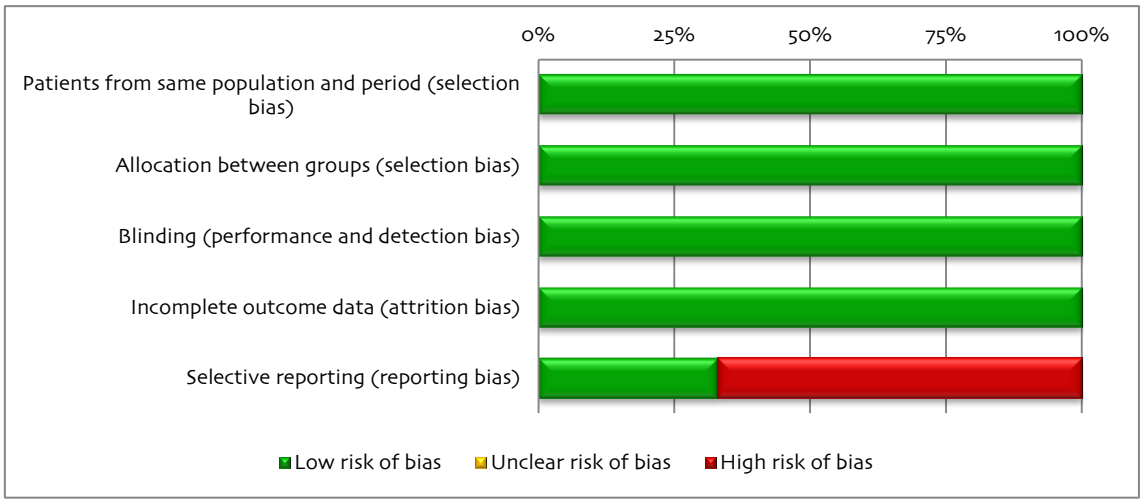

Figure 3.1-12: Risk of bias of non-randomised controlled studies for 20 mg aescin-containing agents for treatment of CVI

Strength of evidence

Evidenzstärke sehr gering

Overall, the strength of evidence of the safety (there was no evidence for assessing the efficacy) of a treatment of CVI with agents containing 20 mg of aescin compared to placebo is very low, since the only identified study was a non-RCT. The strength of evidence is summarised in the Tables 3.1-13 (for efficacy, whereby there was no available evidence) and 3.1-14.

keine Evidenz zu Vergleich mit anderen Behandlungen

There was no evidence to compare a treatment of CVI with agents containing 20 mg of aescin to other interventions, such as lifestyle changes or further local, medical and surgical treatment, mentioned in Chapter 1.1.2.

Table 3.1-13: Evidence profile: Efficacy of 20 mg aescin-containing agents for treatment of CVI compared to placebo

No of studies/patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy: 20 mg aescin-containing agents							
Change of CVI stage: no evidence							
CVI signs: no evidence							
CVI symptoms: no evidence							
Quality of life: no evidence							

Table 3.1-14: Evidence profile: Safety of 20 mg aescin-containing agents for treatment of CVI compared to placebo

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Safety: 20 mg aescin-containing agents vs. placebo							
Adverse events (general): in %							
1/60	CT	10 vs. 10; p=n/a	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[105]	Very low
Adverse events (treatment-related): in %							
1/60	CT	3 vs. 7; p=n/a	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[105]	Very low

Abbreviations: CT = controlled trial; n/a = data not available; N.S. = not statistically significant; S.S. = statistically significant; vs. = versus

3.1.4 50 mg aescin-containing agents

Study characteristics

1 systematischen Review eingeschlossen

For evaluating the efficacy and safety of capillary stabilising agents containing 50 mg of aescin, we identified 1 systematic review [58].

Insgesamt 1.292 PatientInnen

There were a total of 1,292 patients in the systematic review comparing agents containing 50 mg of aescin, supplemented by compression stockings with either placebo or compression stockings alone for the treatment of CVI [58]. Patients received agents containing 50 mg of aescin once or twice per day. However, the systematic review included also two studies in which patients received a 75 mg aescin dosage form. Since this dosage form is not included in the Austrian EKO, we excluded the outcomes of these two studies from our extraction.

Vergleichsgruppen: Placebo und/oder Kompressionsstrümpfe

[105] Low incidence, study not powered to detect difference.

The patients were on average between 41 and 53 years in the treatment groups and between 38 and 48 years in the control groups. The majority of the patients were females: 50-100%. Furthermore, patients had CVI grade I-II according to Widmer (see Chapter 1.1.2), the duration of treatment was 0.5-4 months. It was not stated whether any study had a follow-up without treatment. The drop-out rate of all studies together was 9% [58].

PatientInnen 38-53 Jahre alt, 50-100 % Frauen

The study characteristics and results (for efficacy and safety) are summarised in Table 3.1-15.

Zusammenfassung Studiencharakteristika

There were no studies identified comparing agents containing 50 mg of aescin with other interventions, such as lifestyle changes or further local, medical and surgical treatment, mentioned in Chapter 1.1.2.

keine Studien mit anderen Vergleichsgruppen

Table 3.1-15: Efficacy and safety-related outcomes of a systematic review of 50 mg aescin-containing agents vs. placebo or compression stockings for CVI

Author, year, reference number	Pittler 2012 [58]
Country	Germany
Study design	Systematic review[106]
Sponsor	None
Intervention/Product	1-2x 50 mg aescin (HCSE) capsules per day 2x 75 mg aescin (HCSE) capsules per day[107]
Comparator	Placebo, compression stockings
Number of pts	1,292
Age of patients (yrs.)	Ø 41-53 vs. 38-48
Sex (% female)	50-100
Height (cm)/Weight (kg)/BMI (kg/m²)	n/a / n/a / n/a
Clinical classification	Grade I-II acc. to Widmer
Primary endpoint	CVI-related symptoms and oedema (of included studies)
Inclusion criteria	Patients with CVI, comparing oral preparations of HCSE with placebo or reference therapy, measuring clinical outcomes
Duration of Treatment (months)	0.5-4
Follow-up (months)	n/a
Drop-outs, n (%)	114 (9)
Efficacy-related outcomes	
Change of CVI stage	n/a
CVI signs (general)	n/a
Trophic alterations	n/a

[106] This systematic review included 17 RCTs on aescin-containing agents. Of these, 11 compared aescin against placebo and/or against compression stockings and four against O-beta-hydroxyethyl rutosides (HR). Information about age, sex ratio and clinical classification was not stated in all included studies.

[107] Outcomes of studies for 75 mg aescin were not extracted, since this dosage form is not in the Austrian EKO.

Author, year, reference number	Pittler 2012 [58]
Oedema (or leg volume or circumference)	**HCSE vs. placebo** 1 study (15 vs. 15 pts.) for reduction of oedema (100 mm VAS): 41.2 vs. 1.1; mean difference=40.10; **p=S.S.** 1 study (173 vs. 173 pts.) for improvement of oedema (dichotomous): 114 (66%) vs. 71 (41%); odds ratio=2.78; **p=S.S.** 5 studies[108] (292 vs. 171 pts.) for reduction of leg volume (ml): 18-114 vs. (-)34-0.55; mean difference=31.44; **p=0.00073** 3 studies (40 vs. 40 pts.) for reduction of circumference at ankle (mm): 6-7.7 vs. -4.3-3; mean difference=4.71; **p=0.0099** 3 studies (40 vs. 40 pts.) for reduction of circumference at calf (mm): 1.3-6.1 vs. -2.3 - 1; mean difference=3.51; **p=0.019** **HCSE vs. compression** 2 studies (238 vs. 241 pts) for reduction of leg volume (ml): 18-43.8 vs. 46.7-89; mean difference=-37.34; **p=N.S.**
Ulcer	n/a
CVI symptoms (general)	**HCSE vs. compression** 1 study (143 vs. 142 pts.) for improvement of symptom score (40 point scale): 4.9 vs. 4.6; **p=N.S.**
Pain	**HCSE vs. placebo:** 1 study (209 vs. 209 pts.) for improvement of pain (dichotomous): 132 (63%) vs. 91 (44%); odds ratio=2.22; **p=S.S.** 1 study (15 vs. 15 pts.) for reduction of pain (100 mm VAS): 42.6 vs. 0.21, mean difference=42.4; **p=S.S.**
Cramps	n/a
Restless legs	n/a
Itching (=tingling sensation)	n/a
Heaviness (=heavy legs)	n/a
Swelling (=sensation of tension)	n/a
Paraesthesias	n/a
QoL	n/a
Safety-related outcomes	
Adverse events, general in % (n) pts.	6 studies (a total of 758 pts. in both groups): 1-36% vs. n/a; p=n/a (gastrointestinal complaints, dizziness, nausea, headache, pruritus vs. n/a)
Major adverse events	n/a
Minor adverse events	n/a
Adverse events, treatment-related in % (n) pts.	4 studies (a total of 356 pts. in both groups): 0 vs. n/a; p=n/a
Major adverse events	n/a
Minor adverse events	n/a

Abbreviations: acc. = according; CVI = chronic venous insufficiency; HCSE = horse chestnut seed extract; n = number (of patients); n/a = data not available; N.S. = not statistically significant; pts. = patients; QoL = quality of life; RCT = randomised controlled trial; VAS = visual analogue score; vs. = versus; yrs. = years

[108] In one additional study (20 vs. 19 pts.), HCSE was standardised to 75 mg aescin. The outcomes of this study were not extracted and the mean difference excludes this study, but the p-value calculation is included in this study.

Efficacy

For evaluating the efficacy of flavonoid fraction-containing capillary stabilising agents, we identified 1 systematic review that met our inclusion criteria [58].

1 systematischen Review eingeschlossen

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.1-16.

Zusammenfassung in GRADE-Tabelle

50 mg aescin-containing agents (+ compression stockings) versus placebo (+ compression stockings)

There was no evidence available to assess the efficacy of a treatment with agents containing 50 mg of aescin versus placebo regarding the following outcomes: change of the CVI stage, CVI signs in general, trophic alternations, ulcer, symptoms of CVI: cramps, restless legs, itching, heaviness, swelling, paraesthesias and quality of life.

mehrere nicht berichtete Endpunkte

Concerning CVI signs, oedema was measured by five different parameters. In one study oedema was measured as the reduction on a score (0-10) and in another study this outcome was measured as improvement (in %) after 1 month. The reduction was statistically significant in favour of 50 mg aescin compared to placebo in both studies (mean difference of score reduction between groups: 4.01 and odds ratio of improvement: 0.278) [58].

Reduktion Ödeme in Behandlungsgruppe signifikant höher

The meta-analysis of the leg volume change (displaying the 5 relevant studies for 50 mg aescin) shows that the difference is statistically significant in favour of a treatment with agents containing 50 mg of aescin versus placebo with a mean difference of -30.66 ml between the groups (Figure 3.1-13).

Gruppenunterschied Ödemreduktion in Forest-Plot ersichtlich

Study name	Statistics for each study			Sample size		Mean difference, 95% CI
	Difference in means	Lower limit	Upper limit	50 mg aescin	Placebo	
Pittler 2012 (from Rudofsky 1986)	-78.2	-182.59	26.19	19	20	
Pittler 2012 (from Steiner 1986)	-114.5	-345.08	116.08	10	10	
Pittler 2012 (from Steiner 1990 a)	-31.09	-142.68	80.5	25	25	
Pittler 2012 (from Diehm 1996 a)	-53.6	-91.67	-15.53	95	46	
Pittler 2012 (from Diehm 2000)	-20.0	-42.12	2.12	143	70	
Total (95% CI)	**-30.66**	**-49.15**	**-12.17**	**292**	**171**	
						-350 -175 0 175 350
Random effects meta-analysis; I^2: 0.0%; p=0.001						Favours 50 mg aescin Favours placebo

Figure 3.1-13: Leg volume change (in ml) after 0.5-4 months for 50 mg aescin-containing agents versus placebo

Furthermore, oedema was measured as ankle and calf circumference change in three studies and both indicators decreased statistically significantly more in the treatment group than in the placebo group (mean differences of change between groups: -4.71 and -3.51) after 0.5 to 1 month of treatment [58]. The forest plots for ankle and calf circumference change are displayed in Figures 3.1-14 and 3.1-15 below.

Gruppenunterschied Reduktion Knöchelumfang in Forest-Plot ersichtlich

Study name	Statistics for each study			Sample size		Mean difference, 95% CI
	Difference in means	Lower limit	Upper limit	50 mg aescin	Placebo	
Pittler 2012 (from Steiner 1986)	-5.9	-16.12	4.32	10	10	
Pittler 2012 (from Pilz 1990)	-4.0	-7.95	-0.05	15	15	
Pittler 2012 (from Cloarec 1992)	-12.0	-26.69	2.69	15	15	
Total (95% CI)	**-4.71**	**-8.28**	**-1.12**	**40**	**40**	
						-30 -15 0 15 30
Random effects meta-analysis; I^2: 0.0%; p=0.01						Favours 50 mg aescin Favours placebo

Figure 3.1-14: Ankle circumference (in mm) change after 0.5-1 month for 50 mg aescin-containing agents versus placebo

Study name	Statistics for each study			Sample size		Mean difference, 95% CI
	Difference in means	Lower limit	Upper limit	50 mg aescin	Placebo	
Pittler 2012 (from Steiner 1986)	-0.6	-7.84	6.64	10	10	
Pittler 2012 (from Pilz 1990)	-4.0	-7.24	-0.76	15	15	
Pittler 2012 (from Cloarec 1992)	-8.4	-31.23	14.43	15	15	
Total (95% CI)	**-3.51**	**-6.45**	**-0.58**	**40**	**40**	
						-35 -17.5 0 17.5 35
Random effects meta-analysis; I^2: 0.0%; p=0.02						Favours 50 mg aescin Favours placebo

Figure 3.1-15: Calf circumference (in mm) change after 0.5-1 month for 50 mg aescin-containing agents versus placebo

Schmerzreduktion in Behandlungsgruppen signifikant besser

The only reported symptom of CVI – pain – was statistically significantly more improved after 3 weeks of treatment in the 50 mg aescin groups than in the placebo groups (dichotomous variable: odds ratio of 2.2). Likewise the score for pain (scale 0-10) was statistically significantly more reduced after 1 month of treatment (mean difference: 42.4) [58].

50 mg aescin-containing agents + compression stockings versus compression stockings alone

keine Evidenz zu mehreren Endpunkten

There was no evidence available assessing the change of the CVI stage, the CVI signs in general, trophic alternations and ulcer, CVI-related symptoms (pain, cramps, restless legs, itching, heaviness, swelling, paraesthesias) and quality of life after a treatment with agents containing 50 mg of aescin and compression stockings versus compression stockings alone.

Ödeme in Behandlungsgruppe nicht signifikant mehr reduziert

One CVI sign – oedema – was reported (based on the results of 2 RCTs) in terms of leg volume change from baseline (in ml). Reduction in leg volume was not statistically significantly higher after 3 to 4 months of treatment in the 50 mg aescin group supplemented by compression stockings compared to the control group (mean difference of reduction: 37.34 ml) [58].

In terms of CVI signs, the score (0-10) for general symptoms was more improved in the treatment group compared to the control group, after 4 months of treatment (mean difference of score improvement: 0.095). However, the difference between the study groups was not statistically significant [58].

generelle CVI-Anzeichen in Behandlungsgruppe nicht signifikant mehr reduziert

Safety

The identified systematic review did not present data on general adverse events in the control groups and therefore general adverse events of the treatment groups only (if reported) were summarised.

unerwünschten Ereignissen in Kontrollgruppen unbekannt

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.1-17.

Zusammenfassung in GRADE-Tabelle

50 mg aescin-containing agents

The general adverse events (stated in 6 studies) ranged from 1 to 36% in the 50 mg aescin groups. The most common events were gastrointestinal complaints, dizziness, nausea, headache and pruritus [58].

generelle unerwünschte Ereignisse: 1-36 % in Behandlungsgruppe

Treatment-related adverse events, reported in 4 studies, occurred in 0% of the patients in the treatment groups [58].

keine Nebenwirkungen

Risk of bias

The identified systematic review shows an overall low risk of bias (see Figure 3.1-16), however, there is some high risk of selection bias due to an unclear research question.

Bias-Risiko generell niedrig

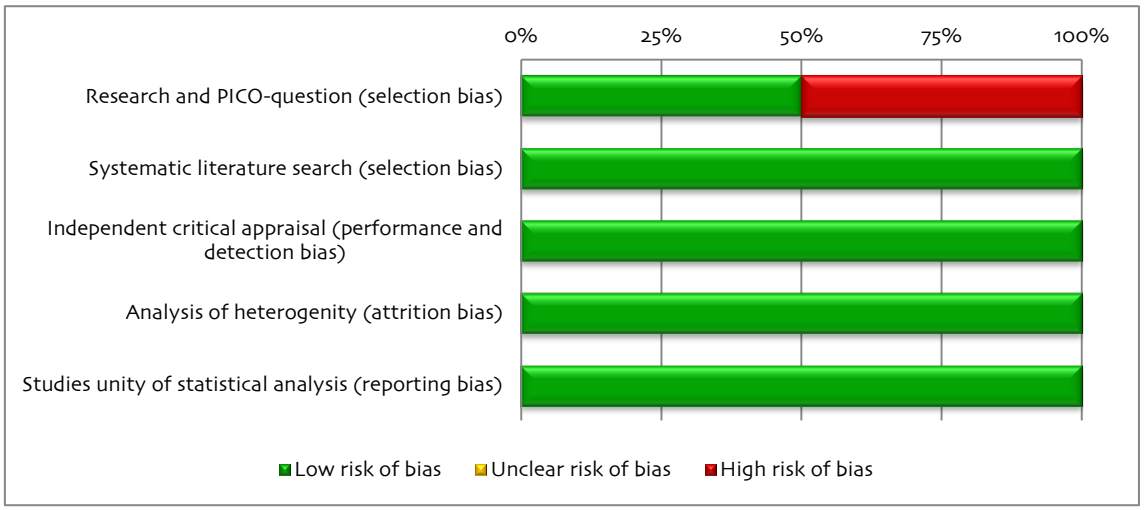

Figure 3.1-16: Risk of bias of systematic review for treatment of CVI with 50 mg aescin-containing agents

Strength of evidence

Evidenzstärke niedrig bis mittel

Overall, the strength of evidence of the efficacy and safety of a treatment of CVI with agents containing 50 mg of aescin, supplemented by compression stockings compared to placebo or compression stockings alone is low. Although the identified study was a systematic review, the majority of the RCTs the systematic review was based on, have shown several limitations and, therefore, the strength of evidence was downgraded. Solely for pain, measured as the percentage of improved patients, the quality of evidence is moderate. The strength of evidence is summarised in Tables 3.1-16 and 3.1-17.

keine Evidenz zu Vergleich mit anderen Behandlungen

There was no evidence to compare a treatment of CVI with agents containing 50 mg of aescin to other interventions, such as lifestyle changes or further local, medical and surgical treatment, mentioned in Chapter 1.1.2.

Table 3.1-16: Evidence profile: Efficacy of 50 mg aescin-containing agents (+ compression stockings) for treatment of CVI compared to placebo or compression stockings alone

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Efficacy: 50 mg aescin-containing agents (+compression stockings) versus placebo (+compression stockings)							
Change of CVI stage: no evidence							
CVI signs (general): no evidence							
CVI signs (trophic alternations): no evidence							
CVI signs (oedema): reduction (score 0-10)							
1/30 (of 1,292)	1 RCT (in syst. Rev.)	1 mo: mean difference: 4.01; CI: 3.16, 4.86; p=S.S.	Serious limitations (-1)[109]	n/a (only 1 trial)	Direct	Imprecise data (-1)[110]	Low
CVI signs (oedema): improvement (in %)							
1/346 (of 1,292)	1 RCT (in syst. Rev.)	1 mo[111]: OR: 2.78; CI: 1.79, 4.3; p=S.S.	Serious limitations (-1)[109]	n/a (only 1 trial)	Direct	Imprecise data (-1)[110]	Low
CVI signs (oedema): leg volume change from baseline (in ml)							
6/502 (of 1,292)	5 RCTs (in syst. Rev.)	0.5-4 mo: mean difference: -32.10; CI: -13.49, -50.72; p=S.S.	Serious limitations (-1)[112]	Important inconsistency[113] (-1)	Direct	None	Low
CVI signs (oedema): ankle circumference change from baseline (in mm)							
3/80 (of 1,292)	3 RCTs (in syst. Review)	0.5-1 mo: mean difference: -4.71; CI: -1.13, -8.28; p=S.S.	No serious limitations[114]	Important inconsistency[113] (-1)	Direct	Imprecise data (-1)[110]	Low
CVI signs (oedema): calf circumference change from baseline (in mm)							
3/80 (of 1,292)	3 RCTs (in syst. Review)	0.5-1 mo: mean difference:- 3.51; CI:- 0.58, -6.45; p=S.S.	No serious limitations[114]	Important inconsistency[113] (-1)	Direct	Imprecise data (-1)[110]	Low
CVI signs (ulcer): no evidence							
CVI symptoms (general): no evidence							
CVI symptoms (pain): improved patients (in %)							
1/418	1 RCT (in syst. Review)	0.75 mo: OR: 2.2; CI: 1.11, 3.53; p=S.S.	Serious limitations (-1)[109]	n/a (only 1 trial)	Direct	None	Moderate
CVI symptoms (pain): reduction (score 0-10)							
1/30	1 RCT (in syst. Review)	1 mo: mean difference: 4.24; CI: 3.49, 4.99; p=S.S.	Serious limitations (-1)[109]	n/a (only 1 trial)	Direct	Imprecise data (-1)[110]	Low

[109] Systematic review itself has no limitations, but study the review is based on has serious limitation due to unclear allocation concealment.

[110] Systematic review itself shows no other modifying factors, but the study/studies the review is based on is/are limited by imprecise data due to low incidence/patient number.

[111] Study duration was 20 days.

[112] Systematic review itself has no limitations, but studies the review is based on have serious limitation due to unclear allocation concealment in only 1 of 3 studies.

[113] Systematic review summarised outcomes of studies from different times (e.g., after 0.5, 1, 3 or 4 months) and in one study patients received 75 mg aescin.

[114] Systematic review itself has no limitations and studies the review is based on have serious limitation due to unclear allocation concealment in 4 of 5 studies.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
CVI symptoms (cramps): no evidence							
CVI symptoms (restless legs): no evidence							
CVI symptoms (itching): no evidence							
CVI symptoms (heaviness): no evidence							
CVI symptoms (swelling): no evidence							
CVI symptoms (paraesthesias): no evidence							
Quality of life: no evidence							
Efficacy: 50 mg aescin-containing agents + compression stocking versus compression stockings alone							
Change of CVI stage: no evidence							
CVI signs (general): no evidence							
CVI signs (trophic alternations): no evidence							
CVI signs (oedema): leg volume change from baseline (in ml)							
2/479 (of 1,292)	2 RCTs (in syst. Rev.)	3-4 mo: mean difference: 37.34; CI: -29.39, 104.07; p=N.S.	Serious limitations (-1)[115]	Important inconsistency[116] (-1)	Direct	None	Low
CVI signs (ulcer): no evidence							
CVI symptoms (general): improvement (score 0-10)							
1/285 (of 1,292)	1 RCT (in syst. Rev.)	4 mo: mean difference: 0.095; CI: -0.27, 0.46; p=N.S.	Serious limitations (-1)[117]	n/a (only 1 trial)	Direct	Imprecise data (-1)[110]	Low
CVI symptoms (pain): no evidence							
CVI symptoms (cramps): no evidence							
CVI symptoms (restless legs): no evidence							
CVI symptoms (itching): no evidence							
CVI symptoms (heaviness): no evidence							
CVI symptoms (swelling): no evidence							
CVI symptoms (paraesthesias): no evidence							
Quality of life: no evidence							

Abbreviations: n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

115 Systematic review itself has no limitations, but studies the review is based on have serious limitation due to unclear allocation concealment in 2 of 2 studies.

116 Systematic review summarised outcomes of studies from different times (e.g., after 3 or 4 months).

117 Systematic review itself has no limitations, but study the review is based on has serious limitation due to unclear allocation concealment.

Table 3.1-17: Evidence profile: Safety of 50 mg aescin-containing agents for treatment of CVI

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Safety: 50 mg aescin-containing agents							
Adverse events (general): in %							
6/1,516	6 RCTs (in syst. Rev.)	1 to 36 vs. n/a; p=n/a	Serious limitations (-1)[118]	No important inconsistency	Direct	Imprecise data (-1)[119]	Low
Adverse events (treatment-related): in %							
4/712	4 RCTs (in syst. Rev.)	0 vs. n/a; p=n/a	Serious limitations (-1)[120]	No important inconsistency	Direct	Imprecise data (-1)[119]	Low

Abbreviations: n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

[118] Systematic review itself has no limitations, but studies the review is based on have serious limitation due to unclear allocation concealment in 6 of 6 studies.

[119] Low incidence, study/studies not powered to detect difference.

[120] Systematic review itself has no limitations, but studies the review is based on have serious limitation due to unclear allocation concealment in 3 of 4 studies.

3.1.5 Calcium dobesilate-containing agents

Study characteristics

1 systematischen Review, 4 RCTs, 1 non-RCT, 2 Ein-Arm-Studien mit 2.768 PatientInnen eingeschlossen

For evaluating the efficacyand safety of calcium dobesilate-containing capillary stabilising agents, we identified 1 systematic review [10], 4 RCTs [59-62], 1 additional non-randomised study [63] and 2 single-arm studies [64, 65] that met our inclusion criteria. The studies are comparing calcium dobesilate-containing agents (in addition to surgery) with either placebo [10, 59-62], or surgery alone [63] or there was no control group [64, 65] for a treatment of CVI. The dosages of calcium dobesilate varied from 500 mg two times to four times a day.

Dosis: 500 mg 2-4 x täglich

Zusammenfassung Studiencharakteristika

The study characteristics and results are summarised in Table 3.1-18 for RCTs and in Table 3.1-19 for the non-randomised controlled trials plus the single-arm studies.

keine Studien mit anderen Vergleichsgruppen

There were no studies identified comparing calcium dobesilate-containing agents with other interventions, such as lifestyle changes or further local, medical and surgical treatment, mentioned in Chapter 1.1.2.

Table 3.1-18: Efficacy and safety-related outcomes of a systematic review and randomised controlled trials of calcium dobesilate-containing agents vs. placebo for CVI

Author, year, reference number	Martinez 2005 [10]	Flota-Cervera 2008 [59]	Martinez-Zapata 2008 [62]	Rabe 2011 [60]	Labs 2004 [61]
Country	Spain	Mexico	Spain	Germany	Switzerland, France
Study design	Systematic review[121]	RCT	RCT	RCT	RCT
Sponsor	none	Quimica Knoll de Mexico	Laboratories Dr. Esteve	OM Pharma	OM Pharma
Intervention/ Product	2-4x 500 mg calcium dobesilate per day	3x 500 mg calcium dobesilate capsules (Doxium®) per day	2x 500 mg calcium dobesilate capsules (Doxium®) per day	3x 500 mg calcium dobesilate (Doxium®) per day[122]	3x 500 mg s calcium dobes-ilate (Doxium®) per day
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo
Number of pts	854	25 vs. 24	246 vs. 263	132 vs. 124	128 vs. 125
Age of patients (yrs.)	10-70	Ø 54 vs. 51	Ø 53 vs. 55	Ø 53 vs. 54	Ø 49 vs. 49
Sex (% female)	86	92 vs. 88	88 vs. 86	84 vs. 86	88 vs. 93
Height (cm)/Weight (kg)/BMI (kg/m²)	n/a / n/a / n/a	158 vs. 158 / 73 vs. 70 / n/a	n/a / n/a / n/a	169 vs. 168 / 74 vs. 73 / n/a	165 vs. 164 / 69 vs. 68 / n/a
Clinical classification	Grade I-III[123] acc. to Widmer or CEAP classification 1-5	Grade I-V acc. to Widmer	CEAP classification 1-6	CEAP classification 3-5	CEAP classification C3-4
Primary endpoint	CVI symptoms + signs	n/a	QoL	Relative leg volume change after 8 weeks compared with baseline	Change of leg volume of the more diseased leg after 1 month
Inclusion criteria	Patients with: CVI grade I-II (Widmer), primary CVI + post-thrombotic syndrome, CEAP 3-5, recent onset of CVI + presence of symptoms and venous oedema	Patients of both sexes, aged >25 yrs. with CVD	Patients of both sexes, aged ≥18 yrs. with CVD, CEAP grade 1-6 and able to complete a QoL questionnaire	Outpatients of both sexes, aged 20-70 yrs., with pitting oedema due to CVI (CEAP classification 3-5) and at least one symptom such as discomfort and pain	Outpatients of both sexes, aged 20-70 yrs., with pitting oedema due to CVI (CEAP classification C3-4)
Duration of Treatment (months)	1-2.8	1.75[124]	3	2[125]	1[126]
Follow-up (months)	n/a	0	9	0.5	0.5
Drop-outs, n (%)	68 of 774 (9)	n/a	61 (25)vs. 70 (27)	23 (17) vs. 9 (7)	14 (11) vs. 7 (6)[127]

121 This systematic review included 44 studies of oral phlebotonics in the analysis, but only the extracted data of 7 RCTs for calcium dobesilate was used for our review.

122 Wearing compression stockings was allowed.

123 One study included, beside 30 CVI patients, also 30 healthy subjects.

124 The study started with a wash-out phase of one week.

125 The study started with a run-in phase of two weeks.

126 The study started with a run-in phase of 1 week.

Author, year, reference number	Martinez 2005 [10]	Flota-Cervera 2008 [59]	Martinez-Zapata 2008 [62]	Rabe 2011 [60]	Labs 2004 [61]
Efficacy-related outcomes					
Change of CVI stage	n/a	n/a	n/a	n/a	n/a
CVI signs (general)	n/a	n/a	n/a	n/a	n/a
Trophic alterations	n/a	n/a	n/a	n/a	n/a
Oedema (leg volume or circumference)	2 studies (148 vs. 142 pts.) for oedema (dichotomous): 13-23% vs. 23-93%; risk ratio=0.41; **p=N.S.** 3 studies (252 vs. 250 pts.) for leg circumference (mm): 230-336 vs.228-356; mean difference=-0.09; **p=N.S.** 2 studies (118 vs. 118 pts.) for leg volume (ml): -3.8-1,097 vs. -1.15-1,205; mean difference=-0.64; **p=0.03**	*Leg circumference (cm):* Baseline: 51.2 vs. 48.4; p=n/a After 1 month: n/a After 1.75 months: 50.3 vs. 48.1; p=n/a After 2; 3; 6; 12 months: n/a *Calf circumference (cm):* Baseline: 40.6 vs. 39.7; p=n/a After 1 month: n/a After 1.75 months: 39.0 vs. 39.7; p=n/a After 2; 3; 6; 12 months: n/a *Ankle circumference (cm):* Baseline: 36.2 vs. 35.9; p=n/a After 1 month: n/a After 1.75 months: 33.6 vs. 35.6; p=n/a After 2; 3; 6; 12 months: n/a	*Ankle circumference (mm):* Baseline: 258.2 vs. 270.1; **p=N.S.** After 1, 2 months: n/a After 3 months: 254.9 vs. 266.8; **p=N.S.** After 6; 12 months: n/a	*Change of leg volume (%)*[128]*:* Baseline: - After 1 month: n/a After 2 months: -2 vs. 0; **p=0.001** After 3; 6, 12 months: n/a *Change of leg volume (cm³)*[128]*:* Baseline: - After 1 month: n/a After 2 months: -64.72 vs. +0.76; **p=0.002** After 3; 6, 12 months: n/a *Leg volume (cm³):* Baseline: 3,088 vs. 3,062; p=n/a After 1 month: n/a After 2 months: 3,039 vs. 3,073; p=n/a After 2.5 months: 3,050 vs. 3,022; p=n/a After 3; 6, 12 months: n/a *Calf circumference (cm):* Baseline: 39.1 vs. 38.9; p=n/a After 1 month: n/a After 2 months: 38.8 vs. 38.9; p=n/a After 2,5 months: 38.9 vs. 38.6; p=n/a After 3; 6, 12 months: n/a	*Change of leg volume (ml/l)*[129]*:* Baseline: 0 vs. 0 After 1 month: -25.5 vs. -13.3; **p=0.0109** After 1.5 months -15 vs. -17.3; **p=N.S.** After 2; 3; 6, 12 months: n/a *Ankle circumference (mm):* Baseline: 231.7 vs. 230.2; p=n/a After 1 month: 227.7 vs. 227.5; p=n/a After 1.5 months: 228.7 vs. 228.2; p=n/a After 2; 3; 6, 12 months: n/a *Calf circumference (mm):* Baseline: 370 vs. 371.7; p=n/a After 1 month: 366.2 vs. 369.4; p=n/a After 1.5 months: 368.7 vs. 369.7; p=n/a After 2; 3; 6, 12 months: n/a

[127] A total of 114 patients in the treatment and of 118 patients in the control group completed the trial. Additional, 5 patients in the treatment and 2 in the control group were excluded after randomization and prior treatment. However, the intention to treat population comprised 128 pts. vs. 125 pts.

[128] Leg volume was given as relative reduction (in %) after 2 months compared with baseline, based on a truncated cone model by using circumferences of the ankle and calf of the most pathological leg, compared with optoelectronic volumetry.

[129] Leg volume was given as absolute reduction (in ml/l) after 1 month compared with baseline, based on a truncated cone model by using circumferences of the ankle and calf.

Author, year, reference number	Martinez 2005 [10]	Flota-Cervera 2008 [59]	Martinez-Zapata 2008 [62]	Rabe 2011 [60]	Labs 2004 [61]
				Ankle circumference (cm): Baseline: 24.2 vs. 24.2; p=n/a After 1 month: n/a After 2 months: 24.1 vs. 24.3; p=n/a After 2,5 months: 24.1 vs. 24.1; p=n/a After 3; 6, 12 months: n/a	
Ulcer	n/a	n/a	n/a	n/a	n/a
CVI symptoms (general)	n/a	n/a	n/a[130]	*Score (100 mm VAS)[131]:* Baseline: 21.4 vs. 21.0; p=n/a After 1 month: n/a After 2 months:14.8 vs. 21.1; p=n/a After 2.5 months:15.2 vs. 20.8; p=n/a	n/a
Pain	4 studies (179 vs. 175 pts.) for presence of pain (dichotomous): 12-54% vs. 60-100%; risk ratio=0.39; **p=0.034** 1 study (35 vs. 31 pts.) for pain score (100 mm): 33 vs. 30; mean difference=0.12; **p=N.S.**	*Patients (%)[132]:* Baseline: n/a; p=n/a After 1 month: n/a After 1.75 months: 32 vs. 100; **p<0.001** After 2; 3; 6; 12 months: n/a	*Score (100 mm VAS):* Baseline: 48.8 vs. 50.3; **p=N.S.** After 1, 2 months: n/a After 3 months: 37.8 vs. 37.8; **p=N.S.** After 6; 12 months: n/a	*Score (100 mm VAS, reduction from baseline in mm):* Baseline: - After 1 month: n/a After 2 months: -10.2 vs. 0.92; **p=0.0071** After 3; 6, 12 months: n/a	n/a
Cramps	2 studies (129 vs. 126 pts.) for presence of cramps (dichotomous): 36-53% vs. 59-67%; mean difference=0.65; **p=0.0011**	n/a	*Score (100 mm VAS):* Baseline: 34.3 vs. 35.9; **p=N.S.** After 1, 2 months: n/a After 3 months: 24.1 vs. 26.9; **p=N.S.** After 6; 12 months: n/a	n/a	n/a
Restless legs	2 studies (129 vs. 126 pts.) for presence of restless legs (dichotomous): 46-67% vs. 62-93%; risk ratio=0.73; **p=0.0027**	n/a	n/a	n/a	n/a

[130] Subjective symptoms were measured with a visual analogue scale (0-100 mm) for pain, swelling, heaviness, cramps and itching.

[131] Subjective symptoms were measured with a visual analogue scale (0-100 mm) for pain and discomfort.

[132] Pain is given in percentage of people without any pain, whereas the baseline values were not stated in the study.

Author, year, reference number	Martinez 2005 [10]	Flota-Cervera 2008 [59]	Martinez-Zapata 2008 [62]	Rabe 2011 [60]	Labs 2004 [61]
Itching (= tingling sensation)	n/a	n/a	*Score (100 mm VAS):* Baseline: 42.4 vs. 42.2; **p=N.S.** After 1, 2 months: n/a After 3 months: 35.9 vs. 31.3; **p=N.S.** After 6; 12 months: n/a	n/a	n/a
Heaviness (= heavy legs)	3 studies (154 vs. 151 pts.) for presence of heaviness (dichotomous): 7-71% vs. 52-93%; risk ratio=0.33; **p=N.S.** 1 study (35 vs. 31 pts.) for heaviness score (100 mm): 36 vs. 32; mean difference=0.17; **p=N.S.**	n/a	*Score (100 mm VAS):* Baseline: 55.2 vs. 59.7; **p=N.S.** After 1, 2 months: n/a After 3 months: 44.5 vs. 46.9; **p=N.S.** After 6; 12 months: n/a	n/a	n/a
Swelling (= sensation of tension)	2 studies (40 vs. 40 pts.) presence of swelling (dichotomous): 12-13% vs. 56-100%; risk ratio=0.19; **p<0.001**	n/a	*Score (100 mm VAS):* Baseline: 45.8 vs. 50.7; **p=N.S.** After 1, 2 months: n/a After 3 months: 36.2 vs. 37.5; **p=N.S.** After 6; 12 months: n/a	n/a	n/a
Paraesthesias	3 studies (154 vs. 151 pts.) for presence of paraesthesia (dichotomous): 33-44% vs. 41-80%; risk ratio=0.74; **p=N.S.**	n/a	n/a	n/a	n/a
QoL	n/a	n/a	*Score (100 mm VAS, measured)*[133]*:* Baseline: 44.5 vs.47.5: **p=N.S.** After 1; 2 months: n/a After 3 months: 37.8 vs. 38.2: **p=N.S.** After 6; 12 months: n/a *Score (100 mm VAS, after multi-factorial analysis):* Baseline: 48.8 vs.45.3: **p=N.S.** After 1; 2 months: n/a After 3 months: 39.8 vs. 40.8: **p=N.S.** After 6 months: n/a After 12 months: 34.3 vs. 50.3; **p=0.02**	*Score (100 mm VAS):* Baseline[134]: 45.4 vs. 44.4; p=n/a After 1 month: n/a After 2 months: 40.6 vs. 40.7; p=n/a After 2.5 months: 41.2 vs. 39.2; **p=N.S.** After 3; 6, 12 months: n/a	n/a

[133] QoL was measured with the Spanish validated Chronic Insufficiency Venous International Questionnaire (CIVIQ), ranging 0-100 points.

Author, year, reference number	Martinez 2005 [10]	Flota-Cervera 2008 [59]	Martinez-Zapata 2008 [62]	Rabe 2011 [60]	Labs 2004 [61]
Safety-related outcomes					
Adverse events, general in % (n) pts.	5 studies (379 vs. 328 pts.): 4-36 vs. 0-68 (Risk ratio: 0.95; CI: 0.44,2.08); **p=N.S.**[135] (type of events not stated)	n/a	n/a; **p=N.S.**	40 (53) vs. 20 (25); p=n/a (type of events not stated)	39 (50) vs. 39 (49); p=n/a (type of events not stated)
Major adverse events	n/a	n/a	1 (3) vs. 1 (3); p=N.S (digestive intolerance: gastric pain, nausea, vomiting vs. digestive intolerance, urticarial, lymphoma)	4 (5) vs. 1 (1); p=n/a (type of events not stated)	n/a
Minor adverse events	n/a	n/a	n/a; **p=N.S.**	36 (48) vs. 19 (24); p=n/a (gastrointestinal, general and skin/tissue complaintsin both groups)	n/a
Adverse events, treatment-related in % (n) pts.	n/a	4 (1) vs. 4 (1); p=n/a (rash vs. n/a)	n/a; **p=N.S.**	27 (33) vs. 8 (10); p=n/a (type of events not stated)	7 (9) vs. 6 (8); p=n/a (type of events not stated)
Major adverse events	n/a	n/a	n/a; **p=N.S.**	2 (2) vs. 0 (0); p=n/a (abdominal pain and gastroenteritis)	n/a
Minor adverse events	n/a	n/a	n/a; **p=N.S.**	25 (33) vs. 8 (10); p=n/a (type of events not stated)	n/a

Abbreviations: acc. = according; CVI = chronic venous insufficiency; n = number (of patients); n/a = data not available; N.S. = not statistically significant; pts. = patients; QoL = quality of life; RCT = randomised controlled trial; VAS = visual analogue score; vs. = versus; yrs. = years

[134] QoL was measured with the Chronic Insufficiency Venous International Questionnaire (CIVIQ), ranging 0-100 points.

[135] The rates of adverse events assume that all withdrawn patients presenting an adverse event.

Table 3.1-19: Safety-related outcomes of non-randomised trials for calcium dobesilate-containing agents for CVI

Author, year, reference number	Mühleder 1988 [63]	Angehrn 1995 [64]	Arceo 2002 [65]
Country	Austria	Switzerland	Mexico
Study design	Non-randomised controlled study[136]	Single-arm study	Single-arm study
Sponsor	n/a	OM Laboratories Ltd.	Quimica Knoll de Mexico
Intervention/Product	2x 500 mg calcium dobesilate capsules (Doxium®) per day + surgery	3x 500 mg calcium dobesilate capsules (Doxium®) per day	3x 500 mg calcium dobesilate (Doxium®) per day
Comparator	No treatment + surgery	none	none
Number of pts	120	375	352
Age of patients (yrs)	Ø 43	Ø 53	Ø 46
Sex (% female)	73	83	81
Height (cm)/Weight (kg)/ BMI (kg/m²)	n/a / n/a / n/a	166 / 72 / n/a	n/a / n/a / n/a
Clinical classification	n/a	n/a	Grade I-II acc. to Widmer
Primary endpoint	n/a	n/a	n/a
Inclusion criteria	Patients with moderate and serious varicosis (due to CVI) who had to undergo stripping surgery	Patients with a known history of CVI, the presence of oedema, pain and/or other symptoms.	Patients of both sexes, aged 18-65 yrs., diagnosed with CVI grade I-II (Widmer) with at least two symptoms (heaviness, cramps, pain or edema)
Duration of treatment (months)	2	1	2.25
Follow-up (months)	0	0	0
Drop-outs, n (%)	n/a	1 (0)[137]	1 (0)
Safety-related outcomes			
Adverse events, general in % (n) pts.	n/a	6 (22) (gastrointestinal disorders, urticarial, paraesthesia, tiredness, oppression and weight gain)	n/a
Major adverse events	n/a	n/a	n/a
Minor adverse events	n/a	n/a	n/a
Adverse events, treatment-related in % (n) pts.	0 vs. n/a	6 (22) (gastrointestinal disorders, urticaria and exanthema, paraesthesia, tiredness, oppression, weight gain)	18 (63) (headache, epigastralgia, dizziness, nausea, pyrosis)
Major adverse events	n/a	n/a	n/a
Minor adverse events	n/a	n/a	n/a

Abbreviations: acc. = according; CVI = chronic venous insufficiency; n = number (of patients); n/a = data not available; pts. = patients; yrs. = years

[136] Study was divided in three groups: group I and II received calcium dobesilate 2 weeks before and 6 weeks after surgery, group III received no medication.

[137] A total 88 patients (23%) were excluded for efficacy analysis, mainly due to prohibited medications. Only one patient withdrew from safety analysis (failed return to control visit).

Efficacy

1 systematischen Review + 4 RCTs eingeschlossen

For evaluating the efficacy of calcium dobesilate-containing capillary stabilising agents, we identified 1 systematic review [10] and a total of 4 additional RCTs [59-62]. All of these studies were placebo-controlled.

insgesamt 1.921 PatientInnen, durchschnittlich 49-55 Jahre alt, vorrangig Frauen

Overall, there were 1,921 patients in the studies. The patients were on average between 49 and 54 years in the calcium dobesilate groups and between 49 and 55 years in the placebo groups [59-62]. The patients in the systematic review were between 10 and 70 years old [10]. The majority of the patients were females: 84-92% in the treatment groups and 86-93% in the control groups [59-62] of the single studies and 86% in the systematic review [10]. Furthermore, the patients had CVI grade I to V according to Widmer in two studies [10, 59] or were CEAP classified 1-6 in three studies [60-62]. In addition, the duration of treatment was 1-3 months [10, 59-62], and there was a follow-up without treatment for 0.5-9 months in three studies [60-62]. The drop-out rate differed between 8 and 26% [10, 60-62].

Zusammenfassung in GRADE-Tabelle

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.1-20.

Calcium dobesilate-containing agents (+ compression stockings) versus placebo (+ compression stockings)

einige nicht berichtete Endpunkte

None of the identified studies assessed the change of the CVI stage, the CVI signs in general, trophic alternations and ulcer (both signs of CVI) of a treatment with calcium dobesilate versus placebo (supplemented by compression stockings).

Ödeme: Beinvolumen in mehreren Studien in Behandlungsgruppen stärker reduziert, zumindest während Behandlungsphase

Regarding CVI signs, oedema was assessed in all studies and measured by several parameters. The leg volume change (reduction) from baseline was statistically significantly higher after 1 month (-26 vs. -13 ml/l) in one study [61], and after 2 months (-2 vs. 0%/cm³ or -65 vs. +1 ml) in another study [61]. In the systematic review (1-1.5 months) the mean difference of change between the groups was -0.64 ml, based on 2 RCTs [10]. However, the change of leg volume was not statistically significant after 0.5 months after treatment has stopped in one study (-15 vs. -17 ml/l) [61].

kein signifikanter Gruppenunterschied bei Reduktion Knöchelumfang

Furthermore, ankle circumference (an indicator for oedema) decreased slightly in both study groups over the treatment periods in four different studies (e.g., -4 vs. -2.7 mm after 1 months or -1 vs. + 1 mm after 2 months) [59-62], whereby after 3 months of treatment the difference of reduction between the treatment and control group was not statistically significant (-3.3 vs. -3.3 mm) [62].

Reduktion Wadenumfang in Gruppen ähnlich

The change of calf circumference (another indicator for oedema) decreased also slightly in both study groups in 3 different studies during the treatment phase [59-61] (after 1 month: -3.8 vs. -2.3 mm, after 2 months: -2 vs. -3 mm) and also in one study 0.5 months after treatment (-2 vs. -3 mm) [60]. Whether the differences are statistically significant was not stated.

Angaben zu Beinumfang in systematischen Review nicht aussagekräftig

Leg circumference was reported in the systematic review (based on 3 RCTs), though, not the change of the leg volume from baseline. The mean difference between the study groups after 1-1.6 months of treatment was -0.09 mm which was not statistically significant [10]. However, due to missing baseline values, the results do not allow any conclusion on efficacy.

Beinumfang in Behandlungsgruppe in 1 RCT etwas mehr reduziert

In addition, the change of leg circumference after 1.75 months was reported in one RCT (-9 vs. -3 mm). Whether the difference between the calcium dobesilate and the placebo group is statistically significant was not stated [59].

Ödeme (in %) in Behandlungsgruppe nicht signifikant mehr reduziert

Oedema was additionally reported as dichotomous variable in percentage of patients with oedema in the systematic review (based on two RCTs). The difference between the study groups was not statistically significant after 1-1.5 months of treatment (risk ratio: 0.41) [10].

Änderung generelle Symptome in beiden Studiengruppen ähnlich

The symptoms of CVI, in general, were more reduced (on a score of 0-10) in the calcium dobesilate groups than in the placebo groups during 2 months of treatment and 0.5 months after treatment (-0.66 vs. +0.01 and -0.62 vs. -0.02) [60]. It was not stated whether the difference between the groups was statistically significant.

Angaben zu Schmerzen in systematischen Review nicht aussagekräftig

Pain was reported in the systematic review (based on one RCT) and in an additional RCT (score 0-10). The difference between the study groups after 3 months of treatment was reported as not statistically significant (3.3-3.8 vs. 3.0-3.8) [10, 62]. However, because of missing baseline values or no stated changes of the scores from baseline, the results do not allow conclusions on the efficacy.

Ausprägung (Score) Schmerzreduktion in RCTs verschieden

In addition, pain was also measured as score reduction (0-10) in one study after 2 months (-1.0 vs. -0.1) [60] and in another study after 3 months (-1.1 vs. -1.25) of treatment [62]. After 2 months, the difference was statistically significant, but not so after 3 months.

Schmerzreduktion (in %) in Behandlungsgruppen signifikant besser

Furthermore, pain was measured with a dichotomous variable: percentage of patients with pain (in %). After 1-1.6 months of treatment the difference between the study groups in the systematic review (based on 4 RCTs) was statistically significant (risk ratio: 0.39) [10]. After 1.75 months of treatment in an additional RCT the difference was still statistically significant (32 vs. 100%) [59].

signifikanter Unterschied Schmerzen (dichotom) in Forest Plot

The meta-analysis for pain (in % of patients, data come from the studies in the systematic review) shows that there are statistically significantly less patients with pain in the treatment than in the placebo group with a risk ratio of 0.40 (Figure 3.1-17). However, the meta-analyses shows also a high heterogeneity with I^2>80%. That means the studies are measuring different effects due to e.g., differences in subject population or intervention.

Study name	Statistics for each study			Sample size		Risk ratio, 95% CI
	Risk ratio	Lower limit	Upper limit	Flavonoid fraction	No treatment	
Martinez 2005 (from Hachen 1982)	0.60	0.33	1.11	9/25	15/25	
Martinez 2005 (from Casley-Smith 1988)	0.21	0.08	0.59	3/15	14/15	
Martinez 2005 (from Widmer 1990)	0.89	0.71	1.11	62/114	68/111	
Martinez 2005 (from Flota 1999)	0.14	0.05	0.36	3/25	24/24	
Total (95% CI)	**0.40**	**0.18**	**0.89**	**77/179**	**121/175**	
						0,01 0,1 1 10 100
Random effects meta-analysis; I^2: 85.0%; p=0.03						Favours calc. dob. Favours placebo

Figure 3.1-17: Pain (dichotomous) for calcium dobesilate-containing agents (+ compression stockings) vs. placebo (+ compression stockings)

Cramps were measured in 1 study in terms of change from baseline (on a scale of 0-10). The reduction was not statistically significant different between the study groups after 3 months of treatment (-1.0 vs. -0.9) [62]. Furthermore, cramps were reported by a dichotomous variable (in % of patients) in 2 studies, summarised in the systematic review, whereas the difference of the values was statistically significant (mean difference between groups of dichotomous variable: 0.65) after 1-1.5 months [10].

Krämpfe in Behandlungsgruppen mehr reduziert

For restless legs, the difference between the treatment and the placebo group was also described as statistically significant in the systematic review (in % of patients, based on 2 RCTs) with a risk ratio of 0.73for the probability of restless legs after 1-1.5 months of treatment with calcium dobesilate compared to placebo [10].

weniger ruhelose Beine in Behandlungsgruppen

Itching was reported in 1 RCT with a slightly higher decrease of the score in the placebo groups after 3 months of treatment. However, the difference between the study groups was not statistically significant (change of score on scale 0-10: -0.65 vs. 1.09) [62].

Juckreiz in beiden Studiengruppen nicht verbessert

Heaviness, measured on a score (0-10), did not show a statistically significant difference between the study groups in 2 RCTs (one was included in the systematic review) after 3 months (3.6 to 4.4 vs. 3.2 to 4.7) [10, 62]. However, since the results do not show a change from baseline, a conclusion on the efficacy cannot be drawn. Nevertheless, in one RCT, heaviness was also assessable as the change from baseline, whereby the difference of the change in the score (0-10) between the groups was not statistically significant (-1.1 vs. -1.3) [62].

Symptom „schwere Beine" in Studiengruppen ähnlich verbessert (auf Skala)

The forest plot of the meta-analysis of heaviness (in % of patients, data come from the studies in the systematic review [10]) is displayed in Figure 3.1-18. The forest plot shows that there are fewer patients with heaviness in the treatment than in the placebo group after 1-1.5 months of treatment, yet the difference is not statistically significant. However, the meta-analyses shows also a high heterogeneity with $I^2 > 80\%$. That means the studies are measuring different effects due to e.g., differences in subject population or intervention.

etwas weniger PatientInnen (in %) mit schweren Beinen in Behandlungsgruppen

Study name	Statistics for each study			Sample size		Risk ratio, 95% CI
	Risk ratio	Lower limit	Upper limit	Flavonoid fraction	No treatment	
Martinez 2005 (from Hachen 1982)	0.31	0.12	0.81	4/25	13/25	
Martinez 2005 (from Casley-Smith 1988)	0.07	0.01	0.48	1/15	14/15	
Martinez 2005 (from Widmer 1990)	0.87	0.75	1.0	81/114	91/111	
Total (95% CI)	**0.36**	**0.10**	**1.20**	**86/154**	**118/151**	
						0,01 0,1 1 10 100
Random effects meta-analysis; I^2: 81.4%; p=0.96						Favours calc. dob. Favours placebo

Figure 3.1-18: Heaviness (dichotomous) for calcium dobesilate-containing agents (+ compression stockings) vs. placebo (+ compression stockings)

Another symptom of CVI – swelling – was measured in 1 RCT by change from baseline on a score (0-10). The swellings were reduced slightly, but not statistically significant, more in the placebo group (-0.96 vs. -1.32) after 3 months

Schwellungen in Placebogruppe etwas mehr reduziert

of treatment [62]. In addition, swelling was given as the percentage of patients with this symptom in the systematic review (results are based on 2 RCTs). The difference between the study groups was statistically significant in favour of calcium dobesilate after 1-1.5 months. The risk ratio risk for the probability of swellings with calcium dobesilate compared to placebo was 0.19 [10].

in Behandlungsgruppen nicht signifikant weniger PatientInnen mit Parästhesie

Paraesthesias were reported in 3 RCTs (included in the systematic review) [10] by stating the percentage of patients with this symptom (in %). The difference between the calcium dobesilate and the placebo group was not statistically significant after 1-1.5 months of treatment (see Figure 3.1-19). The risk ratio was 0.74 for the probability of paraesthesias after 1-1.5 months of treatment with calcium dobesilate compared to placebo [10].

Study name	Statistics for each study			Sample size		Risk ratio, 95% CI
	Risk ratio	Lower limit	Upper limit	Flavonoid fraction	No treatment	
Martinez 2005 (from Hachen 1982)	0.92	0.50	1.67	11/25	12/25	
Martinez 2005 (from Casley-Smith 1988)	0.42	0.20	0.89	5/15	12/15	
Martinez 2005 (from Widmer 1990)	0.82	0.58	1.16	38/114	45/111	
Total (95% CI)	**0.74**	**0.51**	**1.08**	**54/154**	**69/151**	
						0,1 0,2 0,5 1 2 5 10
Random effects meta-analysis; I^2: 32.8%; p=0.12						Favours calc. dob. Favours placebo

Figure 3.1-19: Paraesthesias (dichotomous) for calcium dobesilate-containing agents (+ compression stockings) vs. placebo (+ compression stockings)

Verbesserung Lebensqualität in Behandlungsgruppen nicht signifikant höher

Finally, quality of life was assessed in 2 RCTs by change from baseline on a scale (0-10), after different durations of treatment. In 1 RCT the reduction of the score was slightly, but not statistically significantly higher in the placebo group after 2 months with treatment plus 0.5 months without treatment (-0.42 vs. -0.52) [60]. Furthermore, another study measured the quality of life after 3 months of treatment, whereby the difference of the score reduction was also not statistically significant (-6.7 vs. -9.3) [62].

Safety

für Bewertung Sicherheit weitere Studien: 1 non-RCT + 2 Ein-Arm-Studien

For evaluating the safety of calcium dobesilate-containing capillary stabilising agents, we identified, beside the previously mentioned systematic review [10] and 4 RCTs [59-62], 1 additional non-randomised controlled trial (non-RCT) and 2 single-arm studies (studies with no control group) that met our inclusion criteria. The study characteristics and results of the non-RCTs are summarised in the Table 3.1-19.

insgesamt 847 PatientInnen, 43-53 Jahre alt, vorrangig Frauen

In the non-RCT a total of 120 patients were receiving either 500 mg calcium dobesilate-containing agents twice a day supplemented by surgery or surgery alone (control group) [63], and in the single-arm studies a total of 727 patients was receiving 500 mg calcium dobesilate-containing agents 3 times a day [64, 65]. The mean ages of the patients were between 43 and 53 years. Between 73 and 83% of the patients in both groups were females. The duration of treatment varied from 1 to 2.25 months. There was no follow-up after treatment. In

addition, there were no drop-outs [64, 65]. Furthermore, the non-RCT did not report adverse events in the control group and was therefore only considered for adverse events of a treatment with calcium dobesilate-containing agents.

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.1-22.

Zusammenfassung in GRADE-Tabelle

Calcium dobesilate-containing agents (+ compression stockings) versus placebo (+ compression stockings)

General adverse events were stated in the systematic review [10] and in 3 RCTs [60-62]. The rates differed from 4 to 40% in the treatment and from 0 to 68% in the control groups [10, 60, 61]. In the systematic review and in one RCT, the difference between the study groups was not statistically significant [10, 62]. The types of general adverse events were not stated in any of these studies.

generelle unerwünschte Ereignisse: 4-40 vs. 0-68 %, Gruppenunterschied nicht signifikant

The meta-analysis of general adverse events (dichotomous variables, data come from 5 studies in the systematic review [10]) is displayed in Figure 3.1-20. The difference in adverse events between the groups is not statistically significant. The risk ratio was 1.08 for the probability of general adverse events with calcium dobesilate compared to placebo. However, the meta-analyses shows also a high heterogeneity with I^2>80%. That means the studies are measuring different effects due to e.g., differences in subject population or intervention.

Forest Plot zeigt nicht signifikanten Gruppenunterschied

Study name	Statistics for each study			Sample size		Risk ratio, 95% CI
	Risk ratio	Lower limit	Upper limit	Flavonoid fraction	No treatment	
Martinez 2005 (from Hachen 1982)	7.00	0.38	128.87	3/25	0/25	
Martinez 2005 (from Widmer 1990)	1.14	0.79	1.65	38/114	45/111	
Martinez 2005 (from Flota 1999)	0.96	0.06	14.50	1/25	1/24	
Martinez 2005 (from Jäger 2001)	1.43	0.72	2.85	18/133	12/127	
Martinez 2005 (from Marinel lo 2002)	0.38	0.25	0.57	21/82	28/41	
Labs 2004	1.00	0.73	1.36	50/128	49/125	
Rabe 2011	1.99	1.32	2.99	53/132	25/124	
Total (95% CI)	**1.08**	**0.65**	**1.80**	**184/639**	**160/577**	
						0,01 0,1 1 10 100
Random effects meta-analysis; I^2: 82.7%; p=0.76						Favours calc. dob. Favours placebo

Figure 3.1-20: General adverse events (dichotomous) for calcium dobesilate-containing agents (+ compression stockings) vs. placebo (+ compression stockings)

Treatment-related adverse events occurred in 4-27% of patients in the treatment and in 4-8% of patients in the control groups [59-61]. Only one RCT stated that the difference of the rates between the study groups was not statistically significant [62].

Nebenwirkungen: in 4-27 vs. 4-8 % der PatientInnen

Nebenwirkungen: Gruppenunterschied nicht signifikant

The results from the meta-analysis of general adverse events (dichotomous variables, coming from 3 studies) show that the difference of adverse events is not statistically significant (Figure 3.1-21).The risk ratio was 1.89 for the probability of treatment-related adverse events with calcium dobesilate compared to placebo.

Study name	Statistics for each study			Sample size		Risk ratio, 95% CI
	Risk ratio	Lower limit	Upper limit	Flavonoid fraction	No treatment	
Labs 2004	1.10	0.44	2.76	9/128	8/125	
Rabe 2011	3.29	1.70	6.35	35/132	10/124	
Flota-Cervera 2008	0.96	0.06	14.50	1/25	1/24	
Total (95% CI)	**1.89**	**0.78**	**4.59**	**45/285**	**19/273**	
						0,01 0,1 1 10 100
Random effects meta-analysis; I^2: 49.7%; p=0.16						Favours calcium dob. Favours placebo

Figure 3.1-21: Treatment-related adverse events (dichotomous) for calcium dobesilate-containing agents (+ compression stockings) vs. placebo (+ compression stockings)

Calcium dobesilate-containing agents

generelle unerwünschte Ereignisse: 6 % der PatientInnen

General adverse events were reported in 1 single-arm study and occurred in 6% of the patients. The most common events were gastrointestinal disorders and urticaria [64].

0-18 % PatientInnen mit Nebenwirkungen

Furthermore there were 0 to 18% treatment-related adverse events in the calcium dobesilate group or the group that did not receive a treatment. The most common events were gastrointestinal disorders, headache, dizziness and nausea [63-65].

Risk of bias

The identified systematic review shows an overall low risk of bias (see Figure 3.1-22), however, there is a high risk of selection bias due to an unclear research question.

Bias-Risiko systematischer Review: gering

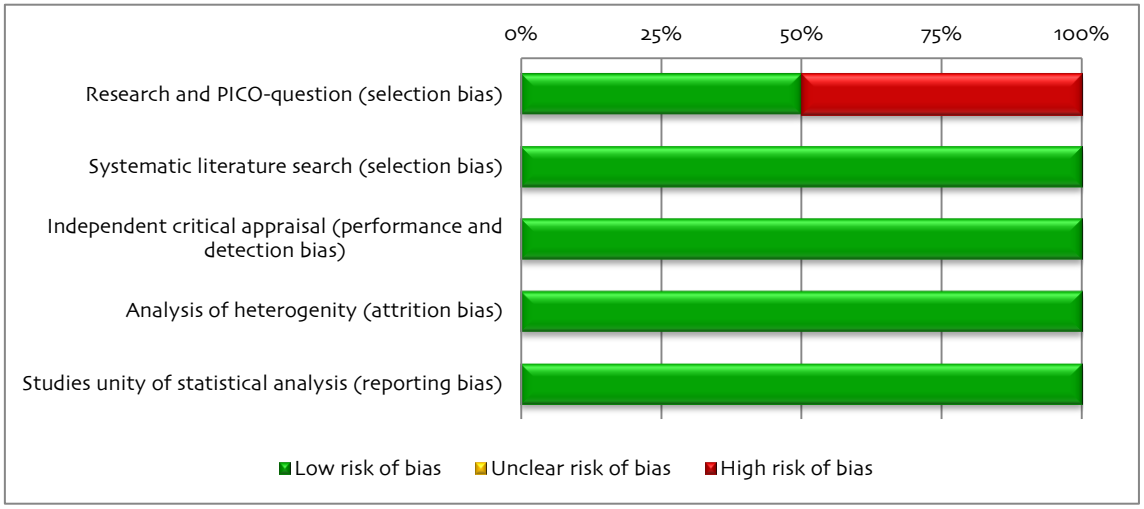

Figure 3.1-22: Risk of bias of systematic review for treatment of CVI with calcium dobesilate-containing agents

The majority of the identified RCTs for a treatment of CVI with calcium dobesilate-containing agents show a low risk of bias for several types of biases (see Figure 3.1-23). A quarter of the studies show a high risk of reporting bias due to not reported baseline values. In summary, the risk of bias is low.

Bias-Risiko RCTs: gering

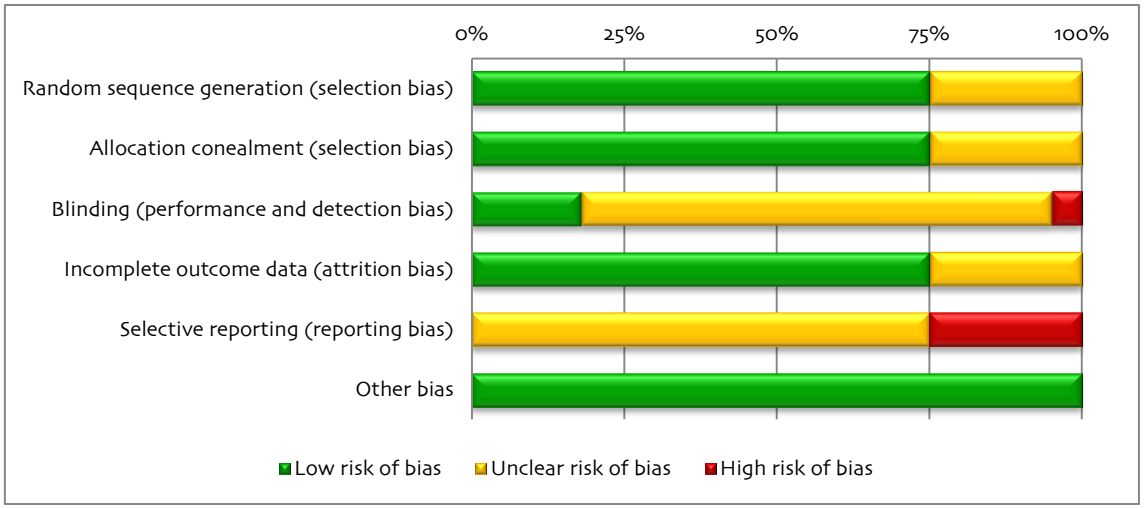

Figure 3.1-23: Risk of bias of RCTs for treatment of CVI with calcium dobesilate-containing agents

Bias-Risiko Ein-Arm-Studien: hoch

Due to the study design of the single-arm studies, several of the individual biases are not relevant (grey-coloured), since there was no control group. The risk of the performance and detection bias is high, due to no blinding of the outcome assessor and two third of the studies show a high risk of reporting bias due to no confounder adjustment (see Figure 3.1-24). In summary, the risk of bias is high.

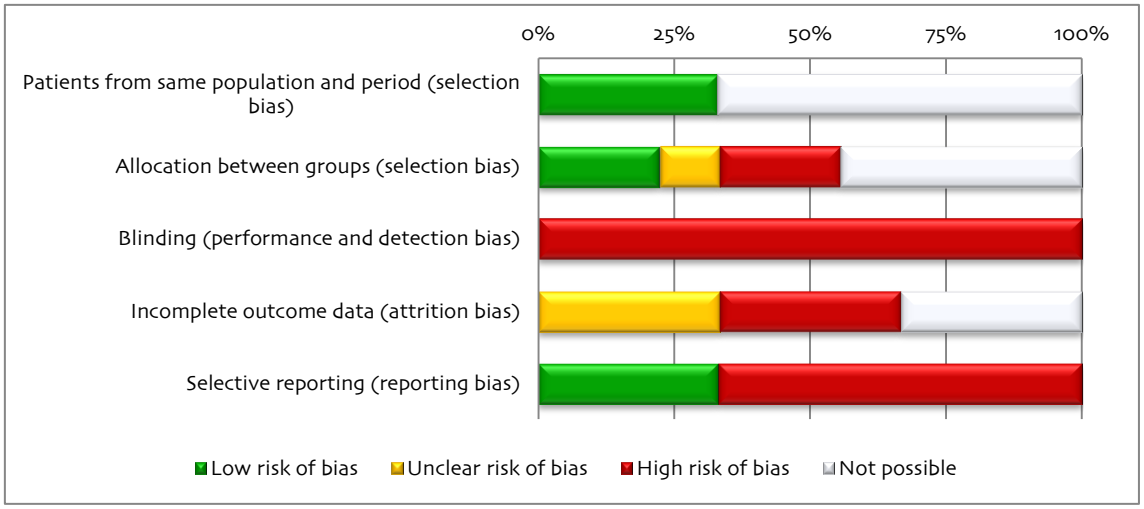

Figure 3.1-24: Risk of bias of (un)controlled studies for treatment of CVI with calcium dobesilate-containing agents

Strength of evidence

moderate Evidenzstärke

Overall, the strength of evidence of the efficacy and safety of a treatment of CVI with calcium dobesilate-containing agents compared to placebo or no treatment (only safety) is moderate. The strength of evidence is summarised in the Tables 3.1-20 and 3.1-21.

keine Evidenz zu Vergleich mit anderen Behandlungen

There was no evidence to compare the efficacy and safety of a treatment of CVI with calcium dobesilate-containing agents with other interventions, such as lifestyle changes or further local, medical and surgical treatment, mentioned in Chapter 1.1.2.

Table 3.1-20: Evidence profile: Efficacy of calcium dobesilate-containing agents (+ compression stockings) for treatment of CVI compared to placebo (+ compression stockings)

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Efficacy: calcium dobesilate-containing agents (+ compression stockings) versus placebo (+ compression stockings)							
Change of CVI stage: no evidence							
CVI signs (general): no evidence							
CVI signs (trophic alternations): no evidence							
CVI signs (oedema): leg volume change from baseline (in ml/l)							
1/253	RCT	1 mo: -26 vs. -13; p=S.S. 1.5 mo: -15 vs. -17; p=N.S.	No serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[139]	Moderate
CVI signs (oedema): leg volume change from baseline (in %/cm³)							
1/256	RCT	2 mo: -2/-65 vs. ±0/+1; p=S.S.	No serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[139]	Moderate
CVI signs (oedema): leg volume change from baseline (in ml)							
2/236 (of 854)	2 RCTs (in syst. Review)	1-1.5 mo: mean difference:-0.64; CI: -1.22,-0.06); p=S.S.	Serious limitations (-1)[140]	Important inconsistency (-1)[141]	Direct	Imprecise data (-1)[139]	Low
CVI signs (oedema): ankle circumference change from baseline (in mm)							
1/253	RCT	1 mo: -4 vs. -2.7; p=n/a	No serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[139]	Moderate
1/253	RCT	1.5 mo: -3 vs. -2; p=n/a	No serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[139]	Moderate
1/49	RCT	1.75 mo: -2.6 vs. -3; p=n/a	Serious limitations (-1)[142]	n/a (only 1 trial)	Direct	Imprecise data (-1)[139]	Low
1/156	RCT	2 mo: -1 vs. +1; p=n/a	No serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[139]	Moderate
1/156	RCT	2.5 mo: -1 vs. -1; p=n/a	No serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[139]	Moderate
1/509	RCT	3 mo: -3.3 vs. -3.3; p=N.S.	No serious limitations[138]	n/a (only 1 trial)	Direct	None	High

[138] Only unclear blinding of outcome assessor.

[139] Low incidence, study/studies not powered to detect difference

[140] Systematic review did not state random sequence generation and blinding of individual studies.

[141] Systematic review summarised outcomes of studies from different times (e.g., after 0.5, 1, 3 or 4 months) and on different scales.

[142] Unclear random sequence generation and blinding of outcome assessor.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
CVI signs (oedema): calf circumference change from baseline (in mm)							
1/253	RCT	1 mo: -3.8 vs. -2.3; p=n/a	No serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[139]	Moderate
1/253	RCT	1.5 mo: -1.3 vs. -2; p=n/a	No serious limitations[138]	n/a (only 1 trial)		Imprecise data (-1)[139]	Moderate
1/49	RCT	1.75 mo: -16 vs. ±0; p=n/a	Serious limitations (-1)[142]	n/a (only 1 trial)		Imprecise data (-1)[139]	Low
256	RCT	2 mo: -3 vs. ±0; p=n/a	No serious limitations[138]	n/a (only 1 trial)		Imprecise data (-1)[139]	Moderate
256	RCT	2.5 mo: -2 vs. -3; p=n/a	No serious limitations[138]	n/a (only 1 trial)		Imprecise data (-1)[139]	Moderate
CVI signs (oedema): leg circumference change from baseline (in mm)							
3/302 (of 454)	3 RCTs (in syst. Review)	1-1.6 mo: mean difference: -0.09, CI: -0.34, 0.16; p=N.S.[143]	Serious limitations (-1)[140]	Important inconsistency (-1)[141]	Direct	Imprecise data (-1)[139]	Low
1/49	RCT	1.75 mo: -9 vs. -3; p=n/a	Serious limitations (-1)[142]	n/a (only 1 trial)		Imprecise data (-1)[139]	Low
CVI signs (oedema): patients (in %)							
2/290 (of 854)	2 RCTs (in syst. Review)	1-1.5 mo: risk ratio:0.41; CI: 0.06,2.82; p=N.S.	Serious limitations (-1)[140]	Important inconsistency (-1)[141]	Direct	Imprecise data (-1)[139]	Low
CVI signs (ulcer): no evidence							
CVI symptoms (general): change from baseline (score 0-10)							
1/256	RCT	2 mo: -0.66 vs. +0.01; p=n/a 2.5 mo: -0.62 vs. -0.02; p=n/a	No serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[139]	Moderate
CVI symptoms (pain): score (0-10)							
2/575	2 RCTs (1 in syst. Review)	3 mo: 3.3 to 3.8 vs. 3.0 to 3.8; p=N.S. in both studies[143]	Serious limitations (-1)[140]	No important inconsistency	Direct	None	Moderate
CVI symptoms (pain): change from baseline (score 0-10)							
1/256	RCT	2 mo: -1.0 vs. -0.1; p=s.s:	No serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[139]	Moderate
1/509	RCT	3 mo: -1.1 vs. -1.25; p=N.S.	No serious limitations[138]	n/a (only 1 trial)	Direct	None	High
CVI symptoms (pain): patients (in %)							
4/354 (of 854)	4 RCTs (in syst. Review)	1-1.6 mo: risk ratio: 0.39; CI: 0.16, 0.93; p=S.S.	Serious limitations (-1)[140]	Important inconsistency (-1)[141]	Direct	Imprecise data (-1)[139]	Very low
1/49	RCT	1.75 mo: 32 vs. 100; p=S.S.	Serious limitations (-1)[142]	n/a (only 1 trial)		Imprecise data (-1)[139]	Low
CVI symptoms (cramps): change from baseline (score 0-10)							
1/509	RCT	3 mo: -1.02 vs. -0.9; p=N.S.	No serious limitations[138]	n/a (only 1 trial)	Direct	None	High

[143] Systematic review did not show the change from baseline, only the measured values during the treatment phase.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
CVI symptoms (cramps): patients (in %)							
2/255 (of 854)	2 RCTs (in syst. Review)	1-1.5 mo: mean difference: 0.65; CI: 0.5, 0.84; p=S.S.	Serious limitations (-1)[140]	Important inconsistency (-1)[141]	Direct	Imprecise data (-1)[139]	Very low
CVI symptoms (restless legs): patients (in %)							
2/255 (of 854)	2 RCTs (in syst. Review)	1-1.5 mo: risk ratio: 0.73; CI: 0.59, 0.9; p=S.S.	Serious limitations (-1)[140]	Important inconsistency (-1)[141]	Direct	Imprecise data (-1)[139]	Very low
CVI symptoms (itching): change from baseline (score 0-10)							
1/509	RCT	3 mo: -6.5 vs. -10.9; p=N.S.	No serious limitations[138]	n/a (only 1 trial)	Direct	None	High
CVI symptoms (heaviness): score (0-10)							
2/575	2 RCTs (1 in syst. Review)	3 mo: 3.6 to 4.4 vs. 3.2 to 4.7; p=N.S. in both studies	Serious limitations (-1)[140]	No important inconsistency	Direct	None	Moderate
CVI symptoms (heaviness): change from baseline (score 0-10)							
1/509	RCT	3 mo: -1.07 vs. -1.28; p=N.S.	No serious limitations[138]	n/a (only 1 trial)	Direct	None	High
CVI symptoms (heaviness): patients (in %)							
3/305	3 RCTs (in syst. Review)	1-1.5 mo: risk ratio: 0.33; CI: 0.08, 1.42; p=N.S.	Serious limitations (-1)[140]	Important inconsistency (-1)[141]	Direct	Imprecise data (-1)[139]	Very low
CVI symptoms (swelling): change from baseline (score 0-10)							
1/509	RCT	3 mo: -0.96 vs. -1.32; p=N.S.	No serious limitations[138]	n/a (only 1 trial)	Direct	None	High
CVI symptoms (swelling): patients (in %)							
2/80	2 RCTs (in syst. Review)	1-1.5 mo: risk ratio: 0.19; CI: 0.08, 0.41; p=S.S.	Serious limitations (-1)[140]	Important inconsistency (-1)[141]	Direct	Imprecise data (-1)[139]	Very low
CVI symptoms (paraesthesias): patients (in %)							
3/305	3 RCTs (in syst. Review)	1-1.5 mo: risk ratio: 0.74; CI: 0.51, 1.08; p=N.S.	Serious limitations (-1)[140]	Important inconsistency (-1)[141]	Direct	Imprecise data (-1)[139]	Very low
Quality of life: change from baseline (score 0-10)							
1/256	RCT	2 mo: -0.48 vs. -0.37; p=n/a	No serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[139]	Moderate
1/256	RCT	2.5 mo: -0.42 vs. -0.52, p=N.S.	No serious limitations[138]	n/a (only 1 trial)		Imprecise data (-1)[139]	Moderate
1/509	RCT	3 mo: -0.67 vs. -0.93; p=N.S.	No serious limitations[138]	n/a (only 1 trial)		None	High

Abbreviations: n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

Table 3.1-21: Evidence profile: Safety of calcium dobesilate-containing agents (+ compression stockings) for treatment of CVI (compared to placebo)

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Safety: calcium dobesilate-containing agents (+ compression stockings) versus placebo (+ compression stockings)							
Adverse events (general): in %							
8/1,756	8 RCTs (5 in syst. Review)	4 to 40 vs. 0 to 68; p=N.S.	Serious limitations (-1)[140]	Important inconsistency (-1)[144]	Direct	None	Low
Adverse events (treatment-related): in %							
4/1,167	4 RCTs	4 to 27 vs. 4 to 8; p=N.S.	No serious limitations[138]	Important inconsistency (-1)[144]	Direct	None	Moderate
Safety: calcium dobesilate-containing agents							
Adverse events (general): in %							
1/375	Single-arm study	6	Serious limitations (-1)[145]	n/a (only 1 trial)	Direct	Imprecise data (-1)[146]	Very low
Adverse events (treatment-related): in %							
3/847	1 non-RCT + 2 single-arm studies	0 to 18	Serious limitations (-1)[103]	No important inconsistency	Direct	Imprecise data (-1)[146]	Very low

Abbreviations: n/a = data not available; non-RCT = non randomised controlled trial; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

[144] Huge difference between rates in studies.

[145] No blinding of outcome assessor (and no randomisation) and no statistical analysis.

[146] Low incidence, study/studies not powered to detect difference.

3.1.6 Comparison between capillary stabilising agents

Study characteristics

For evaluating the efficacy and safety of capillary stabilising agents in comparison to each other for a treatment of CVI, we identified 1 systematic review [58], 2 RCTs [41, 66] and 1 additional non-randomised study [67] that met our inclusion criteria.

1 systematischen Review, 2RCTs + 1 non-RCT eingeschlossen

Furthermore, one extracted RCT [41] is already included in the systematic review [58], thus the outcomes that are included in the systematic review and the RCT will not be reported twice (those are grey marked in the extraction Table 3.1-22)

ein RCT aus systematischen Review zusätzlich extrahiert

The studies are comparing agents containing oxerutin (0-beta-hydroxyethyl-rutoside, HR) with either 50 mg aescin [41, 58] or with agents containing flavonoid fraction (MPFF) [66, 67] for a treatment of CVI.

Vergleich Oxerutin mit 50 mg Aescin oder Flavonoidfraktion

The study characteristics and results are summarised in Table 3.1-22 for the systematic review and the RCTs and in Table 3.1-23 for the non-randomised controlled trial.

Studiencharakteristika in Tabelle

There were no studies identified comparing other capillary stabilising agents with each other.

keine Studien zu anderen Vergleichen

Table 3.1-22: Efficacy and safety-related outcomes of a systematic review and randomised controlled trials of capillary stabilising agents versus other capillary stabilising agents for CVI

Author, year, reference number	Rehn 1996 (b) [41]	Belcaro 2002 [66]	Pittler 2012 [58]
Country	Germany	Italy, UK	Germany
Study design	RCT[147]	RCT	Systematic review[148]
Sponsor	n/a	n/a	None
Intervention/Product	2x 500 mg HR per day | 2x 500 mg HR per day for 1 months, following 1x 500 mg per day (Venoruton®) tablet	2x 1,000 mg HR granulate per day (Venoruton®) + compression stockings	1-2x 50 mg aescin (HCSE) capsules per day 2x 75 mg aescin (HCSE) capsules per day
Comparator	2x 50 mg Aescin (HSCE) capsules per day	3x 500 mg MPFF tablets per day (Daflon) + compression stockings	Rutoside, HR
Number of pts	51 | 35 vs. 51	46 vs. 44	261
Age of patients (yrs)	Ø 58 | 63 vs. 59	Ø 41 vs. 41	Ø 55-58 vs. 54-63
Sex (% female)	100 | 100 vs. 100	~50[149] vs. 48	67-100
Height (cm)/Weight (kg)/BMI (kg/m²)	163 | 162 vs. 165 / 75 | 78 vs. 81 / n/a	n/a / n/a / n/a	n/a / n/a / n/a
Clinical classification	Grade II acc. to Widmer	n/a	Grade I-II acc. to Widmer
Primary endpoint	Leg volume	n/a	CVI-related symptoms and oedema (of included studies)
Inclusion criteria	Female menopausal patients, maximum aged 70 yrs., with uni- or bilateral CVI grade II (Widmer)	Patients with severe venous hypertension (ambulatory venous pressure > 60 mm Hg, refilling time < 8 seconds), with ankle swelling and lipodermatosclerosis	Patients with CVI, comparing oral preparations of HCSE with placebo or reference therapy, measuring clinical outcomes
Duration of Treatment (months)	3[150]	2[151]	1-3
Follow-up (months)	1.5	0	n/a
Drop-outs, n (%)	21 (15)	0 (0)	24 (9)
Efficacy-related outcomes			
Change of CVI stage	n/a	n/a	n/a
CVI signs (general)	n/a	n/a	n/a
Trophic alternations	n/a	n/a	n/a

147 This study is included in Pittler 2012, whereas not all outcomes of this study were extracted and, therefore, the study appears in this extraction table.

148 This systematic review included 17 RCTs on HCSE. Of these, 11 compared HCSE against placebo and/or against compression stockings and four against O-beta-hydroxyethyl rutosides (HR). Information about age, sex ratio and clinical classification was not stated in all included studies.

149 The shown number of the sex ratio in the HR-group is not exact.

150 The study started with a placebo run-in phase of 1 week.

151 The study started with a wash-out period of 2 weeks.

Author, year, reference number	Rehn 1996 (b) [41]	Belcaro 2002 [66]	Pittler 2012 [58]
Oedema (leg volume or circumference	*Leg volume (ml)*[152]*:* Baseline: 2,182 | 2,220 vs. 2,219; p=n/a After 1; 2 months: n/a After 3 months: 2,124 |2,179 vs. 2,191; **p=0.02**[153] After 4.5 months: 2,135 | 2,199 vs. 2,193; p=n/a After 6; 12 months: n/a	n/a	**HCSE vs. HR** 1 study (17 vs. 13 pts.) for reduction of oedema (VAS): 0.65 vs. 1.58; mean difference=-0.93; **p=N.S.** 2 studies (32 vs. 28 pts.) for reduction of circumference at ankle (mm): 2-4 vs. 2-4; mean difference=2.38; **p=N.S.** 1 study (17 vs. 13 pts.) for reduction of circumference at calf (mm): 1.8 vs. -5; mean difference=6.8; **p=S.S.** 1 study (51 vs. 51 pts.) for leg volume (ml): 26 vs. 46.4; mean difference=-20.4; p=N.S.
Ulcer	n/a	n/a	n/a
CVI symptoms (general)	n/a[154]	*Score (0-10)*[155]*:* Baseline: 9.6 vs. 9.5; p=n/a After 1 month: n/a After 2 months: 3.1 vs. 8.9; p=n/a After 3; 6; 12 months: n/a	n/a
Pain	n/a	n/a	**HCSE vs. HR** 1 study (17 vs. 13 pts.) for reduction of pain (VAS): 1.85 vs. 1.2; mean difference=0.65; **p=N.S.**
Cramps	n/a	n/a	n/a
Restless legs	n/a	n/a	n/a
Itching (=tingling sensation)	*Score (0-10):* Baseline: 2.8 | 3.1 vs. 1.9; p=n/a After 1 month: 1.9 | 3.0 vs. 2.1; p=n/a After 2 months: 1.9 | 3.0 vs. 1.9; p=n/a After 3 months: 1.9 | 2.4 vs. 2.0; p=n/a After 4.5 months: 1.7 | 2.4 vs. 2.7; p=n/a After 6; 12 months: n/a	n/a	n/a

[152] Leg volume was measured by water-displacement. This outcome is also extracted in Pittler 2012.

[153] The difference of the reduction between the group that received 2 x 500 mg HR and the group that received HCSE was statistically significant.

[154] Subjective symptoms were measured with a visual analogue scale (0-10) for itching (tingling sensation), heavy legs (heaviness) and swelling (tingling sensation).

[155] Subjective symptoms were measured with a composite analogue scale (0-10), for oedema, pain, restless legs, swelling, skin alternations.

Author, year, reference number	Rehn 1996 (b) [41]	Belcaro 2002 [66]	Pittler 2012 [58]
Heaviness (=heavy legs)	*Score (0-10):* Baseline: 4.1 | 3.8 vs. 3.0; p=n/a After 1 month: 3.1 | 3.3 vs. 3.8; p=n/a After 2 months: 2.9 | 3.3 vs. 3.0; p=n/a After 3 months: 2.8 | 2.4 vs. 2.7; p=n/a After 4.5 months: 2.6 | 2.8 vs. 2.8; p=n/a After 6; 12 months: n/a	n/a	n/a
Swelling (=sensation of tension)	*Score (0-10):* Baseline: 3.6 | 4.0 vs. 2.8; p=n/a After 1 month: 2.9 | 3.5 vs. 3.3; p=n/a After 2 months: 2.9 | 3.5 vs. 3.1; p=n/a After 3 months: 2.6 | 2.6 vs. 2.5; p=n/a After 4.5 months: 2.3 | 2.3 vs. 2.7; p=n/a After 6; 12 months: n/a	n/a	n/a
Paraesthesia	n/a	n/a	n/a
QoL	n/a	n/a	n/a
Safety-related outcomes			
Adverse events, general in % (n) pts.	n/a	n/a	n/a (see also Table 3.1-15)
Major adverse events	n/a	n/a	n/a (see also Table 3.1-15)
Minor adverse events	n/a	n/a	n/a (see also Table 3.1-15)
Adverse events, treatment-related in % (n) pts.	5.1 (3)| 16.2 (6) vs. 3.2 (2); p=n/a (gastrointestinal complaints, headache, dizziness in all groups)	0 vs. 0	n/a (see also Table 3.1-15)
Major adverse events	n/a	0 vs. 0	n/a (see also Table 3.1-15)
Minor adverse events	n/a	0 vs. 0	n/a (see also Table 3.1-15)

Abbreviations: acc. = according; CVI = chronic venous insufficiency; HCSE = horse chestnut seed extract; n = number (of patients); n/a = data not available; N.S. = not statistically significant; pts. = patients; QoL = quality of life; RCT = randomised controlled trial; VAS = visual analogue score; vs. = versus; yrs. = years

Table 3.1-23: Safety-related outcomes of controlled trials for capillary stabilising agents versus other capillary stabilising agents

Author, year, reference number	Cesarone 2005[156] [67]
Country	Italy
Study design	Non-randomised controlled registry study
Sponsor	n/a
Intervention/Product	2 x 1,000 mg HR granulate per day (Venoruton®)
Comparator	3 x 500 mg MPFF tablets per day (Daflon®)
Number of pts.	62 vs. 60[157]
Age of patients (yrs.)	Ø 43 vs. 42
Sex (% female)	47 vs. 53
Height (cm)/Weight (kg)/BMI (kg/m²)	n/a / n/a / n/a
Clinical classification	n/a
Primary endpoint	n/a
Inclusion criteria	Patients with chronic venous hypertension (ambulatory venous pressure > 60 mm Hg, refilling time < 8 seconds), associated with ankle swelling and lipodermatosclerosis
Duration of Treatment (months)	2
Follow-up (months)	2
Drop-outs, n (%)	11 (18) vs. 10 (17)
Safety-related outcomes	
Adverse events, general (in %)	n/a
Major adverse events	n/a
Minor adverse events	n/a
Adverse events, treatment-related (in %)	0 vs. 0
Major adverse events	0 vs. 0
Minor adverse events	0 vs. 0

Abbreviations: CVI = chronic venous insufficiency, HR = 0(beta-hydroxyethyl)-rutosides; MPFF = miconised purified flavonoid fraction; n = number (of patients); n/a = data not available; pts. = patients; yrs. = years

Efficacy

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.1-24.

Zusammenfassung in GRADE-Tabelle

Oxerutin-containing agents versus 50 mg aescin-containing agents

For evaluating the efficacy of oxerutin-containing capillary stabilising agents compared to agents containing 50 mg of aescin, we identified 1 systematic review and an additional RCT that met our inclusion criteria. The results of the systematic review are also extracted in Chapter 3.1.4.

1 systematischen Review + 1 RCT eingeschlossen

Overall, there were 398 patients in the relevant studies. Patients in the oxerutin group received a 500 mg dosage form 1-2 times per day (only stated in the RCT) and patients in the aescin group received a 50 mg dosage form1-2

insgesamt 398 PatientInnen ...

[156] The results of two different studies were described in this article (one RCT and one registry study), but only the results of the registry study were extracted, whereas the results of the RCT are already described in the previous table under Belcaro 2002 [66].

[157] A total of 143 pts. were included, but only 122 were considered in the study.

times a day [41, 58]. Furthermore, in one study, included in the systematic review, patients received 75 mg aescin and therefore this study was excluded from our data extraction.

... durchschnittlich über 50 Jahre alt, 6-100 % Frauen

The patients were on average between 54 and 63 years in the oxerutin groups and between 55 and 59 years in the 50 mg aescin groups. The majority of the patients in the studies were females: 6-100%. Furthermore, the patients had CVI grade I and II according to Widmer. In addition, the duration of treatment was 1-3 months, whereby the follow-up without treatment was 1.5 months in the RCT. The drop-out rate ranged from 9 to 15% [41, 58].

mehrere nicht berichtete Endpunkte

None of the identified studies assessed the change of the CVI stage, the CVI signs in general, trophic alternations, ulcer, cramps, restless legs, paraesthsia and quality of life of a treatment of CVI with oxerutin versus 50 mg aescin.

Ödeme verschiedentlich gemessen, jedoch Reduktion in Studiengruppenteilweise widersprüchlich

Regarding the signs of CVI, oedema was assessed in the systematic review by several parameters: In 1 study of the review, oedema, measured on a score (scaling was not stated), decreased slightly, but not statistically significant, more in the oxerutin group than in the aescin group (mean difference of reduction between groups: -0.93). The reduction of the circumference at the ankle (in mm) was nearly equal in both study groups (mean difference of reduction between groups: 2.38 mm, based on 2 studies). However, the reduction of the calf circumference was statistically significant higher in the aescin group than in the oxerutin group (mean difference of reduction between groups: 6.8 ml, based on 1 study) [58]. Furthermore, the reduction of the leg volume (in ml) was reported in the additional RCT and after 3 months of treatment there was a statistically significant difference in favour of oxerutin (-58 to -41 vs. -28 ml). Thus, 1.5 months after the treatment period the significance of the group difference was not stated anymore (-47 to -21 vs. -26 ml) [41].

Schmerzreduktion in Studiengruppen ähnlich

Pain, a symptom of CVI, was reported in a study of the systematic review. The reduction in the score for pain (scaling not stated) was not statistically significantly different between the study groups after 2 months of treatment (mean difference of reduction between groups: 0.65) [58].

keine eindeutige Überlegenheit eines Medikaments bei Reduktion von Juckreiz, schwere Beine und Schwellungen

Itching, heaviness and swelling were reported in the additional extracted RCT on a scale (0-10), whereby it is unclear if the scores were statistically significantly more reduced in one of the study groups. After 3 months of treatment and 1.5 months later the score for itching was reduced slightly in the oxerutin group and increased in the 50 mg aescin group (-0.9 to -0.7 vs. +1 and -1.1 to -0.7 vs. +0.8 respectively). The scores for heaviness and swelling were reduced slightly in both study groups after 3 months of treatment and 1.5 months after treatment.

Oxerutin-containing agents versus flavonoid fraction-containing agents

1 RCT mit 90 PatientInnen eingeschlossen

For evaluating the efficacy of oxerutin-containing capillary stabilising agents compared to flavonoid fraction-containing agents, we identified 1 RCT with 90 patients [66] that met our inclusion criteria.

1.000 mg Oxerutin 2x vs. 500 mg Flavonoid-fraktion 3x täglich

Patients in the oxerutin group received a 1,000 mg dosage form two times per day and patients in the flavonoid fraction group received a 500 mg dosage form 3 times a day [66].

PatientInnen durchschnittlich 41 Jahre alt, ca. 50 % Frauen

The patients were on average 41 years in the oxerutin and in the flavonoid fraction group, respectively. Around half of the patients were females. The CVI grade of patients was not stated. The duration of treatment was 2 months with no additional follow-up. There were no drop-outs [66].

The identified RCT did not report on the change of the CVI stage, the CVI signs in general, trophic alternations, oedema, ulcer, symptoms like pain, cramps, restless legs, itching, heaviness plus paraesthsia and quality of life of a treatment of CVI with oxerutin- versus flavonoid fraction-containing agents.

mehrere nicht berichtete Endpunkte

The only efficacy-related outcome parameter available was general symptoms of CVI which was measured on a scale (0-10). The decrease of the score was slightly higher in the oxerutin group than in the flavonoid fraction group after 2 months of treatment (-6.5 vs. -0.6) [66]. It was not stated whether the difference was statistically significant.

generelle Symptome mit Oxerutin etwas mehr reduziert

Safety

Oxerutin-containing agents versus 50 mg aescin-containing agents

For evaluating the safety of oxerutin-containing agents versus 50 mg aescin-containing agents for the treatment of CVI only the previously mentioned identified RCT [41] was considered. The systematic review did only report safety-related outcomes for agents containing 50 mg of aescin in general (see also Chapter 3.1.4.

nur RCT beschrieb unerwünschte Ereignisse

There was no evidence available to assess general adverse events. Treatment-related adverse events occurred in 5 to 16% in the oxerutin groups (the study contained of two groups receiving oxerutin-containing agents, but with different dosage forms) and in 3% of the 50 mg aescin group [41]. Whether the difference between the groups was statistically significant was not stated.

Nebenwirkungen: 5-16 % mit Oxerutin, 3 % mit 50 mg Aescin

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.1-25.

Zusammenfassung in GRADE-Tabelle

Oxerutin-containing agents versus flavonoid fraction-containing agents

For evaluating the safety of oxerutin-containing agents versus flavonoid fraction-containing agents for the treatment of CVI we identified one RCT [66] and one additional non-randomised controlled trial [67].

1 RCT + zusätzlich 1 non-RCT eingeschlossen

The non-RCT included 122 patients, aged 43 years in the oxerutin and 42 years in the flavonoid fraction group. Around 50% of the patients were females, the grade of the CVI disease was not stated, treatment lasted for at leasts 2 months, follow-up after treatment was 2 months and there were around 17.5% of drop-outs [67].

non-RCT: 122 PatientInnen, 42-43 Jahre alt, 50 % Frauen

Overall, there was no evidence available to assess general adverse events. Treatment-related adverse events occurred in none of the study groups [66, 67].

keine Nebenwirkungen

Risk of bias

Bias-Risiko systematischer Review: gering

The identified systematic review shows an overall low risk of bias (see Figure 3.1-25), however, there is some high risk of selection bias due to an unclear research question (see also Chapter 3.1.4).

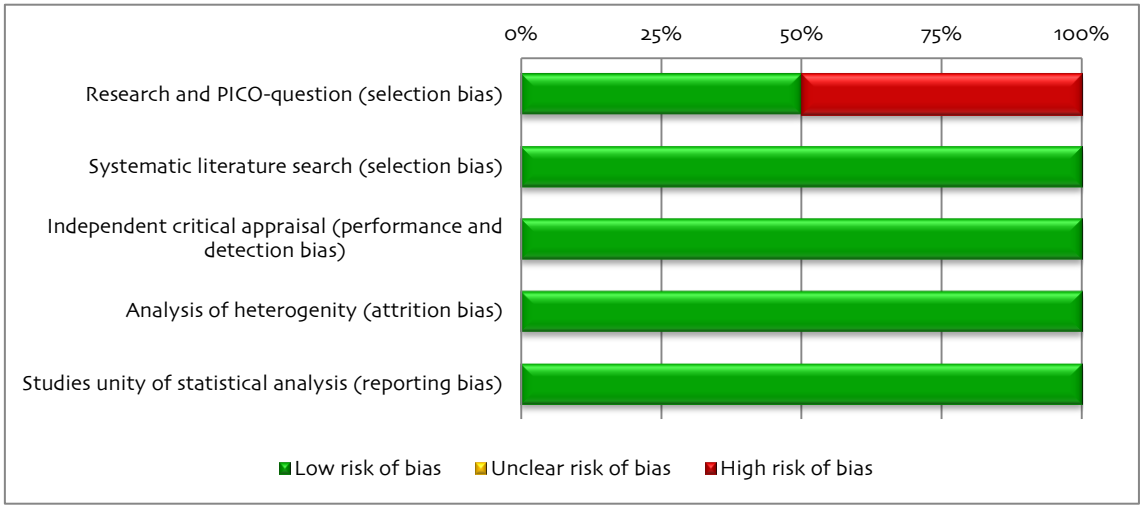

Figure 3.1-25: Risk of bias of systematic review for treatment of CVI comparing capillary stabilising agents

Bias-Risiko RCTs: unklar

The majority of the identified RCTs for a treatment of CVI comparing capillary stabilising agents with each other show a low or unclear risk of bias for several types of biases (see Figure 3.1-26). Around 40% of the studies show a high risk of performance and detection bias due to not reported blinding of study personnel or patients. Furthermore, half of the studies show a high risk of reporting bias due to reporting of pooled data for several outcomes. In summary, the risk of bias is unclear.

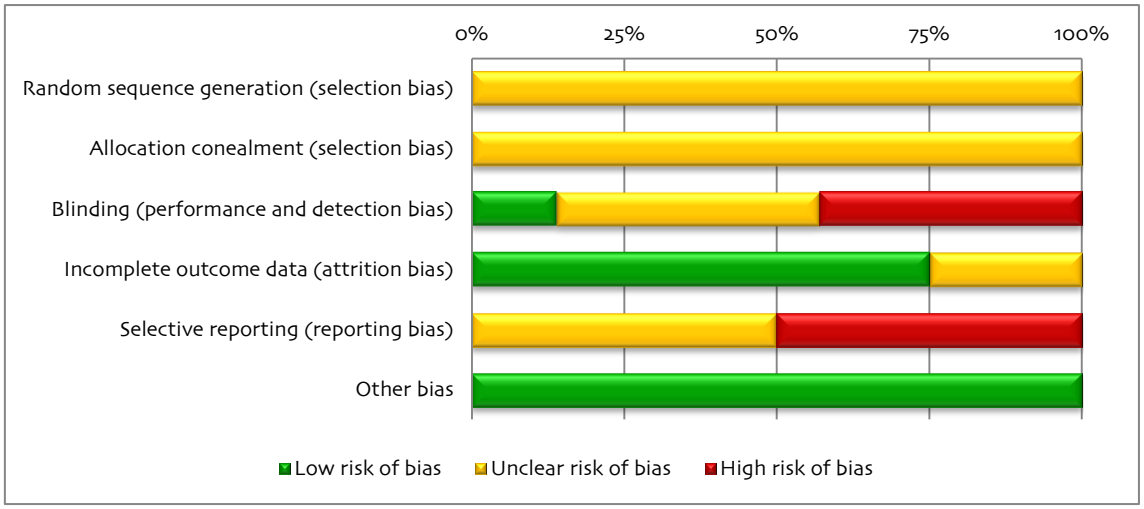

Figure 3.1-26: Risk of bias of RCTs for treatment of CVI comparing capillary stabilising agents

In the non-RCTs the risk of the performance and detection bias is high, due to no blinding of the outcome assessor and two third of the indicators show a high risk of reporting bias due to missing confounder adjustment (see Figure 3.1-27). In summary, the risk of bias is high.

Bias-Risiko non-RCTs: hoch

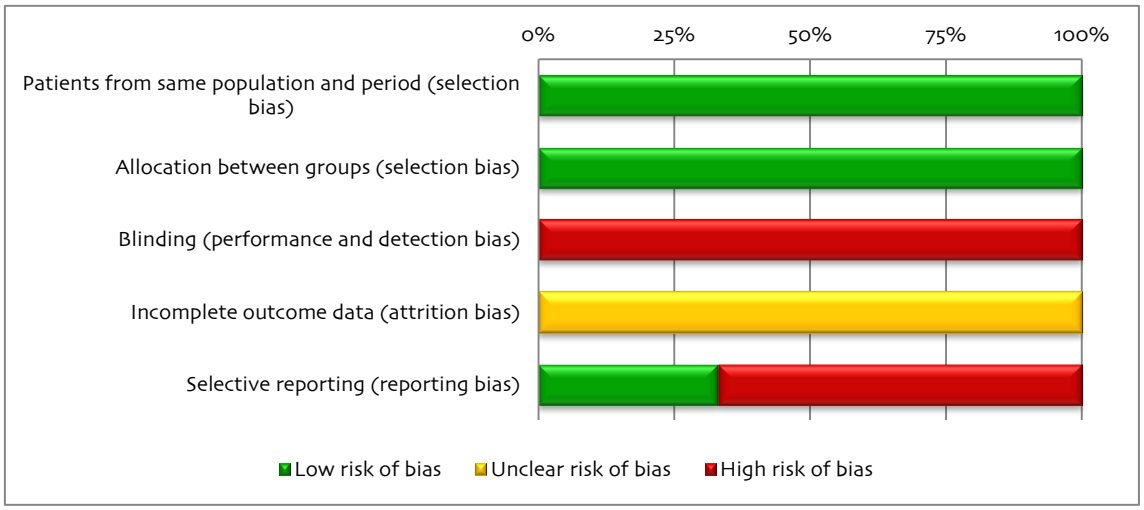

Figure 3.1-27: Risk of bias of non-RCT fortreatment of CVI comparing capillary stabilising agents

Strength of evidence

Overall, the strength of evidence of the efficacy and safety of comparing capillary stabilising agents with each other for a treatment of CVI is low to very low. Although the majority of studies were RCTs, due to several study limitations and a low number of patients in the studies, the strength of evidence was downgraded. The strength of evidence is summarised in Tables 3.1-24 for efficacy and 3.1-25 for safety comparing oxerutin-containing agents with agents containing 50 mg of aescin or flavonoid fraction-containing agents.

Evidenzstärke insgesamt gering bis sehr gering

There was no further evidence available to compare other capillary stabilising agents with each other, like 20 mg aescin- or calcium dobesilate-containing agents mentioned in Chapter 1.2.

keine Evidenz zu Vergleich mit anderen kapillarstabilisierenden Mitteln

Table 3.1-24: Evidence profile: Efficacy of capillary stabilising agents versus other capillary stabilising agents for treatment of CVI

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
Efficacy: oxerutin-containing agents (+ compression stockings) versus 50 mg aescin-containing agents (+ compression stockings)							
Change of CVI stage: no evidence							
CVI signs (general): no evidence							
CVI signs (trophic alternations): no evidence							
CVI signs (oedema): change from baseline (score n/a)							
1/30 (of 261)	RCT (in syst. Review)	2 mo: mean difference: -0.93; CI: -3.52,-1.66; p=N.S.	Serious limitations[158]	n/a (only 1 trial)	Direct	Imprecise data (-1)[159]	Low
CVI signs (oedema): leg volume reduction (in ml)							
1/137[160]	RCT	3 mo: -58 to -41 vs. -28; p=S.S.[161] 4.5 mo: -47 to -21 vs. -26; p=n/a	Serious limitations (-1)[162]	n/a (only 1 trial)	Direct	Imprecise data (-1)[159]	Low
CVI signs (oedema): ankle circumference reduction (in mm)							
2/60 (of 261)	2 RCTs (in syst. Review)	1-2 mo: mean difference: 2.38; CI:-1.47, 6.23; p=N.S.	Serious limitations (-1)[138]	Important inconsistency (-1)[163]	Direct	Imprecise data (-1)[159]	Very low
CVI signs (oedema): calf circumference reduction(in mm)							
1/30 (of 261)	RCT (in syst. Review)	2 mo: mean difference: 6.8; CI: 4.26,9.34; p= S.S., in favour of 50 mg aescin	Serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[159]	Low
CVI signs (ulcer): no evidence							
CVI symptoms (general): no evidence							
CVI symptoms (pain): change from baseline (score n/a)							
1/30 (of 261)	RCT (in syst. Review)	2 mo: mean difference: 0.65; CI: -1.74,3.04; p=N.S.	Serious limitations[138]	n/a (only 1 trial)	Direct	Imprecise data (-1)[159]	Low

158 Unclear blinding of outcome assessor and allocation concealment.

159 Low incidence, study/studies not powered to detect difference.

160 Study consisted of 3 groups: two groups received oxerutin-containing agents in two different dosages, results of these two groups were summarised in this table.

161 Reduction was statistically significant for group that receive 2 x 500 mg oxerutin-containing agents vs. the group that received 50 mg aescin-containing agents.

162 Unclear blinding of outcome assessor and random sequence generation in study.

163 Systematic review summarised outcomes of studies from different times (e.g., after 0.5, 1, 3 or 4 months) and on different scales.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
CVI symptoms (cramps): no evidence							
CVI symptoms (restless legs): no evidence							
CVI symptoms (itching): change from baseline (score 0-10)							
1/137[160]	RCT	1 mo: -0.9 to -0.1 vs. +0.2; p=n/a 2 mo: -0.9 to -0.1 vs.±0; p=n/a 3 mo: -0.9 to -0.7 vs.+0.1; p=n/a 4.5 mo: -1.1 to -0.7 vs. +0.8; p=n/a	Serious limitations (-1)[140]	n/a (only 1 trial)	Direct	Imprecise data (-1)[159]	Low
CVI symptoms (heaviness): change from baseline (score 0-10)							
1/137[160]	RCT	1 mo: -1 to -0.5 vs. +0.8; p=n/a 2mo: -1.2 to -0.5 vs.. ±0; p=n/a 3 mo: -1.4 to -1.3 vs. -0.3; p=n/a 4.5 mo: -1.5 to -1 vs. -0.2; p=n/a	Serious limitations (-1)[140]	n/a (only 1 trial)	Direct	Imprecise data (-1)[159]	Low
CVI symptoms (swelling): change from baseline (score 0-10)							
1/137[160]	RCT	1 mo: -0.7 to -0.5 vs. +0.5; p=n/a 2mo: -0.7 to -0.5 vs. +0.3; p=n/a 3 mo: -1.4 to -1 vs. -0.3; p=n/a 4.5 mo: -1.7 to -1.3 vs. -0.1; p=n/a	Serious limitations (-1)[140]	n/a (only 1 trial)	Direct	Imprecise data (-1)[159]	Low
CVI symptoms (paraesthesias): no evidence							
Quality of life: no evidence							
Efficacy: oxerutin-containing agents (+ compression stockings) versus flavonoid fraction-containing agents (+ compression stockings)							
Change of CVI stage: no evidence							
CVI signs (general): no evidence							
CVI signs (trophic alternations): no evidence							
CVI signs (oedema): no evidence							
CVI signs (ulcer): no evidence							
CVI symptoms (general): change from baseline (score 0-10)							
1/90	RCT	2mo: -6.5 vs. -0.6; p=n/a	Serious limitations (-1)[164]	n/a (only 1 trial)	Direct	Imprecise data (-1)[159]	Low
CVI symptoms (pain): no evidence							

[164] Study is likely to be open.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirect-ness	Other modifying factors	Strength of evidence
CVI symptoms (cramps): no evidence							
CVI symptoms (restless legs): no evidence							
CVI symptoms (itching): no evidence							
CVI symptoms (heaviness): no evidence							
CVI symptoms (swelling): no evidence							
CVI symptoms (paraesthesias): no evidence							
Quality of life: no evidence							

Abbreviations: n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

Table 3.1-25: Evidence profile: Safety of capillary stabilising agents versus other capillary stabilising agents for treatment of CVI

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Safety: oxerutin-containing agents (+ compression stockings) versus 50 mg aescin-containing agents (+ compression stockings)							
Adverse events (general): no evidence							
Adverse events (treatment-related): in %							
1/137	RCT	5 to 16 vs. 3; p=n/a	Serious limitations (-1)[140]	n/a (only 1 trial)	Direct	Imprecise data (-1)[159]	Low
Safety: oxerutin-containing agents (+ compression stockings) versus flavonoid fraction-containing agents (+ compression stockings)							
Adverse events (general): no evidence							
Adverse events (treatment-related): in %							
1/90 1/122	RCT Non-RCT	0 vs. 0; p=N.S. 0 vs. 0; p=N.S.	Serious limitations (-1)[165] Serious limitations (-1)[166]	n/a (only 1 trial) n/a (only 1 trial)	Direct	Imprecise data (-1)[159]	Low Very low

Abbreviations: n/a = data not available; Non-RCT = non-randomised controlled trial; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

[165] Study is likely to be open.

[166] No blinding.

3.2 Treatment of haemorrhoidal diseases

Overall, 17 randomised controlled trials (RCTs), 1 non-randomised controlled trial (non-RCT) and 1 uncontrolled trial (single-arm study), were identified to assess either the efficacy or safety or both of capillary stabilising agents for the treatment of haemorrhoidal diseases (HD).

insgesamt 17 RCTs, 1 non-RCT und 1 Ein-Arm-Studie eingeschlossen

3.2.1 Oxerutin-containing agents

Study characteristics

For evaluating the efficacy and safety of capillary stabilising agents containing oxerutin (0-beta-hydroxyethyl-rutoside, HR), we identified 1 RCT [68] that met our inclusion criteria. The study is comparing oxerutin-containing agents with placebo for a treatment of HD. The dosage of oxerutin was 500 mg two times a day [68].The study characteristics and results are summarised in Table 3.2-1.

1 RCT mit 97 PatientInnen eingeschlossen

Dosis: 500 mg 2 x täglich vs. Placebo

There were no studies identified comparing oxerutin-containing agents with other interventions, such as lifestyle changes or further medical, office-based (or local) and surgical treatment, mentioned in Chapter 1.1.3.

keine Studien mit anderen Vergleichsgruppen

Table 3.2-1: Efficacy and safety-related outcomes of a randomised controlled trial of oxerutin-containing agents vs. placebo for HD

Author, year, reference number	Wijayanegara 1992 [68]
Country	Indonesia
Study design	RCT
Sponsor	n/a
Intervention/product	2x 500 mg HR tablets (Venoruton®) per day
Comparator	Placebo
Number of pts.	48 vs. 49
Age of patients (yrs.)	29 vs. 30
Sex (% female)	100
Clinical classification	Grade 1-3[167]
Primary endpoint	n/a
Inclusion criteria	Women with severe haemorrhoids (grade 1-3), between gestation weeks 12-34; uncomplicated pregnancy and with no other treatment
Duration of Treatment (weeks)	4
Follow-up (weeks)	0
Drop-outs, n (%)	3 (3)[168]

[167] It was not stated on which grading the stage of HD was based.

[168] A total of 100 patients were included in the study and 3 of them withdrew.

Author, year, reference number	Wijayanegara 1992 [68]
Efficacy-related outcomes	
Change of HD stage	n/a
HD signs (general)	*Improved pts. (%)*[169]*:* Baseline: - After <1; 1 week: n/a After 2 weeks: 21 vs. 0; p=n/a After 4 weeks: 67 vs. 0; p=n/a After 8, 12; 24, 50 weeks: n/a
Prolapse (or swelling)	n/a
Discharge (or leakage)	n/a
Incontinence	n/a
HD symptoms (general)	*Improved pts. (%)*[170]*:* Baseline: - After <1 week: n/a After 1 week: n/a After 2 weeks: 84 vs. 12; p=n/a After 4 weeks: 94 vs. 14; p=n/a After 8, 12; 24, 50 weeks: n/a
Pain	n/a
Bleeding	n/a
Itching (or pruritus)	n/a
QoL	n/a
Recurrence rate	n/a
Safety-related outcomes	
Adverse events, general in % (n) pts.	n/a
Major adverse events	n/a
Minor adverse events	n/a
Adverse events, treatment-related in % (n) pts.	63 (3) vs. n/a; p=n/a (abdominal discomfort, dizziness vs. n/a)
Major adverse events	n/a
Minor adverse events	n/a

Abbreviations: HD = haemorrhoidal diseases; HR = 0(beta-hydroxyethyl)-rutosides (also called oxerutin); n = number (of patients); n/a = data not available; N.S. = not statistically significant; pts. = patients; QoL = quality of life; RCT = randomised controlled trial; vs. = versus; yrs. = years

169 Assessment of objective signs was given in percentage of patients with improvement (in %), based on bleeding, inflammation and vein dilatation.

170 Assessment of subjective symptoms was given in percentage of patients with improvement (in %), based on pain, bleeding, exudation, pruritus.

Efficacy

für Wirksamkeit: 1 RCT

For evaluating the efficacy of capillary stabilising agents containing oxerutin (0-beta-hydroxyethyl-rutoside, HR), we identified 1 RCT that met our inclusion criteria [68].

insgesamt 97 PatientInnen, im Durchschnitt ca. 30 Jahre alt, 100 % Frauen

There were 97 patients in the study, of whom 48 were treated with 500 mg oxerutin tablets (treatment group) and 49 received placebo (control group). The patients were on average 29 years in the treatment and 30 years in the control group. All patients were females. Furthermore, the patients had HD grade 1 to 3, yet, it was not stated on which grading the reported stage was based. In addition, the duration of treatment was 4 weeks. There was no follow-up without treatment. The drop-out rate was 3% [68].

Zusammenfassung in GRADE-Tabelle

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.2-2.

Oxerutin-containing agents versus placebo

zahlreiche nicht erhobende Endpunkte

The identified study did not assess the change of the HD stage, the HD signs prolapse, discharge and incontinence, the symptoms pain, bleeding and itching, quality of life and recurrence rate of a treatment of HD with oxerutin versus placebo.

generelle Anzeichen von Hämorrhoiden in Behandlungsgruppe verbessert

After 2 and 4 weeks of treatment the general signs of HD were more improved in the treatment than in the control group (improved patients, after 2 weeks: 21 vs 0%, after 4 weeks: 67 vs. 0%). It was not stated whether the difference between the study groups was statistically significant or not [68].

generelle Symptome in Behandlungsgruppe stärker verbessert

General symptoms of HD improved in more patients in the treatment than in the control group after 2 and 4 weeks of treatment respectively (improved patients after 2 weeks: 84 vs. 12%, after 4 weeks: 94 vs. 14%) [68]. Whether the difference between the study groups was statistically significant or not was not mentioned.

Safety

für Bewertung Sicherheit keine weiteren Studien

For evaluating the safety of capillary stabilising agents containing oxerutin (0-beta-hydroxyethyl-rutoside, HR), we identified no other study beside the previously mentioned RCT [68] that met our inclusion criteria.

Zusammenfassung in GRADE-Tabelle

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.2-2.

Oxerutin-containing agents versus placebo

Nebenwirkungen bei 63 % der PatientInnen in Oxerutin-Gruppe

There was no available evidence to assess general adverse events. Treatment-related adverse events occurred in 63% of the patients treated with oxerutin-containing agents [68]. Treatment-related adverse events in the control group were not stated.

Risk of bias

Bias-Risiko insgesamt unklar

The identified RCT for a treatment of HD with oxerutin-containing agents shows an unclear risk of bias for several types of biases (see Figure 3.2-1). In addition there is a high risk of reporting bias due to missing description of outcomes (only percentage of improved patients for efficacy-related outcomes stated). In summary, the risk of bias is mostly unclear.

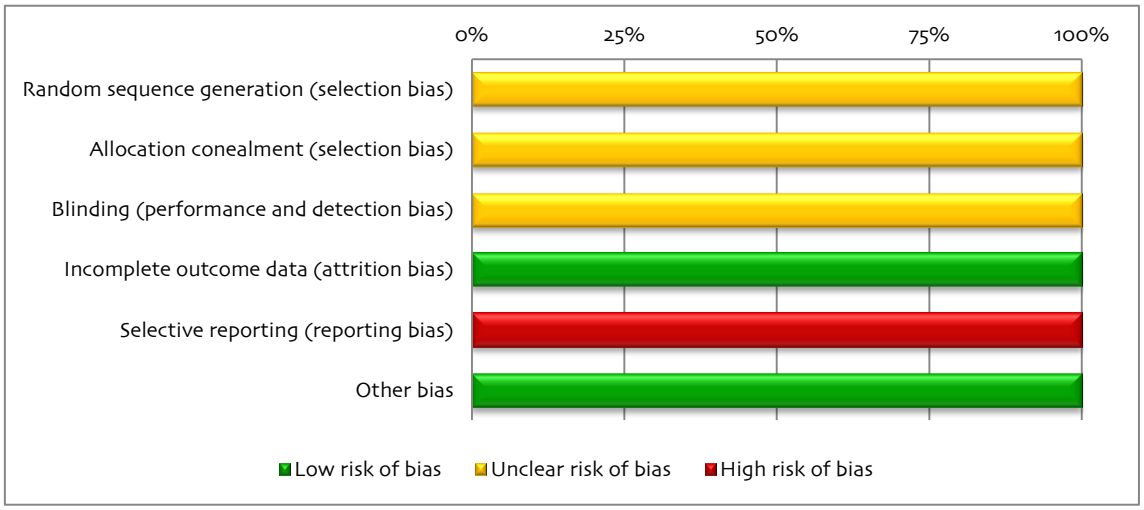

Figure 3.2-1: Risk of bias of RCTs for treatment of HD with oxerutin-containing agents

Strength of evidence

Evidenzstärke insgesamt niedrig

Overall, the strength of evidence of the efficacy and safety of a treatment of HD with oxerutin-containing agents is low. Although the only identified study was a RCT, due to several study limitations and a low number of patients in the study the strength of evidence was downgraded. The strength of evidence is summarised in the Table 3.2-2.

keine Evidenz zu Vergleich mit anderen Behandlungen

There was no evidence available to compare a treatment of HD with oxerutin-containing agents with other interventions, such as lifestyle changes or further office-based and surgical treatment, mentioned in Chapter 1.1.3.

Table 3.2-2: Evidence profile: Efficacy and safety of oxerutin-containing agents for treatment of HD compared to placebo

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy: oxerutin-containing agents versus placebo							
Change of HD stage: no evidence							
HD signs (general): improved patients (in %)							
1/97	RCT	2 we: 21 vs. 0; p=n/a 4 we: 67 vs. 0; p=n/a	Serious limitations (-1)[171]	n/a (only 1 trial)	Direct	Imprecise data (-1)[172]	Low
CVI signs (prolapse): no evidence							
CVI signs (discharge): no evidence							
CVI signs (incontinence): no evidence							
CVI symptoms (general): improved patients (in %)							
1/97	RCT	2 we: 84 vs. 12; p=n/a 4 we: 94 vs. 14; p=n/a	Serious limitations (-1)[171]	n/a (only 1 trial)	Direct	Imprecise data (-1)[172]	Low
CVI symptoms (pain): no evidence							
CVI symptoms (bleeding): no evidence							
CVI symptoms (itching): no evidence							
Quality of life: no evidence							
Safety: oxerutin-containing agents versus placebo							
Adverse events (general): no evidence							
Adverse events (treatment-related): in %							
1/97	RCT	63 vs. n/a; p=n/a	Serious limitations (-1)[173]	n/a (only 1 trial)	Direct	Imprecise data (-1)[174]	Low

Abbreviations: n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

171 Unclear random sequence generation, allocation concealment and blinding of outcome assessors.

172 Low incidence, study/studies not powered to detect difference.

173 Unclear random sequence generation, allocation concealment and blinding of outcome assessors.

174 Low incidence, study/studies not powered to detect difference.

3.2.2 Flavonoid fraction-containing agents

Study characteristics

13 RCTs + 1 Ein-Arm-Studie eingeschlossen

For evaluating the efficacy and safety of flavonoid fraction-containing capillary stabilising agents for a treatment of HD, we identified 13 RCTs [23, 69-80] and 1 single-arm study (study with no control group) [81] that met our inclusion criteria. In addition, we included another publication that was described as a non-randomised controlled trial [82]; however, this study consisted of the same patient population as another study [70] (conducted as RCT). Therefore, we added the non-RCT to the RCT, due to the fact that adverse events were not reported in the RCT.

Vergleichsgruppen: Placebo, keine Behandlung, ambulante Maßnahmen, Gabe von Entzündungshemmern

Overall, 6 studies compared flavonoid fraction-containing agents with placebo [69-72, 74, 75], 3 studies gave the drug after surgery and compared to no treatment after surgery [73, 79, 80], in 3 studies the control groups received an office-based treatment [23, 76, 77], in 1 study, the control group was treated with anti-inflammatory medication [78] and in another study a second control group did not receive a treatment (except fibre supplements) [77].

Dosis: 500 mg 2-6x täglich

The dosage of flavonoid fraction-containing agents in the treatment groups was 500 mg two to six times a day [23, 69-82].

Studiencharakteristika in Tabelle

The study characteristics and results are summarised in Table 3.2-3 for RCTs and in Table 3.2-4 for the single-arm study.

keine Studien mit anderen Vergleichsgruppen

There were no studies identified comparing flavonoid fraction-containing agents with further lifestyle changing or further medical, office-based and surgical treatment options, mentioned in Chapter 1.1.3.

Table 3.2-3: Efficacy and safety-related outcomes of randomised controlled trials of flavonoid fraction-containing agents vs. placebo, no treatment, infrared photocoagulation, sclerotherapy, fibre supplements, rubber band ligation or anti-inflammatory medication for HD

Author, year, reference number	Thana-pongsathorn 1992 [72]	Cospite 1994 [71]	Godeberge 1994 [70] (Godeberge 1992 [82])	Ho 1995 [79]	Ho 2000 [77]	Misra 2000 [74]	Colak 2003 [80]	La Torre 2004 [78]	Dimitrou-lopoulos 2005 [23]	Mlakar 2005 [73]	Jiang 2006 [69]	Yuksel 2008 [76]	Panpi-manmas 2010 [75]
Country	Thailand	Italy	France	Singapore	Singapore	India	Turkey	Italy	Greece	Slovenia	China	Turkey	Thailand
Study design	RCT	RCT	RCT[175]	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT[176]
Sponsor	n/a	n/a	Servier	n/a	n/a	Serdia Pharmaceuticals	n/a	n/a	n/a	n/a	Servier	n/a	National Research Council Thailand
Intervention/ product	2-3x 500 mg MPFF tablets (Daflon®) per day[177]	4-6x 500 mg MPFF tablets (Daflon®) per day[178]	2x 500 mg MPFF tablets (Daflon®) per day	3-6x 500 mg MPFF tablets (Daflon®) per day[179], after haemorrhoidectomy	4-6x 500 mg MPFF tablets (Daflon®) per day[180] + fibre supplements	2-6x 500 mg MPFF tablets (Daflon®) per day[181]	4-6x 500 mg MPFF tablets (Daflon®) per day[182], after haemorrhoidectomy	2-4x 500 mg MPFF tablets (Daflon®) per day[183]	6x 500 mg MPFF tablets (Daflon®) per day alone | 6x500 mg MPFF tablets (Daflon®) per day + infrared photocoagulation alone	6x 500 mg MPFF tablets (Detralex®) per day, after haemorrhoidopexy	4-6x 500 mg MPFF tablets (Daflon®) per day[184]	2x 500 mg MPFF tablets (Daflon®) per day	2-6x 500 mg MPFF tablets (Daflon®) per day[185]
Comparator	Placebo	Placebo	Placebo	No treatment, after haemorrhoidectomy	Not treatment + fibre supplements | rubber band ligation	Placebo	No treatment, after haemorrhoidectomy	Anti-inflammatory medication	Infrared photocoagulation alone	No treatment, after haemorrhoidopexy	Placebo	Sclerotherapy	Placebo
Number of pts.	50 vs. 50	50 vs. 50	60 vs. 60	114 vs. 114	39 vs. 66 | 57	50 vs. 50	56 vs. 56	25 vs. 25	117 | 117 vs. 117	30 vs. 33	49 vs. 41	64 vs. 62	189 vs. 190

[175] Additionally, the results for adverse events of Godeberge 1992 [82] were extracted since no safety-related outcomes in Godeberge 1994 [70] were reported. Both articles reported the results of the same study.

[176] This study consisted of three study groups, whereas one group received Cissus quadrangularis L. that did not met our inclusion criteria.

[177] In the first 4 days of treatment patients received 3 x 500 mg MPFF followed by 2 x 500 gm MPFF per day for the rest of the treatment phase.

[178] In the first 4 days of treatment patients received 6 x 500 mg MPFF followed by 4 x 500 gm MPFF per day for the rest of the treatment phase.

[179] In the first 3 days of treatment patients received 6 x 500 mg MPFF followed by 3 x 500 mg MPFF per day for the rest of the treatment phase.

[180] In the first 5 days of treatment patients received 6 x 500 mg MPFF followed by 4 x 500 mg MPFF per day for the rest of the treatment phase.

[181] In the first 4 days of treatment patients received 6 x 500 mg MPFF followed by 4 x 500 gm MPFF per day for 3 days. In a second period, patients with stopped bleeding received 2 x 500 mg MPFF per day for the rest of the treatment phase.

[182] In the first 3 days of treatment patients received 6 x 500 mg MPFF followed by 4 x 500 mg MPFF per day for the rest of the treatment phase.

[183] In the first 10 days of treatment patients received 4 x 500 mg MPFF followed by 2 x 500 mg MPFF per day for the rest of the treatment phase.

[184] In the first 4 days of treatment patients received 6 x 500 mg MPFF followed by 4 x 500 gm MPFF per day for the rest of the treatment phase.

[185] In the first 4 days of treatment patients received 6 x 500 mg MPFF followed by 4 x 500 gm MPFF per day for 3 days. In a second period, patients with stopped bleeding received 2 x 500 mg MPFF per day for the rest of the treatment phase.

Author, year, reference number	Thana-pongsathorn 1992 [72]	Cospite 1994 [71]	Godeberge 1994 [70] (Godeberge 1992 [82])	Ho 1995 [79]	Ho 2000 [77]	Misra 2000 [74]	Colak 2003 [80]	La Torre 2004 [78]	Dimitrou-lopoulos 2005 [23]	Mlakar 2005 [73]	Jiang 2006 [69]	Yuksel 2008 [76]	Panpi-manmas 2010 [75]
Age of patients (yrs.)	Ø 32 vs. 32	Ø 45 vs. 43	Ø 46 vs. 48	Ø 40	Ø 41 vs. 44 | 45	Ø 35 vs. 33	Ø 41 vs. 45	Ø 57 vs. 56	Ø 49 | 48 vs. 50	Ø 49	Ø 44 vs. 42	Ø 44 vs. 44	n/a[186]
Sex (% female)	56 vs. 62	46 vs. 56	60 vs. 50	46	28 vs. 29 | 32	24 vs. 18	43 vs. 39	36 vs. 36	50 | 52 vs. 52	70	45 vs. 46	48 vs. 48	55 vs. 54
Clinical classification	Grade 1-2 acc. to Goligher	Grade 1-3[187]	n/a	n/a	Grade 1-2[188]	Grade 1-2[188]	Grade 3-4[188]	Grade 2-4[188]	Grade 1-3[188]	Grade 3-4[188]	n/a	Grade 1-2 acc. to Goligher	Grade 1-3[188]
Primary endpoint	n/a	n/a	n/a	n/a	n/a	Number of patients with no bleeding after 3 days	n/a	n/a	Rate of bleeding cessation within 5 days after intervention	n/a	Assessment of signs and symptoms of HD	n/a	n/a
Inclusion criteria	Pts. with acute symptoms due to grade 1-2 of internal haemorrhoids (Goligher)	Adult pts., regardless of age and sex, with history of HD, suffering from uncomplicated + untreted haemorrhoidal attack + with/without proctorrhagia, lasting <3 days,	Ambulatory pts., aged >18 yrs., with symptomatic haemorrhoids + acute episode in preceding 2 months, indicated for medical treatment	n/a	Pts. with bleeding nonprolapsed haemorrhoids	Pts. of both sexes, aged >18 yrs., with a history of haemorrhoids in the last 18 months + acute rectal bleeding in the last 3 days + visible distended or displaced anal cushions, conforming to grade 1 or 2 internal haemorrhoids	n/a	Pts. aged >18 yrs., with indication for haemorrhoidectomy, past history of haemorrhoids longer than 6 months, symptomatic irreducible prolapsed haemorrhoids	Ambulatory pts of both sexes, aged 18 yrs. or older, presenting with rectal bleeding due to grade I-III acute internal haemorrhoids, with no previous treatment for haemorrhoids within 6 months and without coexisting colon diseases	n/a	Pts. of both sexes, aged >18 yrs., presenting acute haemorrhoidal episode for first time	Pts. who suffered from symptomatic haemorrhoids grade 1-2 (acc. to Goligher)	Acute rectal bleeding within 5 days
Duration of Treatment (weeks)	2	1	8	1	4	12	1	4	<1[189]	<1[189]	1	12	1
Follow-up (weeks)	0	0	0	Ø 62	24	0	0	8	12	4	0	96	0
Drop-outs, n (%)	0 (0) vs. 2 (4)	1 (2) vs. 5 (10)	5 (8) vs. 2 (3)	n/a	0 vs. 0 | 0	13 (26) vs. 22 (44)	n/a	n/a	49 (42) | 34 (29) vs. 52 (44)	0 vs. 0	0	13 (10)	41 (7)[190]

[186] Mean age was not stated, but all patients were younger than 50 years.

[187] It was not stated on which grading the stage of HD was based.

[188] It was not stated on which type of grading the stage of HD was based.

[189] Duration of treatment with MPFF was 5 days.

[190] From 570 patients a total of 41 patients withdraw from study.

Author, year, reference number	Thana-pongsathorn 1992 [72]	Cospite 1994 [71]	Godeberge 1994 [70] (Godeberge 1992 [82])	Ho 1995 [79]	Ho 2000 [77]	Misra 2000 [74]	Colak 2003 [80]	La Torre 2004 [78]	Dimitrou-lopoulos 2005 [23]	Mlakar 2005 [73]	Jiang 2006 [69]	Yuksel 2008 [76]	Panpi-manmas 2010 [75]
Efficacy-related outcomes													
Change of HD stage	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
HD signs (general)	*Improved pts. (%)*[191]*:* Baseline: - After <1 week: 52 vs. 22; p=n/a After 1 week:: n/a After 2 weeks: 72 vs. 67; **p=N.S.** After 4; 8; 12; 24; 50weeks: n/a	n/a	*Score (n/a)*[192]*:* Baseline: 4.9 vs. 4.5; **p=N.S.** After<1; 1; 2; 4 weeks: n/a After 8weeks: 0.9 vs. 2.9; **p<0.01** After 12; 24; 50 weeks: n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a[193]	n/a	n/a
Prolapse (or swelling)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	*Score (0-3):* Baseline: 1.3 vs. 1.5; **p=N.S.** After <1 week: 1.2 vs. 1.3; **p<0.05** After 1 week: 1.1 vs. 1.3; **p<0.05** After 2; 4; 8; 12; 24; 50 weeks: n/a *Patients (%):* Baseline: 12 vs. 12; p=n/a After <1 week: 2 vs. 5; p=n/a After 1 week: 0 vs. 5; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a	n/a	*Improved pts. (%):* Baseline: - After <1 week: n/a After 1 week: 3.5 vs. 6.2; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a

[191] Signs were measured for swelling, congestion, bleeding, exudation and prolapse, but only given as percentage (in %) of improvements.

[192] Signs were measured on a scale of 0-3 (nil to severe), whereas the score for general signs was not clear.

[193] Signs were measured for prolapse and discharge on a 4-point grading scale (0-3) and additionally given as percentage of patients (in %) with this sign.

Author, year, reference number	Thana-pongsathorn 1992 [72]	Cospite 1994 [71]	Godeberge 1994 [70] (Godeberge 1992 [82])	Ho 1995 [79]	Ho 2000 [77]	Misra 2000 [74]	Colak 2003 [80]	La Torre 2004 [78]	Dimitrou-lopoulos 2005 [23]	Mlakar 2005 [73]	Jiang 2006 [69]	Yuksel 2008 [76]	Panpi-manmas 2010 [75]
Discharge (or leakage)	n/a	*Score (0-3)*[194]*:* Baseline: n/a After <1 week: n/a After 1 week: 0.03 vs. 0.91; **p<0.001** After 2; 4; 8; 12; 24; 50 weeks: n/a	*Improved pts. (%):* Baseline: - After <1; 1; 2; 4 weeks: n/a After 8 weeks: 97 vs. 54; **p<0.01** After 12; 24; 50 weeks: n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	*Score (0-3):* Baseline: 1.3 vs. 1; **p=N.S.** After <1 week: 1.2 vs. 1.2; **p=N.S.** After 1 week: 1.1 vs. 1.2; **p=N.S.** After 2; 4; 8; 12; 24; 50 weeks: n/a *Patients (%):* Baseline: 2 vs. 7; p=n/a After <1 week: 2 vs. 2; p=n/a After 1 week: 0 vs. 2; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a	n/a	*Improved pts. (%):* Baseline: - After <1 week: n/a After 1 week: 5.2 vs. 6.2; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a
Incontinence	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
HD symptoms (general)	*Improved pts. (%)*[195]*:* Baseline: - After <1 week: 74 vs. 60; p=n/a After 1 week: n/a After 2 weeks: 97 vs. 94; **p=N.S.**	*Score (n/a)*[196]*:* Baseline: n/a After <1 week[197]: 1.06 vs. 0.42; **p<0.001** After 1 week: 2.56 vs. 1.2; **p<0.001**	*Score (0-3)*[198]*:* Baseline: 6.6 vs. 6.0; **p=N.S.** After <1; 1; 2; 4 weeks: n/a After 8 weeks: 1.1 vs. 4.0; **p<0.01**	n/a	n/a	n/a	n/a	n/a[199]	n/a	n/a	n/a[200]	*Score (0-2)*[201]*:* Baseline: 1.57 vs. 1.87; **p=N.S.** After <1; 1 week: n/a After 2 weeks: 1.38 vs. 1.45; p=n/a	n/a

194 Measured on a scale of 0-3 (nil to severe).

195 Symptoms were measured for swelling, congestion, bleeding, exudation and prolapse, but only given as percentage (in %) of improvements.

196 Measurement of individual symptoms (pain etc.) were measured on a scale of 0-3 (nil to severe) for the severity of symptoms, whereas the score for general symptoms was not clear.

197 Results after 3 days are reported.

198 Symptoms were measured on a scale of 0-3, whereas the score at baseline for overall symptoms was >3.

199 Symptoms were measured on a score of 0-3 for pain, tenesmus, pruritus and bleeding. Assessment for <0.25 months was done after 3 days. P-Values were calculated for a global score.

200 Symptoms were measured for pain, bleeding and itching on a 4-point grading scale and additionally given as percentage of patients (in %) with this symptom.

201 Symptoms were measured on a score of 0-2 points for bleeding, pain, heaviness, pruritis and discharge.

Author, year, reference number	Thana-pongsathorn 1992 [72]	Cospite 1994 [71]	Godeberge 1994 [70] (Godeberge 1992 [82])	Ho 1995 [79]	Ho 2000 [77]	Misra 2000 [74]	Colak 2003 [80]	La Torre 2004 [78]	Dimitrou-lopoulos 2005 [23]	Mlakar 2005 [73]	Jiang 2006 [69]	Yuksel 2008 [76]	Panpi-manmas 2010 [75]
	After 4; 8; 12; 24; 50 weeks: n/a	After 2; 4; 8; 12; 24; 50 weeks: n/a	After 12; 24; 50 weeks: n/a									After 4 weeks: 0.8 vs. 1.12; **p<0.05,** in favour of MPFF After 8; 12 weeks: n/a After 24 weeks: 0.08 vs. 0.24; p=n/a After 50 weeks: 0.9 vs. 0.42; **p<0.001**, in favour of SCL After 100 weeks: 1.32 vs. 0.68; **p<0.001**, in favour of SCL	
Pain	n/a	*Score (0-3):* Baseline: n/a After <1 week: n/a After 1 week: 0.24 vs. 1.26; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a	*Improved pts. (%):* Baseline: - After <1; 1; 2; 4 weeks: n/a After 8 weeks: 98 vs. 47; **p<0.01** After 12; 24; 50 weeks: n/a	n/a	n/a	n/a	*Score (0-10)*[202]*:* Baseline: 7 vs. 6; **p=N.S.** After <1 week: 3.5 vs. 5; **p=0.011** After 1 week: 2 vs. 3.5; **p=0.001** After 2; 4; 8; 12; 24; 50 weeks: n/a	*Score (0-3):* Baseline: 1.56 vs. 2.24; p=n/a After <1 week: 0.72 vs. 1.76; **p<0.001** After 1 week: 0.24 vs. 1.36; p= n/a After 2 weeks: 0.16 vs. 0.6; p=n/a After 4 weeks: 0 vs. 0.2; p=n/a After 8 weeks: 0 vs. 0 After 12; 24; 50 weeks: n/a	n/a	*Score (0-10)*[202]*:* Baseline: n/a After <1 week: n/a After 1 week: 3.48 vs. 3.40; **p=N.S.** After 2; 4; 8; 12; 24; 50 weeks: n/a	*Score (0-3):* Baseline: 3.2 vs. 3.1; **p=N.S.** After <1 week: 2.0 vs. 2.1; **p=N.S.** After 1 week: 1.4 vs. 1.8; p=0.001 After 2; 4; 8; 12; 24; 50 weeks: n/a *Patients (%):* Baseline: 73 vs. 85; p=n/a After <1 week: 18 vs. 20; p=n/a After 1 week: 6 vs. 15; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a	n/a	*Improved pts. (%):* Baseline: - After <1 week: n/a After 1 week: 33 vs. 33; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a

[202] Pain was measured on a 10 cm visual analogue scale.

Author, year, reference number	Thana-pongsathorn 1992 [72]	Cospite 1994 [71]	Godeberge 1994 [70] (Godeberge 1992 [82])	Ho 1995 [79]	Ho 2000 [77]	Misra 2000 [74]	Colak 2003 [80]	La Torre 2004 [78]	Dimitrou-lopoulos 2005 [23]	Mlakar 2005 [73]	Jiang 2006 [69]	Yuksel 2008 [76]	Panpi-manmas 2010 [75]
Bleeding	n/a	*Score (0-3):* Baseline: n/a After <1 week: n/a After 1 week: 0.05 vs. 0.83; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a	*Improved pts. (%):* Baseline: - After <1; 1; 2; 4 weeks: n/a After 8 weeks: 91 vs. 59; **p<0.01** After 12; 24; 50 weeks n/a	n/a[203]	*Days of bleeding:* 3.9 vs. 10.6 | 5.6; **p=0.043** in favour of MPFF compared with not treatment; **p=N.S.** comparing MPFF with rubber band ligation; **p=N.S.** comparing no treatment + fibre supplements with rubber band ligation	*Days of bleeding:* 4.9 vs. 7.0, **p<0.01**	n/a	*Score (0-3):* Baseline: 1.04 vs. 1.8; p=n/a After <1 week: 0.24 vs. 1.08; **p<0.001** After 1 week: 0 vs. 0.52; p=n/a After 2 weeks: 0 vs. 0.52; p=n/a After 4 weeks: 0 vs. 0 After 8 weeks: 0 vs. 0 After 12; 24; 50 weeks: n/a	*Pts. with stopped bleeding (%):* Baseline: – After <1 week: 59.6 | 74.8 vs. 55.6; **p=N.S.** between MPFF alone and IRP alone| **p=S.S.** between MPFF + IRP and MPFF and IRP After 1; 2; 4; 8; 12; 24; 50 weeks: n/a *Days of bleeding:* 3.6 | 3.2 vs. 3.5; **p=N.S.**	*Days of bleeding:* 2.30 vs. 1.97, **p=N.S.**	*Score (0-3):* Baseline: 2.1 vs. 2.1; **p=N.S.** After <1 week: 1.3 vs. 1.5; **p<0.05** After 1 week: 1.2 vs. 1.4; **p<0.05** After 2; 4; 8; 12; 24; 50 weeks: n/a *Patients (%):* Baseline: 37 vs. 39; p=n/a After <1 week: 4 vs. 5; p=n/a After 1 week: 2 vs. 7; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a	*Pts with bleeding (%):* Baseline: 79 vs. 87; p=n/a After <1; 1 week: n/a After 2 weeks: 60 vs. 88; p=n/a After 4 weeks: 40 vs. 80; p=n/a After 8; 12 weeks: n/a After 24 weeks: 20 vs. 24; p=n/a After 50 weeks: 48 vs. 28; p=n/a After 100 weeks: 68 vs. 29; p=n/a	*Improved pts. (%)*[204]*:* Baseline: - After <1 week: n/a After 1 week: 67.8/16.1 vs. 74.2/14.0; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a
Itching (or pruritus)	n/a	n/a	*Improved pts. (%):* Baseline: - After <1; 1; 2; 4 weeks: n/a After 8 weeks: 86 vs. 58; **p<0.01** After 12; 24; 50 weeks: n/a	n/a	n/a	n/a	n/a	*Score (0-3):* Baseline: 0.88 vs. 1.68; p=n/a After <1 week: 0.24 vs. 0.92; **p<0.001** After 1 week: 0.12 vs. 0.64; p=n/a After 2 weeks: 0 vs. 0.2; p=n/a After 4 weeks: 0 vs. 0.16; p=n/a After 8 weeks: 0 vs. 0 After 12; 24; 50 weeks: n/a	n/a	n/a	*Score (0-3):* Baseline: 1.4 vs. 1.6; **p=N.S.** After <1 week: 1.2 vs. 1.3; **p=N.S.** After 1 week: 1.1 vs. 1.3; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a *Patients (%):* Baseline: 10 vs. 12; p=n/a After <1 week: 2 vs. 5; p=n/a After 1 week: 0 vs. 5; n/a	n/a	*Improved pts. (%):* Baseline: - After <1 week: n/a After 1 week: 6.9 vs. 9.6; p=n/a After 2; 4; 8; 12; 24; 50 weeks: n/a

[203] There was some information regarding to bleeding, but the information was not clear and was therefore not extracted.

[204] Assessed by patients/investigators.

Author, year, reference number	Thana-pongsathorn 1992 [72]	Cospite 1994 [71]	Godeberge 1994 [70] (Godeberge 1992 [82])	Ho 1995 [79]	Ho 2000 [77]	Misra 2000 [74]	Colak 2003 [80]	La Torre 2004 [78]	Dimitrou-lopoulos 2005 [23]	Mlakar 2005 [73]	Jiang 2006 [69]	Yuksel 2008 [76]	Panpi-manmas 2010 [75]
											After 2; 4; 8; 12; 24; 50 weeks: n/a		
QoL	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	*Score (0-10)*[205]: Baseline: n/a After <1, 1; 2; 4; 8; 12; 24; 50 weeks: n/a After 100 weeks: 4.25 vs. 6.87; p=n/a *Increase of QoL (%):* Baseline: - After 2; 4; 8; 12; 24; 50 weeks: n/a After 100 weeks: 36 vs. 68; p=n/a	n/a
Recurrence rate	n/a	n/a	0.6 vs. 2.1; **p<0.01**[206]	1 vs. 6, **p=0.03** (during follow-up) [208]	5 | 12 vs. 21; **p=N.S.** (after 24 weeks) [208]	*Days until next episode*[207]*:* 53.1 vs. 34.2; **p=N.S.**	n/a	n/a	13.2 | 4.8 vs. 13.8; **p=N.S.** (after 12 weeks)[208]	n/a	n/a	n/a, **p<0.05 in favour of sclerotherapy**.[209]	n/a

[205] QoL was measured on a visual analogue scale (0-10).

[206] Number of haemorrhoidal episodes after start of treatment.

[207] Patients with stopped bleeding (30 vs. 47) were eligible for preventive HD treatment and for those the days until the next episode of HD were reported.

[208] Recurrence rate was given for relapse in bleeding.

[209] It was stated that the recurrence rate (relapse in bleeding) was statistically significantly higher in the treatment group.

Author, year, reference number	Thana-pongsathorn 1992 [72]	Cospite 1994 [71]	Godeberge 1994 [70] (Godeberge 1992 [82])	Ho 1995 [79]	Ho 2000 [77]	Misra 2000 [74]	Colak 2003 [80]	La Torre 2004 [78]	Dimitrou-lopoulos 2005 [23]	Mlakar 2005 [73]	Jiang 2006 [69]	Yuksel 2008 [76]	Panpi-manmas 2010 [75]
Safety-related outcomes													
Adverse events, general in % (n) pts.	0 vs. 0	8 (4) vs. 6 (3); p=n/a (gastralgia, diarrhoea, abdominal pain, headache vs. gastralgia, dyspepsia, nausea)	3 (2) vs. 5 (3); p=n/a (no information about events)	5 (6) vs. 6 (8); p=n/a (faecal impaction vs. faecal impaction and anal stricuters)	n/a	2 (1) vs. 4 (2); p=n/a (gastritis vs. gastritis)	11 (6) vs. 20 (8); **p=N.S.** (acute urine retention in both groups)	n/a	2 (2) | 3 (4) vs. 2 (2)[210]; p=n/a (nausea, epigastric discomfort | pain, diarrhoea, gastrointestinal adverse events vs. gastrointestinal adverse events)	n/a	2 (1) vs. 0; p=n/a (abdominal discomfort)	0 vs. 3 (2); **p=N.S.** (pain)	0 (0) vs. 1 (2)[211]; p=n/a (headache, drowsiness, gastritis vs. headache, drowsiness, gastritis)
Major adverse events	0 vs. 0	0 vs. 0	n/a	n/a	n/a	n/a	n/a	n/a	0 | 0 vs. 0	0 vs. 0	n/a	n/a	n/a
Minor adverse events	0 vs.0	8 (4) vs. (6) 3; p=n/a (gastralgia, diarrhoea, abdominal pain, headache vs. gastralgia, dyspepsia, nausea)	n/a	n/a	n/a	n/a	n/a	n/a	2 (2) | 3 (4) vs. 2 (2); p=n/a[210] (nausea, epigastric discomfort | pain, diarrhoea, gastrointestinal adverse events vs. gastrointestinal adverse events)	n/a	n/a	n/a	n/a
Adverse events, treatment-related in % (n) pts.	0 vs.0	n/a	n/a	0 vs. n/a	0 vs. 0 | 0	n/a	0 vs. n/a	n/a	n/a	0 vs. n/a	n/a	0 vs. 3 (2); **p=N.S.** (pain)	n/a
Major adverse events	0 vs.0	n/a	n/a	0 vs. n/a	0 vs. 0 | 0	n/a	0 vs. n/a	n/a	n/a	n/a	n/a	n/a	n/a
Minor adverse events	0 vs.0	n/a	n/a	0 vs. n/a	0 vs. 0 | 0	n/a	0 vs. n/a	n/a	n/a	n/a	n/a	n/a	n/a

Abbreviations: acc. = according; HD = haemorrhoidal diseases; MPFF = micronised purified flavonoid fraction); n = number (of patients); n/a = data not available; N.S. = not statistically significant; pts. = patients; QoL = quality of life; RCT = randomised controlled trial; SCL = sclerotherapy; vs. = versus; yrs. = years

[210] Furthermore, it was stated that a total of 111 patients that received IRP reported pain, whereas the rates for the individual groups were not stated.

[211] It was not stated whether adverse events were related to treatment or not, but it was stated that these events were the only ones.

Table 3.2-4: Safety-related outcomes of non-randomised trials for flavonoid fraction-containing agents vs. placebo for treatment of HD

Author, year, reference number	Buckshee 1997 [81]
Country	India
Study design	Single-arm study
Sponsor	n/a
Intervention/product	2-6x 500 mg MPFF tablet (Daflon®) per day[212]
Comparator	None
Number of pts.	50
Age of patients (yrs.)	Ø 27
Sex (% female)	100
Clinical classification	Grade 1-2[213]
Primary endpoint	n/a
Inclusion criteria	Pts. with amenorrhea >28 weeks, with a history of haemorrhoids, aged >18 yrs. and visibly distended or displaced anal cushion on proctoscopy in association with at least on symptom of bleeding, pain, exudation or discomfort
Duration of Treatment (weeks)	5-12[214]
Follow-up (weeks)	0
Drop-outs, n (%)	9 (18)
Safety-related outcomes	
Adverse events, general in % (n) pts.	18 (9) (nausea, diarrhoea)
Major adverse events	n/a
Minor adverse events	n/a
Adverse events, treatment-related in % (n) pts.	n/a
Major adverse events	n/a
Minor adverse events	n/a

Efficacy

13 RCTs eingeschlossen

For evaluating the efficacy of flavonoid fraction-containing capillary stabilising agents for a treatment of HD, we identified 13 RCTs [23, 69-80] that met our inclusion criteria.

insgesamt 1.981 PatientInnen

3 der Studien nach OP

Overall, there were 1,981 patients in the studies, of whom patients in the treatment groups received agents containing 500 mg of flavonoid fraction (Daflon®) two to six times per day. Patients in the control groups received either placebo, were treated with office-based procedures or did not receive a treatment. Furthermore, three studies were conducted after surgery.

[212] In the first 4 days of treatment patients (pregnant women) received 6 x 500 mg MPFF followed by 4 x 500 mg MPFF per day for 3 days. In a second phase patients received 2 x 500 mg MPFF per day the rest of the study duration.

[213] It was not stated on which type of grading the stage of HD was based.

[214] The treatment in this study started with a one week high-dosage phase (all patients were pregnant women), followed by a phase that lasted for the rest of the pregnancy (median 8 weeks) and a phase of 4 weeks after delivery.

PatientInnen im Durchschnitt 32-57 Jahre alt, 18-62 % Frauen

50 % der Studien mit Nachbetrachtungszeit

The patients were on average between 32 and 57 years in the treatment groups and between 32 and 56 years in the control groups respectively. There were around 24 to 60% females in the treatment and 18 to 62% females in the control groups. If stated, the HD grade was 1 to 4 either according to Goligher (see Chapter 1.1.3) or it was not stated which grading was used. The duration of treatment was from less than one week up to 12 weeks. Half of the studies had a follow-up without treatment of 4-96 weeks and half of the studies had no follow-up. The drop-out rate differed between 0 and 42% in the treatment groups and between 0 and 44% in the control groups.

Zusammenfassung in GRADE-Tabelle

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.2-5.

Flavonoid fraction-containing agents versus placebo

einige nicht berichtete Endpunkte

None of the identified studies assessed the change of the HD stage, incontinence and the quality of life of a treatment with flavonoid fraction-containing agents versus placebo.

Anzeichen von Hämorrhoiden in Behandlungsgruppe etwas mehr verbessert

The general HD signs improved slightly, but not statistically significant, more in the flavonoid fraction group than in the placebo group during 2 weeks of treatment (72 vs. 67% improved patients) [72]. In addition, the score for general HD signs could be statistically significantly more reduced in the flavonoid fraction group than in the control group after 8 weeks of treatment in one study (-4 vs. -1.6, however, the scale used was not stated) [70].

mehr Verbesserungen von Prolaps in Behandlungsgruppen als in Vergleichsgruppen

Prolapses (also described as swellings) improved during 1 week of treatment in less patients in the flavonoid fraction group than in the placebo group (3.5 vs. 6.2%) [75]. Furthermore, prolapses, measured on a scale (0-10) were reduced likewise in both study groups during one week of treatment (-0.67 vs. -0.67) [69]. In addition, the percentage of patients with prolapses were more reduced in the flavonoid fraction group than in the placebo group during one week of treatment (-100% vs. -58%) [69]. Whether the difference between the groups was statistically significant was not stated.

mehr Verbesserungen von „Nässen" in Behandlungsgruppen als in Vergleichsgruppen

There were statistically significantly more improved patients regarding discharge (or leakage) in the flavonoid fraction group than in the placebo group after 8 weeks of treatment (97 vs. 54%) [70]. Likewise, the percentage of patients with discharge were more reduced in the flavonoid fraction group than in the placebo group during one week of treatment (-100% vs. -71%), however, if the difference between the groups was statistically significant or not was not stated.

generelle Symptome in Behandlungsgruppen mehr verbessert

The general symptoms improved in more patients in the treatment group compared to the control group after 2 weeks of treatment (97 vs. 94%), yet the difference was not statistically significant [72]. In contrast, measured by a score (scaling was not stated), the general symptoms were reduced more in the flavonoid group than in the placebo group after 8 weeks of treatment (-5.5 vs. -2.0). The group difference was statistically significant [70].

Schmerzen in % der PatientInnen ...

Pain improved in statistically significantly more patients in the flavonoid fraction group during 8 weeks of treatment than in the placebo group (98 vs. 47%) [70].

Furthermore, the score for pain (0-10) was more reduced in the treatment group compared to placebo (-6.0 vs. -4.33) during 1 week of treatment. The difference between the study groups was statistically significant [69]. In addition, the percentage of patients with pain were more reduced in the flavonoid fraction group than in the placebo group during one week of treatment (-92% vs. -82%) [69].

... und gemessen als Score verbesserten sich mehr in Behandlungsgruppen

Bleeding was measured with several parameters: there was a statistically significant difference in favour of flavonoid-containing agents compared to placebo regarding the percentage of improved patients after 8 weeks of treatment (91 vs. 59%) [70]. Measured on a score (0-10), after 1 week of treatment the results were also statistically significant in favour of the treatment group (-0.9 vs. -0.7) [69]. The average days of bleeding were 5 and 7 in the treatment and control group respectively [74]. In addition, the percentage of patients with bleeding was more (not stated if statistically significantly) reduced in the treatment than in the placebo group after 1 week of treatment [69].

Paramater bezüglich Blutungenveränderten sich zum Vorteil der Behandlungsgruppen

After 8 weeks of treatment, itching improved in statistically significantly more patients in the flavonoid fraction group than in the placebo group (86 vs. 58%) [70]. The number of patients with itching was more (not stated if statistically significantly) reduced in the treatment group (-100% vs. -58%) and the score (0-10) for itching was reduced by the same value in both study groups (-0.3 vs. -0.3) after 1 week of treatment [69].

Verbesserungen bezüglich Juckreiz waren in Behandlungsgruppen stärker

The recurrence rate was lower in the flavonoid fraction group (0.6 vs. 2.1) in one study. The group difference was statistically significant [70]. However, the difference of days until the next haemorrhoidal episode was not statistically significant between the groups in another study (53 vs. 34) [74].

Rückfallrate in Behandlungsgruppe geringer

Flavonoid fraction-containing agents after surgery versus no treatment after haemorrhoidectomy

None of the identified studies assessed the change of the HD stage, any of the HD signs, HD symptoms in general, itching (a typical HD symptom) and the quality of life resulting from treatment with flavonoid fraction-containing agents versus no treatment after previous surgery.

mehrere nicht berichtete Endpunkte

The score for pain (0-10) was more reduced during 1 week of treatment after haemorrhoidal surgery in the group that received flavonoid fraction-containing agents than the group that did not receive a treatment (-5 vs. -2.5). The difference between the study groups was statistically significant [80].

Schmerzen mit Flavonoidfraktion nach OP mehr reduziert

One RCT reported no statistically significant difference between the study groups regarding the days of bleeding after surgery (2.3 vs. 2 days) [73].

Tage mit Blutungen ähnlich

The recurrence rate (relapse in bleeding) was lower in the flavonoid fraction group than in the group that did not receive a treatment during the follow-up (Ø 62 weeks) (1 vs. 6%). The difference between the study groups was statistically significant [79].

Rückfallrate in Behandlungsgruppe geringer

Flavonoid fraction-containing agents versus anti-inflammatory medication

There was no evidence available assessing the change of the HD stage, any of the HD signs, the HD symptoms in general, the quality of life and recurrence rate of a treatment with flavonoid fraction-containing agents versus anti-inflammatory medication.

zahlreiche nicht berichtete Endpunkte

Schmerzen, Blutungen + Juckreiz mit Entzündungshemmern etwas mehr reduziert

After 4 weeks without treatment, the scores (0-10) for pain, bleeding and itching were reduced slightly, but not statistically significant, less in the group that had received flavonoid fraction-containing agents compared to the control group that had received anti-inflammatory medications (pain: -5.3 vs. -7.3, bleeding: -3.3 vs. -6.0, itching: -3.0 vs. -5.67) [78].

Flavonoid fraction-containing agents (+ fibre supplements) versus office-based treatment (+ fibre supplements)

mehrere nicht berichtete Endpunkte

There was no evidence available assessing the change of the HD stage, any of the HD signs, the HD symptoms pain and itching after treatment with flavonoid fraction-containing agents (partly supplemented by fibre supplements) versus office-based treatments (also partly supplemented by fibre supplements).

generelle Symptome in Studiengruppen gleichermaßen reduziert

The scores (0-10) for general HD symptoms were likewise reduced in the flavonoid fraction and in the control group during the treatment phase (after 4 weeks: -4 vs. -4) and also 38 weeks after the treatment has stopped (after 50 weeks: -7.5 vs. -7.5). However, after 88 weeks without treatment the score reduction was statistically significantly lower in the flavonoid fraction group (-1.5 vs. -6.0) [76].

mehr Blutungen nach 100 Wochen in Kontrollgruppe gestoppt

During the treatment phase, there were more patients with stopped bleeding in the flavonoid fraction group than in the group that received an office-based treatment (after 4 weeks: 60 vs. 20%), whereas 88 weeks after the treatment phase there were fewer patients with stopped bleeding in the treatment group (after 100 weeks: 32 vs. 71%) [23, 76]. Whether the differences are statistically significant is unknown. Furthermore, two studies reported differences between the study groups regarding days of bleeding (3.6 to 3.9 vs. 3.5 to 5.6 days). However, the differences were not statistically significant [23, 77].

Lebensqualität stieg in Kontrollgruppe mehr

After 100 weeks – 88 weeks after the treatment phase – patients in the flavonoid fraction group had a lower increase in quality of life than patients in the control group (36 vs. 68%) [76].

Rückfallraten in Gruppen von Studie zu Studie verschieden

Finally, the differences of the recurrence rate between the study groups were not statistically significant in two studies [23, 77] and statistically significant in one study in favour of the office-based treatment [76] (5 to 13 vs. 21 to 14%).

Flavonoid fraction-containing agents (+ fibre supplements) versus no treatment (+ fibre supplements)

zahlreiche nicht berichtete Endpunkte

The identified study did not assess the change of the HD stage, any of the HD signs, HD symptoms in general, pain plus itching and the quality of life of a treatment with flavonoid fraction-containing agents (and additional fibre supplements) versus no treatment (and additional fibre supplements).

nicht signifikanter Gruppenunterschied bei Tagen mit Blutungen ...

The number of days of bleeding was lower in the flavonoid fraction group than in the group that did not receive a treatment (3.9 vs. 10.6 days). However, the difference was not statistically significant [77].

... und Rückfallrate

In addition, the recurrence rate was lower in the treatment group compared to the control group (5 vs. 12%). The difference was not statistically significant [77].

Safety

For evaluating the safety of flavonoid fraction-containing agents for treatment of HD, we identified, beside the previous mentioned RCTs [23, 69-80], an additional single-arm study with 50 patients. All of them were females, aged 27 years on average, with HD grade 1-2 (based on unknown grading) [81]. Furthermore, we added another publication [82] to an already included study [70], since safety-related outcomes were only reported in the additional one.

zusätzlich 1 Ein-Arm-Studie eingeschlossen

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.2-6.

Zusammenfassung in GRADE-Tabelle

Flavonoid fraction-containing agents versus placebo

General adverse events differed between 0 and 8% in the flavonoid fraction groups and between 0 and 6% in the control groups. It was not stated whether the difference was statistically significant or not. The most common adverse events in both groups were abdominal discomfort, nausea, headache, pain and drowsiness [69, 71, 72, 74, 75, 82].

generelle unerwünschte Ereignisse: 0-8 % vs. 0-6 %

The meta-analysis of the general adverse events is displayed in Figure 3.2-2. The risk ratio was 0.84 for the probability of general adverse events with flavonoid fraction-containing agents compared to placebo. The results show that there is no statistically significant difference between occurred adverse events in the treatment and in the placebo group.

Meta-Analyse zeigt keinen signifikanten Gruppenunterschied

Study name	Statistics for each study			Sample size		Risk ratio, 95% CI
	Risk ratio	Lower limit	Upper limit	Flavonoid fraction	No treatment	
Cospite 1994	1.33	0.31	5.65	4/50	3/50	
Godeberge 1994/1992	0.67	0.12	3.85	2/60	3/60	
Misra 2000	0.50	0.05	5.34	1/50	2/50	
Jiang 2006	2.52	0.11	60.25	1/49	0/41	
Panpimanmas 2010	0.20	0.32	2.71	0/189	2/190	
Total (95% CI)	**0.84**	**0.34**	**2.11**	**8/398**	**10/391**	
						0,01 0,1 1 10 100
Random effects meta-analysis; I^2: 0.0%; p=0.72						Favours MPFF Favours placebo

Figure 3.2-2: General adverse events (dichotomous) for flavonoid fraction-containing agents vs. placebo

There were no treatment-related adverse events in any of the study groups [72].

keine Nebenwirkungen

Flavonoid fraction-containing agents after haemorrhoidectomy versus no treatment after haemorrhoidectomy

generelle unerwünschte Ereignisse: 5-11 % vs. 6-20 %

General adverse events occurred in 5 to 11% of the patients in the flavonoid fraction groups and in 6-20% of the patients in the control groups after haemorrhoidectomy [79, 80]. The difference between the groups was not statistically significant in one study [80]. The most common adverse events were faecal impaction and acute urine retention in both groups [79, 80].

keine Nebenwirkungen

In addition, all 3 identified studies mentioned that there were no treatment-related adverse events in the flavonoid fraction group [73, 79, 80]

Flavonoid fraction-containing agents versus anti-inflammatory medication

keine Evidenz

There was no evidence available to assess the safety of a treatment with flavonoid fraction-containing agents versus anti-inflammatory medication.

Flavonoid fraction-containing agents (+ fibre supplements) versus office-based treatment (+ fibre supplements)

generelle unerwünschte Ereignisse: 0-2 % vs. 2-3 %

A total of 2 RCTs reported general adverse events in 0-2% of the patients in the treatment and in 2-3% of the patients in the control groups [23, 76]. The difference between the study groups was not statistically significant in one study [76].

Nebenwirkungen zu 3 % in Kontrollgruppe

Treatment-related adverse events did not occur in the flavonoid fraction groups, though, in up to 3% of the patients in the groups that received an office-based treatment [76, 77]. The difference between the study groups was not statistically significant in both studies [76, 77].

Flavonoid fraction-containing agents (+ fibre supplements) versus no treatment(+ fibre supplements)

keine Evidenz

There was no evidence available to assess general adverse events of a treatment of flavonoid fraction-containing agents versus no treatment.

keine Nebenwirkungen

On the other hand, treatment-related adverse events did not occur in any of the study groups [77].

Flavonoid fraction-containing agents

18 % generelle unerwünschte Ereignisse

In addition, the included single-arm study reported general adverse events in 18% of the patients with treatment of HD with flavonoid fraction-containing agents [81].

Nebenwirkungen unbekannt

Treatment-related adverse events were not stated in the study.

Risk of bias

Bias-Risiko der RCTs generell unklar

The majority of the identified RCTs for a treatment of HD with flavonoid fraction-containing agents show a low or unclear risk of bias for several types of biases (see Figure 3.2-3). Around 15% of the studies show a high risk of attrition bias due to high drop-out rates and no intention to treat analysis. Furthermore, 38% of the studies show a high risk of reporting bias due to reporting incomplete data for several outcomes. In summary, the risk of bias is low to unclear.

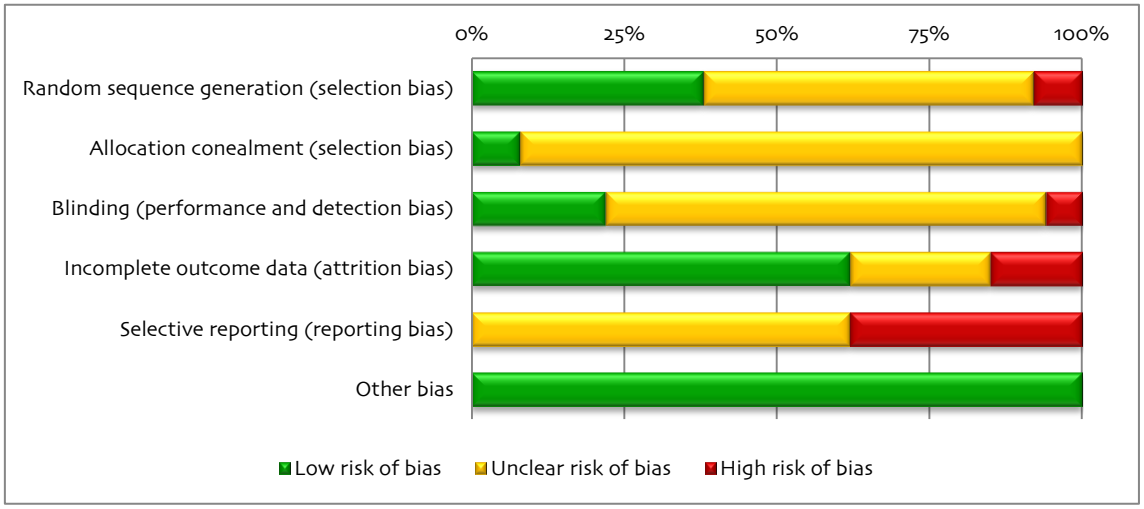

Figure 3.2-3: Risk of bias of RCTs for treatment of HD with flavonoid fraction-containing agents

Ein-Arm-Studie: hohes Bias-Risiko

In the uncontrolled studies, the risk of the performance and detection bias is high, due to no blinding of the outcome assessor and more than half of the indicators show a high risk of reporting bias due to no confounder adjustment (see Figure 3.2-4). In summary, the risk of bias is high, due to the uncontrolled study design.

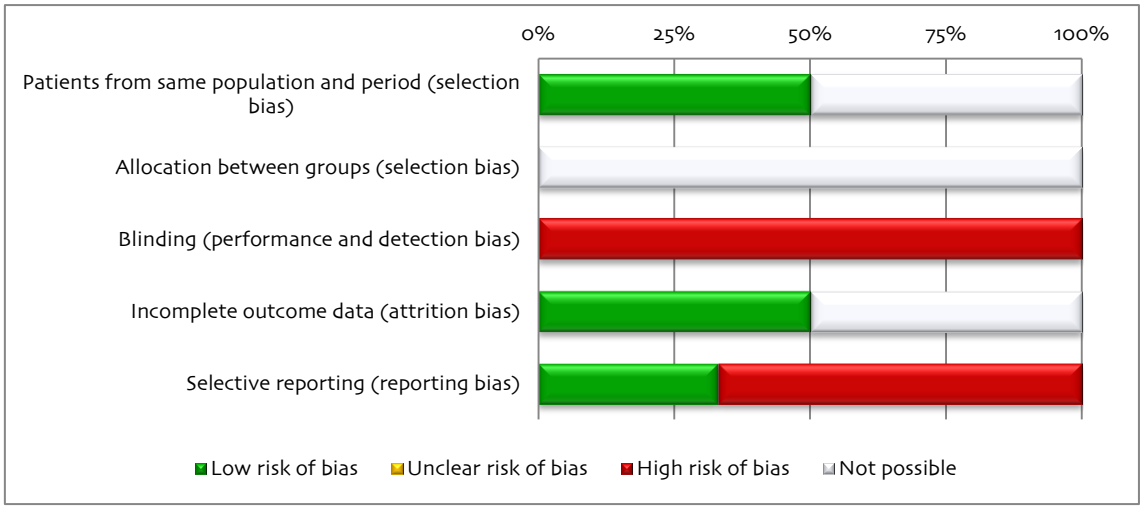

Figure 3.2-4: Risk of bias of (un)controlled trials for treatment of HD with flavonoid fraction-containing agents

Strength of evidence

Evidenzstärke insgesamt niedrig bis moderat

Overall, the strength of evidence of the efficacy and safety of flavonoid fraction-containing agents for a treatment of HD is low to moderate. Although the majority of studies were RCTs, due to several study limitations and a low number of patients in the studies, the strength of evidence was downgraded. The strength of evidence is summarised in Tables 3.2-5 for efficacy and 3.2-6 for safety.

keine Evidenz zu Vergleich mit anderen Behandlungen

There was no evidence available to compare a treatment of HD with flavonoid fraction-containing agents with other interventions, such as further lifestyle changes or further medical, office-based and surgical treatment, mentioned in Chapter 1.1.3.

Table 3.2-5: Evidence profile: Efficacy of flavonoid fraction-containing agents for treatment of HD

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy: flavonoid fraction-containing agents versus placebo							
Change of HD stage: no evidence							
HD signs (general): improved patients (in %)							
1/100	RCT	<1 we: 52 vs. 22; p=n/a 2 we: 72 vs. 67; p=N.S.	Serious limitations (-1)[215]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
HD signs (general): change from baseline (score, not stated)							
1/120	RCT	8 we: -4 vs. -1.6; p=S.S.	Serious limitations (-1)[217]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
HD signs (prolapse): improved patients (in %)							
1/379	RCT	1 we: 3.5 vs. 6.2; p=n/a	Serious limitations (-1)[217]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
HD signs (prolapse): patients change from baseline (in %)							
1/90	RCT	<1 we: -83 vs. -58; p=n/a 1 we: -100 vs. -58; p=n/a	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Moderate
HD signs (prolapse): change from baseline (score 0-10)							
1/90	RCT	<1 we: -0.33 vs. -0.67; p=n/a 1 we: -0.67 vs. -0.67; p=n/a	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Moderate
HD signs (discharge): improved patients (in %)							
1/379 1/120	RCT RCT	1 we: 5.2 vs. 6.2; p=n/a 8 we: 97 vs. 54; p=S.S.	Serious limitations (-1)[217] Serious limitations (-1)[217]	n/a (only 1 trial) n/a (only 1 trial)	Direct Direct	Imprecise data (-1)[216] Imprecise data (-1)[216]	Low Low
HD signs (discharge): patients change from baseline (in %)							
1/90	RCT	<1 we: ±0 vs. -71; p=n/a 1 we: -100 vs. -71; p=n/a	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Moderate
HD signs (incontinence): no evidence							
HD symptoms (general): improved patients (in %)							
1/100	RCT	<1 we: 74 vs. 60; p=n/a 2 we: 97 vs. 94; p=N.S.	Serious limitations (-1)[215]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
HD symptoms (general): change from baseline (score, not stated)							
1/120	RCT	8 we: -5.5 vs. -2.0; p=S.S.	Serious limitations (-1)[217]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low

[215] Unclear allocation concealment and blinding of outcome assessor.

[216] Low incidence, study/studies not powered to detect difference.

[217] Unclear random sequence generation, allocation concealment and blinding of outcome assessor.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
HD symptoms (pain): improved patients (in %)							
1/379 1/120	RCT RCT	1 we: 33 vs. 33; p=n/a 8 we: 98 vs. 47; p=S.S.	Serious limitations (-1)[217] Serious limitations (-1)[217]	n/a (only 1 trial) n/a (only 1 trial)	Direct	Imprecise data (-1)[216] Imprecise data (-1)[216]	Low Low
HD symptoms (pain): patients change from baseline (in %)							
1/90	RCT	<1 we: -75 vs. -76; p=n/a 1 we: -92 vs. -82; p=n/a	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Moderate
HD symptoms (pain): change from baseline (score 0-10)							
1/90	RCT	<1 we: -4.0 vs. -3.33; p=N.S. 1 we: -6.0 vs. -4.33; p=S.S.	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Moderate
HD symptoms (bleeding): improved patients (in %)							
1/379 1/120	RCT RCT	1 we: 16 to 68 vs. 14 to 74; p=n/a 8 we: 91 vs. 59; p=S.S.	Serious limitations (-1)[217] Serious limitations (-1)[217]	n/a (only 1 trial) n/a (only 1 trial)	Direct	Imprecise data (-1)[216] Imprecise data (-1)[216]	Low Low
HD symptoms (bleeding): patients change from baseline (in %)							
1/90	RCT	<1 we: -89 vs. -87; p=n/a 1 we: -95 vs. -82; p=n/a	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Moderate
HD symptoms (bleeding): change from baseline (score 0-10)							
1/90	RCT	<1 we: -0.8 vs. -0.6; p=S.S. 1 we: -0.9 vs. -0.7; p=S.S.	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Moderate
HD symptoms (bleeding): days of bleeding							
1/100	RCT	5 vs. 7; p=S.S.	Serious limitations (-1)[217]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
HD symptoms (itching): improved patients (in %)							
1/379 1/120	RCT RCT	1 we: 7 vs. 10; p=n/a 8 we: 86 vs. 58; p=S.S.	Serious limitations (-1)[217] Serious limitations (-1)[217]	n/a (only 1 trial) n/a (only 1 trial)	Direct	Imprecise data (-1)[216] Imprecise data (-1)[216]	Low Low
HD symptoms (itching): patients change from baseline (in %)							
1/90	RCT	<1 we: -80 vs. -58; p=n/a 1 we: -100 vs. -58; p=n/a	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Moderate
HD symptoms (itching): change from baseline (score 0-10)							
1/90	RCT	<1 we: -0.2 vs. -0.3; p=N.S. 1 we: -0.3 vs. -0.3; p=n/a	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Moderate
Quality of life: no evidence							
Recurrence rate: in %							
1/120	RCT	0.6 vs. 2.1; p=S.S.	Serious limitations (-1)[217]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Recurrence rate: days until next episode							
1/100	RCT	53 vs. 34; p=N.S.	Serious limitations (-1)[217]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
Efficacy: flavonoid fraction-containing agents after haemorrhoidectomy versus no treatment after haemorrhoidectomy							
Change of HD stage: no evidence							
HD signs: no evidence							
HD symptoms (general): no evidence							
HD symptoms (pain): change from baseline (score 0-10)							
1/112	RCT	<1 we: -3.5 vs. -1; p=S.S. 1 we: -5 vs. – 2.5; p=S.S.	No serious limitations[218]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Moderate
HD symptoms (bleeding): days of bleeding							
1/63	RCT	2.3 vs.. 2; p=N.S.	Serious limitations (-1)[217]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
HD symptoms (itching): no evidence							
Quality of life: no evidence							
Recurrence rate: in %							
1/128	RCT	1 vs. 6; p=S.S.	No serious limitations[218]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Moderate
Efficacy: flavonoid fraction-containing agents versus anti-inflammatory medication							
Change of HD stage: no evidence							
HD signs: no evidence							
HD symptoms (general): no evidence							
HD symptoms (pain): change from baseline (score 0-10)							
1/50	RCT	<1 we: -3.0 vs. -1.67; p=S.S. 1 we: -4.4 vs. -3.0; p=n/a 2 we: -4.67 vs. -5.33; p=n/a 4 we: -5.33 vs. -6.67; p=n/a 8 we: -5.33 vs. -7.33; p=N.S.	Serious limitations (-1)[219]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low

[218] Only unclear allocation concealment and blinding of personnel and participants, but random sequence generation and blinded outcome assessor.

[219] High risk of bias due to non-blinded study design.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
HD symptoms (bleeding): change from baseline (score 0-10)							
1/50	RCT	<1 we: -2.67 vs. -2.33; p=n/a 1 we: -3.33 vs. -4.33; p=n/a 2 we: -3.33 vs. -4.33; p=n/a 4 we: -3.33 vs. -6.0; p=N.S. 8 we: -3.33 vs. -6.0; p=N.S.	Serious limitations (-1)[219]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
HD symptoms (itching): change from baseline (score 0-10)							
1/50	RCT	<1 we: -2.0 vs. -2.67; p=n/a 1 we: -2.67 vs. -3.33; p=n/a 2 we: -3.0 vs. -5.0; p=n/a 4 we: -3.0 vs. -5.0; p=n/a. 8 we: -3.0 vs. -5.67; p=N.S.	Serious limitations (-1)[219]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
Quality of life: no evidence							
Recurrence rate: no evidence							
Efficacy: flavonoid fraction-containing agents (+ fibre supplements) versus office-based treatment (+ fibre supplements)							
Change of HD stage: no evidence							
HD signs: no evidence							
HD symptoms (general): change from baseline (score 0-10)							
1/126	RCT	2 we: -1.0 vs. -2.0; p=n/a 4 we: -4.0 vs. -4.0; p=n/a 24 we: -7.5 vs. -8.0; p=n/a 50 we: -7.5 vs. -7.5; p=n/a 100 we: -1.5 vs. -6.0; p=S.S.	Serious limitations (-1)[220]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
HD symptoms (pain): no evidence							
HD symptoms (bleeding): patients with stopped bleeding (in %)							
1/234[221]	RCT	<1 we: 59.6 vs.55.6; p=N.S.	Serious limitations (-1)[222]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
1/126	RCT	2 we: 40 vs. 12; p=n/a	Serious limitations (-1)[220]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
1/126	RCT	4 we: 60 vs. 20; p=n/a	Serious limitations (-1)[220]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
1/126	RCT	24 we: 80 vs. 76; p=n/a	Serious limitations (-1)[220]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
1/126	RCT	50 we: 52 vs. 72; p=n/a	Serious limitations (-1)[220]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
1/126	RCT	100 we: 32 vs. 71; p=n/a	Serious limitations (-1)[220]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
				n/a (only 1 trial)	Direct		Low

[220] High risk of bias due to random sequence generation by hospital registration number. Furthermore, blinding of participants not possible and blinding of outcome assessor unclear.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
HD symptoms (bleeding): days of bleeding							
2/330[223]	RCT	3.6 to 3.9 vs. 3.5 to 5.6; p=N.S. in both studies	Serious limitations (-1)[224]	No important inconsistency	Direct	Imprecise data (-1)[216]	Low
HD symptoms (itching): no evidence							
Quality of life: increase (in %)							
1/126	RCT	100 we: 36 vs. 68; p=n/a	Serious limitations (-1)[220]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
Recurrence rate: in %							
3/456[225]	RCTs	5 to 13 vs. 21 to 14; p=N.S. in two studies; p=S.S. in one study in favour of sclerotherapy	Serious limitations (-1)[226]	No important inconsistency	Direct	None	Moderate
Efficacy: flavonoid fraction-containing agents (+ fibre supplements) versus no treatment (+ fibre supplements)							
Change of HD stage: no evidence							
HD signs: no evidence							
HD symptoms (general): no evidence							
HD symptoms (pain): no evidence							
HD symptoms (bleeding): days of bleeding							
1/105[227]	RCT	3.9 vs. 10.6; p=N.S.	Serious limitations (-1)[217]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low
HD symptoms (itching): no evidence							
Quality of life: no evidence							
Recurrence rate: in %							
1/105[227]	RCT	5 vs. 12; p=N.S.	Serious limitations (-1)[217]	n/a (only 1 trial)	Direct	Imprecise data (-1)[216]	Low

Abbreviations: n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

[221] This study consisted of three groups, whereas one group received flavonoid fraction-containing agents and an office-based treatment and was therefore excluded from this analysis.

[222] Unclear random sequence generation and allocation concealment and unclear blinding of outcome assessor.

[223] Two studies contained of three groups, whereas in one study a group received fibre supplements alone and in the other study a group received flavonoid fraction-containing agents and an office-based treatment. Therefore, both groups were excluded from this analysis.

[224] Unclear random sequence generation, allocation concealment and blinding of outcome assessor in both studies.

[225] Both studies contained of three groups, whereas in one study a group received fibre supplements alone and in the other study a group received flavonoid fraction-containing agents and an office-based treatment. Therefore, both groups were excluded from this analysis.

[226] Unclear random sequence generation in two studies, high risk of bias due to randomisation generation by hospital registration number, unclear allocation concealment and blinding of outcome assessor in all studies.

[227] This study consisted of three groups, whereas one group received an office-based treatment and was therefore excluded from this analysis.

Table 3.2-6: Evidence profile: Safety of flavonoid fraction-containing agents for treatment of HD

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Safety: flavonoid fraction-containing agents versus placebo							
Adverse events (general): in %							
6/889	RCTs	0 to 8 vs. 0 to 6; p=N.S.	Serious limitations (-1)[228]	No important inconsistency	Direct	none	Moderate
Adverse events (treatment-related): in %							
1/100	RCT	0 vs. 0; p=N.S.	No serious limitations	n/a (only 1 trial)	Direct	Imprecise data (-1)[229]	Moderate
Safety: flavonoid fraction-containing agents after haemorrhoidectomy versus no treatment after haemorrhoidectomy							
Adverse events (general): no evidence							
2/340	RCTs	5 to 11 vs. 6 to 20; p=N.S. in one study	No serious limitations	Important inconsistency (-1)[230]	Direct	Imprecise data (-1)[229]	Low
Adverse events (treatment-related): in %							
3/403	RCTs	0 vs. n/a; p=n/a	Serious limitations (-1)[231]	No important inconsistency	Direct	Imprecise data (-1)[229]	Low
Safety: flavonoid fraction-containing agents (+ fibre supplements) versus office-based treatment (+ fibre supplements)							
Adverse events (general): in %							
2/360[232]	RCTs	0 to 2 vs. 2 to 3; p=N.S. in one study	Serious limitations (-1)[233]	No important inconsistency	Direct	Imprecise data (-1)[229]	Low
Adverse events (treatment-related): in %							
2/222[234]	RCTs	0 vs. 0-3; p=N.S. in both studies	Serious limitations (-1)[233]	No important inconsistency	Direct	Imprecise data (-1)[229]	Low
Safety: flavonoid fraction-containing agents versus anti-inflammatory medication							
no evidence							

[228] Unclear random sequence generation in 4 studies and unclear allocation concealment and blinding of outcome assessor in 5 studies.

[229] Low incidence, study/studies not powered to detect difference.

[230] Rates in control groups differed more than 10%.

[231] Unclear random sequence generation, allocation concealment and blinding of outcome assessor in one study.

[232] One study consisted of three groups, whereas one group received flavonoid fraction-containing agents and an office-based treatment and was therefore excluded from this analysis.

[233] High risk of bias in one study due to random sequence generation by hospital registration number. Furthermore, unclear random sequence generation in second study und unclear blinding of outcome assessor unclear in both studies.

[234] One study consisted of three groups, whereas one group received fibre supplements alone and was therefore excluded from this analysis.

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Safety: flavonoid fraction-containing agents (+ fibre supplements) versus no treatment (+ fibre supplements)							
Adverse events (general): no evidence							
Adverse events (treatment-related): in %							
1/105[235]	RCT	0 vs. 0; p=N.S.	Serious limitations (-1)[236]	n/a (only 1 trial)	Direct	Imprecise data (-1)[229]	Low
Safety: flavonoid fraction-containing agents							
Adverse events (general): in %							
1/50	Single-arm study	18	Serious limitations (-1)[237]	n/a (only 1 trial)	Direct	Imprecise data (-1)[229]	Low
Adverse events (treatment-related): no evidence							

Abbreviations: n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

[235] This study consisted of three groups, whereas one group received an office-based treatment and was therefore excluded from this analysis.

[236] Unclear random sequence generation, allocation concealment and blinding of outcome assessor.

[237] Unclear random sequence generation, allocation concealment and blinding of outcome assessor.

3.2.3 20 mg aescin-containing agents

keine Studien identifiziert

We could not identify any studies evaluating agents containing 20 mg of aescin for the treatment of HD. It is essential to consider that Reparil® 20 mg dragées (the only agent containing 20 mg of aescin listed in the Austrian EKO [1]) are not explicitly indicated for HD (see also Chapter 1.2.2) [24, 25].

eine Studie relevant, aber keine Angabe zu Dosis

Nevertheless, there was a study (received from the manufacturer) that seemed to be relevant, yet, the administered dosage was not stated and therefore the study was excluded.

3.2.4 50 mg aescin-containing agents

keine Studien identifiziert

We could not identify any studies evaluating capsules containing 50 mg of aescin for the treatment of HD. It is essential to consider that Venosin retard® 50 mg capsules (the only agent containing 50 mg of aescin listed in the Austrian EKO [1]) are mainly indicated for a treatment of CVI and not explicitly for HD (see also Chapter 1.2.2) [26].

3.2.5 Calcium dobesilate-containing agents

keine Studien identifiziert

Doxium® 500 mg capsules (the only calcium dobesilate containing agent listed in the Austrian EKO [1]) are not explicitly indicated for a treatment of HD (see also Chapter 1.2.2), according to the package insert [27]. We did not identify any studies evaluating 500 mg calcium dobesilate-containing capsules for the treatment of HD.

3.2.6 Comparison between capillary stabilising agents

Study characteristics

1 RCT eingeschlossen

For evaluating the efficacy and safety of capillary stabilising agents in comparison with each other for a treatment of HD, we identified 1 RCT that met our inclusion criteria.

Calciumdobesilat vs. Flavonoidfraktion

The study compares the treatment of HD by using calcium dobesilate-containing agents or flavonoid fraction (MPFF)-containing, agents [83]. The study characteristics and results are summarised in Table 3.2-7.

keine Studien zu anderen Vergleichen

There were no studies identified comparing other capillary stabilising agents with each other.

Table 3.2-7: Efficacy and safety-related outcomes of a randomised controlled trial of capillary stabilising agents versus other capillary stabilising agents for HD

Author, year, reference number	**Sarabia 2001 [83]**
Country	Venezuela
Study design	RCT
Sponsor	Laboratories Leti SAV
Intervention/product	3x 500 mg calcium dobesilate capsules (Doxium®) per day[238]
Comparator	6x 500 mg MPFF tablets (Daflon®) per day
Number of pts.	25 vs. 26
Age of patients (yrs.)	n/a
Sex (% female)	n/a
Clinical classification	n/a
Primary endpoint	n/a
Inclusion criteria	Pts. of both sexes, ages 18-75 yrs. with acute haemorrhoidal episode
Duration of Treatment (weeks)	4[239]
Follow-up (weeks)	0
Drop-outs, n (%)	n/a
Efficacy-related outcomes	
Change of HD stage	n/a
HD signs (general)	n/a
Prolapse (or swelling)	n/a
Discharge (or leakage)	n/a
Incontinence	n/a
HD symptoms (general)	*Score (0-21)[240]:* Baseline: 8.94 vs. 7.81; **p=N.S.** After <1 week: 3.16 vs. 3.26; p=n/a After 1 week 1.81 vs. 1.21; p=n/a After 2 weeks: n/a After 4 weeks: 0.74 vs. 0.61; **p=N.S.** After 8, 12; 24, 50weeks: n/a
Pain	*Score (0-3):* Baseline: 1.52 vs. 1.31; **p=N.S.** After <1 weeks: 0.67 vs. 0.66; p=n/a After 1 week: 0.53 vs. 0.25; p=n/a After 2 weeks: n/a After 4 weeks: 0.09 vs. 0.14; **p=N.S.** After 8, 12; 24, 50weeks: n/a

[238] Patients received 3 x 500 mg per day in the first 7 days, followed by 2 x 500 mg per day for the rest of the treatment phase.

[239] Study started with a placebo run-in phase of 10 days.

[240] Subjective symptoms were measured on a scale of 0-3 for pain, discharge, bleeding, edema, inflammation, pruritus and anal pressure. The score for general symptoms was 0-21.

Author, year, reference number	Sarabia 2001 [83]
Bleeding	*Score (0-3):* Baseline: 1.72 vs. 1.09; **p=N.S.** After <1 week: 0.59 vs. 0.39; p=n/a After 1 week: 0.28 vs. 0.13; p=n/a After 2 weeks: n/a After 4 weeks: 0.14 vs. 0.05; **p=N.S.** After 8, 12; 24, 50weeks: n/a
Itching (or pruritus)	*Score (0-3):* Baseline: 1.09 vs. 0.88; **p=N.S.** After <1 week: 0.38 vs. 0.46; p=n/a After 1 week: 0.28 vs. 0.28; p=n/a After 2 weeks: n/a After 4 weeks: 0.14 vs. 0.18; **p=N.S.** After 8, 12; 24, 50weeks: n/a
QoL	n/a
Recurrence rate in %	12 vs. 12; **p=N.S.**
Safety-related outcomes	
Adverse events, general in % (n) pts.	12 (3) vs. 8 (2); p=n/a (cephalgia, vertigo, colic pain vs. vertigo, severe anal pressure)
Major adverse events	n/a
Minor adverse events	n/a
Adverse events, treatment-related in % (n) pts.	n/a
Major adverse events	n/a
Minor adverse events	n/a

Abbreviations: HD = haemorrhoidal diseases; n = number (of patients); n/a = data not available; N.S. = not statistically significant; pts. = patients; QoL = quality of life; RCT = randomised controlled trial; vs. = versus; yrs. = years

Efficacy

Zusammenfassung in GRADE-Tabelle

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.2-8.

Calcium dobesilate-containing agents versus flavonoid fraction-containing agents

3x 500 mg Calciumdobesilat vs. 6x 500 mg Flavonoid-fraktion am Tag

For evaluating the efficacy of calcium dobesilate, 25 patients in the calcium dobesilate group received 500 mg capsules three times per day and the 26 patients in the flavonoid fraction group received a 500 mg tablet six times a day [83].

keine Informationen zu Alter, Geschlecht und Krankheitsstadium PatientInnen

There was no information about the age, the sex and the clinical classification of the patients. The duration of treatment was 4 weeks, whereby there was no follow-up without treatment [83]. The drop-out rate was not reported.

mehrere nicht berichtete Endpunkte

The identified study did not assess the change of the HD stage, any of the HD signs (general, prolapse, discharge and incontinence), and quality of life.

The scores (0-10) for general symptoms of CVI (pain, bleeding and itching) were reduced slightly more in the calcium dobesilate group during 4 weeks of treatment than in the flavonoid fraction group (general symptoms: -4.0 vs. -3.3, pain: -4.7 vs. -4.0, bleeding: -5.3 vs. -3.3, itching: -3.3 vs. -2.3). However, the difference between the groups was not statistically significant for any of the outcomes [83].

generelle Symptome etwas mehr mit Calciumdobesilat reduziert

Furthermore, the difference of the recurrence rate between the study groups was also not statistically significant (12 vs. 12%) [83].

Rückfallrate in Gruppen gleich

Safety

Calcium dobesilate-containing agents versus flavonoid fraction-containing agents

General adverse events occurred in 12% of the patients in the calcium dobesilate group and in 8% in the flavonoid fraction group. It was not stated whether the difference between the study groups was statistically significant or not. The most common adverse events in the calcium dobesilate group were headache (cephalgia), dizziness (vertigo) and pain. Dizziness and severe anal pressure were the most common adverse events in the flavonoid fraction group [83].

generelle unerwünschte Ereignisse: 12 % vs. 8 %

However, there was no available evidence to assess treatment-related adverse events.

keine Evidenz zu Nebenwirkungen

A summary of the effect sizes for the individual outcome indicators is presented in Table 3.2-8.

Zusammenfassung in GRADE-Tabelle

Risk of bias

The identified RCT comparing capillary stabilising agent with each other for a treatment of HD shows an unclear risk of bias for the majority of types of biases (see Figure 3.2-5). In addition there is a high risk of performance and detection bias due the discontinued double-blind design after 10 days. In summary, the risk of bias is unclear.

unklares Bias-Risiko

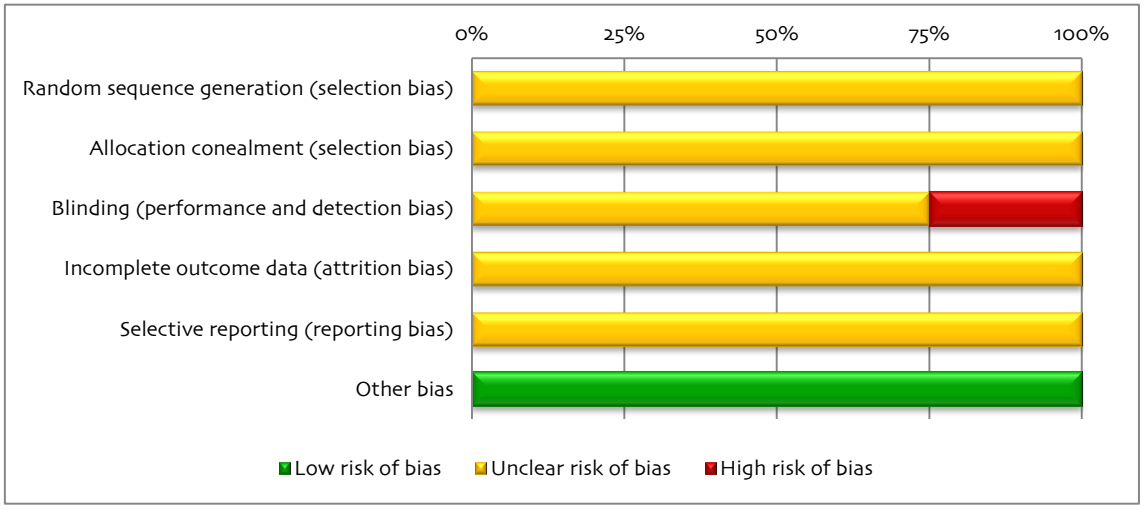

Figure 3.2-5: Risk of bias of RCTs for treatment of HD comparing capillary stabilising agents

Strength of evidence

Evidenzstärke gering

Overall, the strength of evidence of the efficacy and safety for a treatment of HD by comparing capillary stabilising agents with each other is low. Although the study was a RCT, due to several study limitations and a low number of patients, the strength of evidence was downgraded. The strength of evidence is summarised in the Table 3.2-8.

keine Evidenz zu Vergleich mit anderen kapillarstabilisierenden Mitteln

There was no evidence available to compare other capillary stabilising agents mentioned in Chapter 1.2 (e.g., oxerutin- or aescin-containing agents), with each other,

Table 3.2-8: Evidence profile: Efficacy and safety of capillary stabilising agents versus other capillary stabilising agents for treatment of HD

No of studies/ patients	Study Design	Estimate of effect	Study Limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy: calcium dobesilate-containing agents versus flavonoid-containing agents							
Change of HD stage: no evidence							
HD signs: no evidence							
HD symptoms (general): change from baseline (score 0-10)[241]							
1/51	RCT	<1 we: -2.67 vs. -2.33; p=n/a 1 we: -3.33 vs. -3.0; p=n/a 4 we: -4.0 vs. -3.33; p=N.S.	Serious limitations (-1)[242]	n/a (only 1 trial)	Direct	Imprecise data (-1)[243]	Low
HD symptoms (pain): change from baseline (score 0-10)							
1/51	RCT	<1 we: -3.0 vs. -2.33; p=n/a 1 we: -3.33 vs. -3.67; p=n/a 4 we: -4.67 vs. -4.0; p=N.S.	Serious limitations (-1)[242]	n/a (only 1 trial)	Direct	Imprecise data (-1)[243]	Low
HD symptoms (bleeding): change from baseline (score 0-10)							
1/51	RCT	<1 we: -3.67 vs. -2.33; p=n/a 1 we: -4.67 vs. -3.33; p=n/a 4 we: -5.33 vs. -3.33; p=N.S.	Serious limitations (-1)[242]	n/a (only 1 trial)	Direct	Imprecise data (-1)[243]	Low
HD symptoms (itching): change from baseline (score 0-10)							
1/51	RCT	<1 we: -2.33 vs. -1.33; p=n/a 1 we: -2.67 vs. -2.0; p=n/a 4 we: -3.33 vs. -2.33; p=N.S.	Serious limitations (-1)[242]	n/a (only 1 trial)	Direct	Imprecise data (-1)[243]	Low
Quality of life: no evidence							
Recurrence rate: in %							
1/51	RCT	12 vs. 12; p=N.S.	Serious limitations (-1)[242]	n/a (only 1 trial)	Direct	Imprecise data (-1)[243]	Low
Safety: calcium dobesilate-containing agents versus flavonoid-containing agents							
Adverse events (general): in %							
1/51	RCT	12 vs. 8; p=n/a	Serious limitations (-1)[244]	n/a (only 1 trial)	Direct	Imprecise data (-1)[245]	Low
Adverse events (treatment-related): no evidence							

Abbreviations: n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; S.S. = statistically significant; vs. = versus

[241] The stated score in study was 0-21. To make the values comparable, the results were divided by 7 to adopt them to a score of 0-3.

[242] Unclear random sequence generation and allocation concealment and high risk of bias due to discontinued blinded drug provision after 10 days.

[243] Low incidence, study/studies not powered to detect difference.

[244] Unclear random sequence generation and allocation concealment and high risk of bias due to discontinued blinded drug provision after 10 days.

[245] Low incidence, study / studies not powered to detect difference.

4 Summary and discussion

chronisch venöse Insuffizienz und Hämorrhoiden häufige Krankheiten

Chronic venous insufficiency (CVI) and haemorrhoidal diseases (HD) are very common, affecting about 20 to 40% of the Austrian population. Since these diseases occur mainly in females and older people, the prevalence in these populations is much higher [9]. Even if CVI and HD are not directly associated with mortality, both diseases severely affect the quality of life, e.g., due to pain and discomfort. Besides, HD is often tabooed in our society.

Ziel dieses Berichts: Bewertung Wirksamkeit und Sicherheit kapillarstabilisierender Mittel bei CVI und Hämorrhoiden

The aim of this systematic review was to assess the efficacy and safety of a treatment of CVI and HD with capillary stabilising agents. We focused on five different agents and seven drugs that are listed in the Austrian Code of Reimbursement (EKO) [1]:

- oxerutin-containing agents (*Venoruton® 300 mg dragées, 500 mg tablets and 1,000 mg granulate*),
- flavonoid fraction-containing agents (*Daflon® 500 mg tablets*),
- 20 mg aescin-containing agents (*Reparil® 20 mg dragées*),
- 50 mg aescin-containing agents (*Venosin retard® 50 mg capsules*) and
- calcium dobesilate-containing agents (*Doxium® 500 mg capsules*).

4.1 Strength of evidence and clinical relevance of outcomes

insgesamt 56 Studien mit 21.606 PatientInnen eingeschlossen

In total, we selected 56 studies with 21,606 patients for evaluating either efficacy and safety or safety only of capillary stabilising agents for CVI or HD. The majority of studies compared capillary stabilising agents with placebo, in much fewer cases other interventions (e.g., compression stockings for CVI and surgery for HD) were used as comparators. We could not identify any evidence where a CVI treatment with capillary stabilising agents was compared with lifestyle changes, medical or surgical treatment. In addition, there was no evidence available to assess capillary stabilising agents for a treatment of HD compared to lifestyle changes and surgical treatment options.

Evidenzstärke gering:

Overall, the strength of evidence is low. This is due to a number of reasons:

neben medikamentöser Behandlung auch andere Behandlungen

On one hand, it has to be mentioned as positive that many of the studies started with a wash-out or placebo period before the treatment to exclude any effects of previous treatments. On the other hand, however, there were many studies that allowed patients with CVI to wear compression stockings and patients with HD had an additional diet in several cases. Thus, we do not know who received additional interventions. Consequently, it is also unknown whether positive effects in the treatment groups were caused by capillary stabilising agents or by the additional interventions.

vorrangig alte Studien

A major quality issue of the studies is related to their age (the oldest study is from 1987 [32]). Because today's standards of study designs and transparency in reporting research results did not exist 30 years ago, it is challenging to assess the risk of bias and the strength of evidence with today's criteria. Most of the studies did not mention the randomisation process, the allocation concealment or the blinding of personnel and participants in detail. Furthermore, we were able to identify a study protocol for only a few studies. This intro-

duces a high risk of bias. Interestingly, the RCT with the lowest risk of bias [62] has shown no benefit of a treatment of CVI with capillary stabilising agents. Hence, it seems most likely that the study results are biased in favour of the treatment.

einige Outcome-Parameter veraltet

Moreover, some of the outcome indicators that have been used in the studies do not match today's standards. Leg volume, for example, which has often been used as an indicator for oedema in the studies, can be regarded as obsolete according to clinical experts. This is also true for scores that use a scaling from 1-3, which have often been used as indicators for CVI or HD symptoms (e.g., pain).

kleine Fallzahlen, kurze Studiendauern

Further weaknesses of the identified studies are the small number of patients, the relatively short treatment durations (especially for CVI) and, particularly, hardly any follow-up after treatment. This is a severe limitation, since the few studies with a follow-up without treatment have shown that differences between study groups (thus, the benefit of treatment over the comparator) decreased dramatically, if there was a benefit at all.

eingeschlossene systematische Reviews mit Schwächen

Moreover, the identified systematic reviews [10, 58] summarised outcomes across different time periods; as a result, treatment effects after, e.g., 1, 2 or 3 months of treatment cannot be distinguished between. Furthermore, several outcomes, e.g., leg circumference, were reported without presenting the change of the leg volume from baseline in one of the systematic reviews [10]. Therefore, the results do not allow any conclusion on the efficacy.

klinische Relevanz einiger Endpunkte nicht gegeben

Overall, the clinical relevance of any improvement presented in the previous chapters is marginal and in many cases even negligible (see Chapter 2.7.3). For example, in terms of score changes for pain, itching, etc., changes below 5 on a scale from 0-10 have been judged by two experts (both are angiologists) as clinically irrelevant. Hence, for many of the outcomes measured on a scale, neither the changes from baseline in the individual study groups, nor the differences between the study groups fulfil the criterion of clinical relevance. Hence, despite statistically significant changes or differences between the study groups in many cases, the improvements are too marginal to be regarded as clinically relevant.

teilweise hohe Heterogenität in Studien mit zusätzlichen Kompressionsstrümpfen

In addition, four meta-analyses for a treatment of CVI have shown a high heterogeneity (with $I^2>80\%$). The high heterogeneity occurred only in studies where patients were allowed to wear additional compression stockings. Therefore, it seems likely that some studies measured a different effect of the capillary stabilising agents compared to placebo when additional compression stockings were worn.

Behandlungsoptionen für CVI und Hämorrhoiden setzen an Linderung der Symptome an

The pathophysiology of the diseases is mostly unclear. As a result, the majority of treatment options focus on the reduction of signs and symptoms of CVI and HD. Not surprising, in the case of capillary stabilising agents, the benefit from medication (if there was one at all) decreased or disappeared as soon as treatment was stopped. Therefore, a benefit can only be expected during medication.

meiste Studien vergleichen mit Placebo

The majority of studies compared capillary stabilising agents with placebo. Hence, we know little about the efficacy of the drugs compared to interventions that are relevant in daily practice.

Furthermore, because of the selective study population and a strongly protocol-driven treatment, the results from a clinical trial cannot automatically be transferred to routine clinical practice where patient characteristics and treatment processes may be different. In this case, however, the characteristics of the study populations seem to be similar to a routine population in terms of age, gender and severity of disease. Moreover, compliance and adherence may also be similar in routine care because the drugs do not have severe side effects.

Studienpopulationen geben durchaus „reale Welt" wieder

Taking these limitations into account, the results on efficacy and safety of capillary stabilising agents can be summarised in the following chapter.

Zusammenfassung Ergebnisse folgend

4.2 Summary of evidence

This chapter will summarise the results from the third chapter for each indication.

Kapitel fasst Ergebnisse zusammen

Although the strength of evidence for safety was mostly low, a treatment of CVI and HD with capillary stabilising agents does not seem to be associated with severe adverse events or side effects.

kapillarstabilisierende Mittel relativ sicher

The efficacy results of comparing the treatment of CVI and HD with capillary stabilising to other treatment options (defined in Chapter 1.1) or with each other are presented in the Tables 4.2-1 and 4.2-2 (one for each indication).

Zusammenfassung in Tabellenform

The conclusions in the tables are based on the summarised estimates of effect from the studies, considering, however, study limitations and associated potential risks of bias as well as further limiting issues as presented in the GRADE tables in Chapter 3. Additionally, the clinical relevance of the effect estimates as described in Chapter 2.7.3 has been taken into account.

Zusammenfassung berücksichtigt Bias-Risiko, Evidenzstärke + klinische Relevanz der Ergebnisse

Overall, from the study results and their individual strength of evidence, we are not able to draw any robust conclusions.

insgesamt schwache Evidenz

From the studies on oxerutin-containing agents (*Venoruton® 300 mg dragées, 500 mg tablets and 1,000 mg granulate*) we can conclude that compression stockings could probably reduce oedema – measured as change in leg volume in ml – more than oxerutin-containing agents. However, leg volume is an outdated surrogate parameter and, therefore, a very weak outcome to draw a conclusion for assessing the overall efficacy.

eventuell mehr Ödemreduktion mit Kompressionsstrümpfen als mit Oxerutin

Furthermore, if patients take oxerutin-containing agents in addition to wearing compression stockings, they may probably experience a slight improvement of CVI signs (oedema, yet measured with an obsolete indicator) and some patients may have fewer single symptoms (heaviness) compared to compression stockings in combination with placebo. In addition, oxerutin-containing agents reduced the severity of signs and symptoms of HD, yet whether this improvement is statistically significant is unknown.

Oxerutin + Kompressionsstrümpfe reduzierten etwas Anzeichen und Symptome

Flavonoid fraction-containing agents (*Daflon® 500 mg tablets*) in addition to wearing compression stockings could probably improve CVI signs slightly (especially ulcer) compared to wearing compression stockings only or to compression stockings combined with placebo. However, we are unable to draw a conclusion on whether patients benefit from taking flavonoid fraction-containing agents after surgery compared to no treatment after surgery.

Flavonoidfraktion hilft eventuell etwas um Anzeichen der CVI zu verbessern

Behandlung Hämorrhoiden mit Flavonoidfraktion sowie Entzündunghemmer ähnlich (in)effektiv

Treating HD with flavonoid fraction-containing agents does not seem more effective (regarding symptoms reduction) than with anti-inflammatory medication. Compared to office-based treatment, flavonoid fraction-containing agents could probably be more effective during medication. Yet, after medication is stopped, office-based treatments could eventually be more effective. Compared to placebo, a treatment of HD with flavonoid fraction-containing agents seems to improve the signs and symptoms in some patients. After surgery, flavonoid fraction-containing agents seem to reduce the severity of pain and the recurrence rate slightly better than no treatment. We are unable to draw a conclusion on whether flavonoid fraction-containing agents have an additional benefit when combined with fibre supplements, compared to no treatment (and fibre supplements).

Wirksamkeit von 20 mg Aescin unbekannt

We could not draw any conclusion regarding the efficacy of 20 mg aescin-containing agents (*Reparil® 20 mg dragées*) for the treatment of CVI and HD, since we could not identify any randomised controlled trials.

50 mg Aescin + Kompressionsstrümpfe eventuell wirksam bei CVI

A treatment with 50 mg aescin-containing agents (*Venosin® retard 50 mg capsules*), in addition to compression stockings, could probably improve some signs (oedema) and some single symptoms of CVI (pain) in some patients, compared to compression stockings with placebo. However, we are unable to draw a conclusion regarding a treatment of HD with 50 mg aescin.

Calciumdobesilat + Kompressionsstrümpfe eventuell wirksam bei CVI

When added to compression stockings, calcium dobesilate (*Doxium® 500 mg capsules)* seems to slightly improve the symptoms of CVI, compared to placebo (and compression therapy). However, we are unable to draw a conclusion on the efficacy of for HD, since the drug is not explicitly indicated for HD.

nicht klar, welches Medikament am besten wirkt

The comparison of capillary stabilising agents has shown that oxerutin-containing agents for the treatment of CVI are probably not more effective than 50 mg aescin- or flavonoid fraction-containing agents. Moreover, the reduction of HD symptoms and the recurrence rate seems to be equal with either calcium dobesilate- or flavonoid fraction-containing agents. We do not know whether one agent is generally superior to others.

medikamentöse Behandlung von CVI und Hämorrhoiden wäre attraktive Alternative

Overall, an effective medical treatment of CVI or HD with capillary stabilising agents would be an attractive alternative, since all further treatment options show several weaknesses. For example, compression stockings may be effective for the treatment of CVI, but they may be inappropriate in several situations, such as application difficulty (due to frailty or arthritis), physical constraints (e.g., limb obesity or contact dermatitis), and coexisting arterial insufficiency. Many patients who are eligible for wearing stockings abandon them due to complaints about tightness and warmth. In the case of HD, surgical and office-based treatments are associated with a higher risk of adverse events. In addition, a long-term application of topical agents and antibiotics should be also discouraged because they may induce erythema from local allergic reactions due to compromise of the dermal barrier.

gefundene Evidenz zu schwach, um Wirksamkeit nachzuweisen

However, the identified evidence is not strong enough to conclude that a treatment of HD and CVI with any of the mentioned capillary stabilising agents without additional therapy (e.g., compression therapy for CVI or diet for HD) is effective.

Table 4.2-1: Summary of the efficacy of capillary stabilising agents for treatment of CVI

Agent	Comparator	Strength of evidence	Conclusion
Oxerutin (*Venoruton®*)	Lifestyle changes	No evidence	-
	Local treatment	Low	Compression stockings could probably reduce oedema (leg volume in ml) more than oxerutin-containing agents. However, leg volume is an obsolete surrogate parameter and, therefore, a very weak outcome to draw a conclusion for efficacy as a whole.
	Medical treatment	No evidence	-
	Surgical treatment	No evidence	-
	Placebo/ no treatment	Low	Added to compression stockings, oxerutin-containing agents could probably be of additional benefit by slightly reducing signs (oedema) and symptoms (heaviness) of CVI compared to placebo and compression stockings.
Flavonoid fraction (*Daflon®*)	Lifestyle changes	No evidence	-
	Local treatment	Low	Added to compression stockings, flavonoid fraction-containing agents could probably support a slight improvement of CVI signs (especially ulcer) compared to compression stockings only.
	Medical treatment	No evidence	-
	Surgical treatment	No evidence	-
	Placebo/ no treatment	Low	Added to compression stockings, flavonoid fraction-containing agents could probably improve CVI signs (especially ulcer healing) slightly, compared to placebo and compression stockings. We are unable to draw a conclusion on whether flavonoid fraction-containing agents after surgery have an additional benefit on CVI signs and symptoms, compared to no treatment after surgery.
20 mg aescin (*Reparil®*)	All	No evidence	We are unable to draw a conclusion, since we could not identify any RCT.
50 mg aescin (*Venosin retard®*)	Lifestyle changes	No evidence	-
	Local treatment	Low	When compared to compression stockings only, 50 mg aescin with additional compression stockings could be similar (in)effective.
	Medical treatment	No evidence	-
	Surgical treatment	No evidence	-
	Placebo/no treatment	Low	When supported by compression stockings, 50 mg aescin could have an additional benefit on signs (oedema) and symptoms of CVI, especially with respect to pain reduction, compared to placebo (with compression therapy).
Calcium dobesilate (*Doxium®*)	Lifestyle changes	No evidence	-
	Local treatment	No evidence	-
	Medical treatment	No evidence	-
	Surgical treatment	No evidence	-
	Placebo/no treatment	Moderate	If added to compression stockings, calcium dobesilate seems to slightly improve some symptoms of CVI (e.g., pain and cramps), when compared to placebo (with compression therapy).
Capillary stabilising agents	Capillary stabilising agents	Low	Oxerutin-containing agents for the treatment of CVI are probably not much more effective than 50 mg aescin. We are unable to draw a conclusion on whether another agent is superior to others.

Table 4.2-2: Summary of the efficacy of capillary stabilising agents for treatment of HD

Agent	Comparator	Strength of evidence	Conclusion
Oxerutin (*Venoruton®*)	Lifestyle changes	No evidence	-
	Medical treatment	No evidence	-
	Local/office-based treatment	No evidence	-
	Surgical treatment	No evidence	-
	Placebo/ no treatment	Low	Oxerutin-containing agents could probably reduce the severity of signs and symptoms of HD compared to placebo, yet whether the differences are statistically significant is unknown.
Flavonoid fraction (*Daflon®*)	Lifestyle changes	No evidence	-
	Medical treatment	Low	The treatment of HD with flavonoid fraction-containing agents does not seem more effective (regarding symptoms reduction) than treatment with anti-inflammatory medication.
	Local/office-based treatment	Low	During medication, flavonoid fraction-containing agents could probably equally effective than office-based treatment, yet after medication is stopped, office-based treatments could eventually be more effective.
	Surgical treatment	No evidence	-
	Placebo/ no treatment	Low-moderate	A treatment of HD with flavonoid fraction-containing agents seems to improve the signs and symptoms of the disease, compared to placebo. However, the conclusion is limited. After surgery, flavonoid fraction-containing agents may slightly more reduce the severity of pain and the recurrence rate than no treatment. We are unable to draw a conclusion on whether flavonoid-containing agents have an additional benefit when combined with fibre supplements, compared to no treatment (and fibre supplements).
20 mg aescin (*Reparil®*)	All	No evidence	We are unable to draw a conclusion. However, *Reparil® 20 mg Dragées* (the only 20 mg aescin-containing agent listed in the Austrian EKO) are not explicitly indicated for HD.
50 mg aescin (*Venosin retard®*)	All	No evidence	We are unable to draw a conclusion. However, *Venosin® retard 50 mg capsules* (the only 50 mg aescin-containing agent listed in the Austrian EKO) are not explicitly indicated for HD.
Calcium dobesilate (*Doxium®*)	All	No evidence	We are unable to draw a conclusion. However, *Doxium® 500 mg capsules* (the only calcium dobesilate-containing agent listed in the Austrian EKO) are not explicitly indicated for HD
Capillary stabilising agents	Capillary stabilising agents	Low	The reduction of HD symptoms and the recurrence rate will probably be similar with calcium dobesilate and flavonoid fraction-containing agents. We do not know whether another agent is superior to others

4.3 Limitations

Naturally, our systematic review has several weaknesses:

Schwächen Review:

First of all, we accepted surrogate parameters like leg volume or ankle and calf circumferences as indicators for oedema, since the measurement of oedema is clinically relevant, yet it cannot be measured directly. Although these parameters have been measured frequently in the studies, their value for drawing conclusions on the drugs' efficacy is marginal.

Surrogatparameter akzeptiert

Besides, the majority of studies measured the signs and symptoms of CVI and HD by a score on a scale of 0-3 or 0-100. However, as stated earlier (Chapter 2.7), a measurement on a scale of, e.g., 0-3 is often associated with imprecise results. Where possible, we adapted the scores to a scale of 0-10 to make the results comparable, yet it is uncertain whether the results from a primary data collection on a 0-10 score would be identical.

Scores der Studien adaptiert zu Skala von 0-10

We excluded many studies due to missing information on dosage forms or due to dose deliveries that did not meet our inclusion criteria (e.g., tablets instead of capsules). Additionally, we excluded studies in which patients received the oxerutin-containing agents as an aqueous solution and not as granulate. The reason was to assess only those capillary stabilising agents that are listed in the Austrian EKO. Hence, the results cannot be transferred to other products.

einige Studien ausgeschlossen, da Dosis nicht in EKO

Another restriction of our systematic review is that for oxerutin-containing agents we did not present the results for each available dosage form separately. However, since the quality of evidence of the individual studies is low, we would not be able to draw a meaningful conclusion with respect to individual dosages.

keine getrennte Betrachtung der Oxerutin-Dosen

Regarding the meta-analyses, it was not possible to perform a sensitivity analysis to verify the results for their robustness, since there were not enough studies with strong evidence (minimum moderate strength of evidence) for one individual outcome.

Sensitivitätsanalyse nicht möglich

In addition, we were not able to identify the most effective capillary stabilising agent for a treatment of CVI or HD, since no evidence was available for some agents and indications. Moreover, the quality of evidence did not allow any quantitative comparative efficacy analysis (such as a network meta-analysis).

nicht möglich wirksamstes kapillarstabilisierendes Mittel zu identifizieren

5 Conclusion

endgültige Wirksamkeit kapillarstabilisierender Mittel nicht bewiesen

Since the strength of the evidence of nearly all identified studies is low, we cannot draw a final conclusion on the efficacy of capillary stabilising agents for the treatment of CVI and HD.

Doxium, Venoruton, Daflon + Venosin retard wirken eventuell

For *Doxium® 500 mg capsules* (for CVI only), *Venoruton®* (for CVI only), *Daflon® 500 mg tablets* (for CVI and HD) and *Venosin retard® 50 mg capsules* (for CVI only) the evidence shows a tendency for a benefit, yet the results are very uncertain.

kaum Evidenz zu Reparil

For *Reparil® 20 mg dragées* we could not identify any efficacy-assessing evidence. Therefore, it is unclear whether the drug is more effective than other alternatives.

wenn Wirkung, dann nur während Medikamentennahme

In any case, there does not seem to be any sustaining benefit for CVI after treatment has been stopped, since the drugs do not treat the causes of CVI, but only the symptoms and signs. That means treatment will have to last for very long time periods in the individual patients.

kaum Nebenwirkungen kapillarstabilisierender Mittel

Even though the quality of evidence of safety-related outcomes is low as well, it is very likely that the drugs do not cause any major adverse events or side effects.

vor Hintergrund jährlicher Ausgaben von 20 Mio. Euro:

It is debatable whether studies from the 1980s can be sensibly assessed with today's quality criteria. However, it is also questionable to continue to publicly spend 20 million Euros annually for capillary stabilising agents based on this relatively weak and uncertain evidence.

stärkere Evidenz unabdingbar, um solidarische Finanzierung kapillarstabilisierender Mittel zu rechtfertigen

Future reimbursement of the drugs should be conditional on the generation of robust evidence concerning patients' benefits. This needs to be provided by the manufacturers. Cooperation with public payers in terms of study design (particularly concerning the selection of outcome parameters) is recommended. The studies need to have a sufficient number of participants and they need to comply with today's standards in study design and transparency.

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[83] Sarabia, M., et al., *Calcium dobesilate versus purified flavonoid fraction of diosmin in the treatment of hemorrhoidal crises: A randomized, controlled study with an initial double-blind, double-dummy period.*Current Therapeutic Research – Clinical and Experimental, 2001. **62**(7): p. 524-529.

7 Appendix

Search strategy for Cochrane

171 Hits

ID	Search
#1	MeSH descriptor: [Venous Insufficiency] explode all trees
#2	venous near insufficienc* (Word variations have been searched)
#3	MeSH descriptor: [Hemorrhoids] explode all trees
#4	H*emorrhoid* (Word variations have been searched)
#5	piles (Word variations have been searched)
#6	#1 or #2 or #3 or #4 or #5
#7	Vasoprotect* (Word variations have been searched)
#8	Oxerutin* (Word variations have been searched)
#9	troxerutin* (Word variations have been searched)
#10	monoxerutin* (Word variations have been searched)
#11	Venoruton* (Word variations have been searched)
#12	Flavonoidf* (Word variations have been searched)
#13	flavonoid fraction* (Word variations have been searched)
#14	Daflon* (Word variations have been searched)
#15	Aescin* (Word variations have been searched)
#16	MeSH descriptor: [Escin] explode all trees
#17	Escin* (Word variations have been searched)
#18	Reparil* (Word variations have been searched)
#19	Venosin* (Word variations have been searched)
#20	Calciumdobesilat* (Word variations have been searched)
#21	MeSH descriptor: [Calcium Dobesilate] explode all trees
#22	calcium dobesilat* (Word variations have been searched)
#23	dobesilate calcium* (Word variations have been searched)
#24	Doxium* (Word variations have been searched)
#25	#7 or #8 or #9 or #10 or #11 or #13 or #14 or #15 or #16 or #17 or #18 or #20 or #21 or #22 or #23 or #24
#26	#6 and #25

Search strategy for CRD (Centre for Research and Dissemination)

13 Hits

1	(Vasoprotect*)
2	(Oxerutin*)
3	(troxerutin*)
4	(monoxerutin*)
5	(Venoruton*)
6	(Flavonoidf*)
7	(flavonoid fraction*)
8	(Daflon*)
9	(Aescin*)
10	MeSH DESCRIPTOR Escin EXPLODE ALL TREES
11	(Escin*)
12	(Reparil*)
13	(Venosin*)
14	(Calciumdobesilat*)
15	MeSH DESCRIPTOR Calcium Dobesilate EXPLODE ALL TREES
16	(calcium dobesilat*)
17	(dobesilate calcium*)
18	(Doxium*)
19	#2 OR #3 OR #7 OR #8 OR #10 OR #11 OR #15 OR #16

Search strategy for Embase

No.	Query Results	Results	Date
#39	'clinical article'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'double blind procedure'/de OR 'evidence based medicine'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'multicenter study'/de OR 'practice guideline'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de AND ('vein insufficiency'/exp OR 'venous insufficiency' OR 'venous insufficiencies' OR 'hemorrhoid'/exp OR hemorrhoid* OR haemorrhoid* OR piles) AND (vasoprotect* OR oxerutin* OR 'troxerutin'/exp OR troxerutin* OR 'monoxerutin'/exp OR monoxerutin* OR venoruton* OR flavonoidf* OR 'flavonoid fraction' OR 'flavonoid fractions' OR 'daflon'/exp OR daflon* OR 'escin'/exp OR aescin* OR escin* OR reparil* OR venosin* OR 'dobesilate calcium'/exp OR calciumdobesilat* OR 'calcium dobesilate' OR 'dobesilate calcium' OR doxium*) AND 'human'/de OR ('vein insufficiency'/exp OR 'venous insufficiency' OR 'venous insufficiencies' OR 'hemorrhoid'/exp OR hemorrhoid* OR haemorrhoid* OR piles AND (vasoprotect* OR oxerutin* OR 'troxerutin'/exp OR troxerutin* OR 'monoxerutin'/exp OR monoxerutin* OR venoruton* OR flavonoidf* OR 'flavonoid fraction' OR 'flavonoid fractions' OR 'daflon'/exp OR daflon* OR 'escin'/exp OR aescin* OR escin* OR reparil* OR venosin* OR 'dobesilate calcium'/exp OR calciumdobesilat* OR 'calcium dobesilate' OR 'dobesilate calcium' OR doxium*) AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim))	365	20 May 2014
#38	'vein insufficiency'/exp OR 'venous insufficiency' OR 'venous insufficiencies' OR 'hemorrhoid'/exp OR hemorrhoid* OR haemorrhoid* OR piles AND (vasoprotect* OR oxerutin* OR 'troxerutin'/exp OR troxerutin* OR 'monoxerutin'/exp OR monoxerutin* OR venoruton* OR flavonoidf* OR 'flavonoid fraction' OR 'flavonoid fractions' OR 'daflon'/exp OR daflon* OR 'escin'/exp OR aescin* OR escin* OR reparil* OR venosin* OR 'dobesilate calcium'/exp OR calciumdobesilat* OR 'calcium dobesilate' OR 'dobesilate calcium' OR doxium*) AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim)	161	20 May 2014
#37	'clinical article'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'double blind procedure'/de OR 'evidence based medicine'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'multicenter study'/de OR 'practice guideline'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de AND ('vein insufficiency'/exp OR 'venous insufficiency' OR 'venous insufficiencies' OR 'hemorrhoid'/exp OR hemorrhoid* OR haemorrhoid* OR piles) AND (vasoprotect* OR oxerutin* OR 'troxerutin'/exp OR troxerutin* OR 'monoxerutin'/exp OR monoxerutin* OR venoruton* OR flavonoidf* OR 'flavonoid fraction' OR 'flavonoid fractions' OR 'daflon'/exp OR daflon* OR 'escin'/exp OR aescin* OR escin* OR reparil* OR venosin* OR 'dobesilate calcium'/exp OR calciumdobesilat* OR 'calcium dobesilate' OR 'dobesilate calcium' OR doxium*) AND 'human'/de	364	20 May 2014
#36	'vein insufficiency'/exp OR 'venous insufficiency' OR 'venous insufficiencies' OR 'hemorrhoid'/exp OR hemorrhoid* OR haemorrhoid* OR piles AND (vasoprotect* OR oxerutin* OR 'troxerutin'/exp OR troxerutin* OR 'monoxerutin'/exp OR monoxerutin* OR venoruton* OR flavonoidf* OR 'flavonoid fraction' OR 'flavonoid fractions' OR 'daflon'/exp OR daflon* OR 'escin'/exp OR aescin* OR escin* OR reparil* OR venosin* OR 'dobesilate calcium'/exp OR calciumdobesilat* OR 'calcium dobesilate' OR 'dobesilate calcium' OR doxium*) AND 'human'/de	543	20 May 2014
#35	'vein insufficiency'/exp OR 'venous insufficiency' OR 'venous insufficiencies' OR 'hemorrhoid'/exp OR hemorrhoid* OR haemorrhoid* OR piles AND (vasoprotect* OR oxerutin* OR 'troxerutin'/exp OR troxerutin* OR 'monoxerutin'/exp OR monoxerutin* OR venoruton* OR flavonoidf* OR 'flavonoid fraction' OR 'flavonoid fractions' OR 'daflon'/exp OR daflon* OR 'escin'/exp OR aescin* OR escin* OR reparil* OR venosin* OR 'dobesilate calcium'/exp OR calciumdobesilat* OR 'calcium dobesilate' OR 'dobesilate calcium' OR doxium*) AND ('clinical article'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de	432	20 May 2014

	OR 'controlled study'/de OR 'double blind procedure'/de OR 'evidence based medicine'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'multicenter study'/de OR 'practice guideline'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de)		
#34	'vein insufficiency'/exp OR 'venous insufficiency' OR 'venous insufficiencies' OR 'hemorrhoid'/exp OR hemorrhoid* OR haemorrhoid* OR piles AND (vasoprotect* OR oxerutin* OR 'troxerutin'/exp OR troxerutin* OR 'monoxerutin'/exp OR monoxerutin* OR venoruton* OR flavonoidf* OR 'flavonoid fraction' OR 'flavonoid fractions' OR 'daflon'/exp OR daflon* OR 'escin'/exp OR aescin* OR escin* OR reparil* OR venosin* OR 'dobesilate calcium'/exp OR calciumdobesilat* OR 'calcium dobesilate' OR	675	20 May 2014
#33	vasoprotect* OR oxerutin* OR 'troxerutin'/exp OR troxerutin* OR 'monoxerutin'/exp OR monoxerutin* OR venoruton* OR flavonoidf* OR 'flavonoid fraction' OR 'flavonoid fractions' OR 'daflon'/exp OR daflon* OR 'escin'/exp OR aescin* OR escin* OR reparil* OR venosin* OR 'dobesilate calcium'/exp OR calciumdobesilat* OR 'calcium dobesilate' OR 'dobesilate calcium' OR doxium*	4,516	20 May 2014
#32	doxium*	177	20 May 2014
#31	'dobesilate calciums'		20 May 2014
#30	'dobesilate calcium'	562	20 May 2014
#29	'calcium dobesilates'		20 May 2014
#28	'calcium dobesilate'	295	20 May 2014
#27	calciumdobesilat*	30	20 May 2014
#26	'dobesilate calcium'/exp	560	20 May 2014
#25	venosin*	5	20 May 2014
#24	reparil*	181	20 May 2014
#23	escin*	1,305	20 May 2014
#22	aescin*	329	20 May 2014
#21	'escin'/exp	877	20 May 2014
#20	daflon*	509	20 May 2014
#19	'daflon'/exp	440	20 May 2014
#18	'flavonoid fractions'	46	20 May 2014
#17	'flavonoid fraction'	316	20 May 2014
#16	flavonoidf*	4	20 May 2014
#15	venoruton*	326	20 May 2014
#14	monoxerutin*	599	20 May 2014
#13	'monoxerutin'/exp	596	20 May 2014
#12	troxerutin*	603	20 May 2014
#11	'troxerutin'/exp	586	20 May 2014
#10	oxerutin*	44	20 May 2014
#9	vasoprotect*	919	20 May 2014
#8	'vein insufficiency'/exp OR 'venous insufficiency' OR 'venous insufficiencies' OR 'hemorrhoid'/exp OR hemorrhoid* OR haemorrhoid* OR piles	20,202	20 May 2014
#7	piles	1,336	20 May 2014
#6	haemorrhoid*	2,094	20 May 2014
#5	hemorrhoid*	8,935	20 May 2014
#4	'hemorrhoid'/exp	7,413	20 May 2014
#3	'venous insufficiencies'	16	20 May 2014
#2	'venous insufficiency'	5,789	20 May 2014
#1	'vein insufficiency'/exp	8,298	20 May 2014

Search strategy for Medline

1	exp Venous Insufficiency/(5885)
2	venous insufficienc*.mp. (6785)
3	exp Hemorrhoids/(4595)
4	H?emorrhoid*.mp. (6005)
5	piles.mp. (885)
6	1 or 2 or 3 or 4 or 5 (14047)
7	Vasoprotect*.mp. (637)
8	Oxerutin*.mp. (23)
9	troxerutin*.mp. (210)
10	monoxerutin*.mp. (0)
11	Venoruton*.mp. (109)
12	Flavonoidf*.mp. (1)
13	flavonoid fraction*.mp. (224)
14	Daflon*.mp. (130)
15	Aescin*.mp. (204)
16	exp Escin/(416)
17	Escin*.mp. (641)
18	Reparil*.mp. (51)
19	Venosin*.mp. (3)
20	Calciumdobesilat*.mp. (13)
21	exp Calcium Dobesilate/(210)
22	calcium dobesilat*.mp. (246)
23	dobesilate calcium*.mp. (4)
24	Doxium*.mp. (44)
25	7 or 8 or 9 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (2208)
26	6 and 25 (268)
27	remove duplicates from 26 (267)