BIBLIOGRAFIA -> NEWS SIF aprile 2023
(a cura di Augusto Farina)

- Robert V O'Toole , Deborah M Stein , Nathan N O'Hara, Katherine P Frey, Tara J Taylor, Daniel O Scharfstein Anthony R Carlini, Kuladeep Sudini, Yasmin Degani, Gerard P Slobogean, Elliott R Haut, William Obremskey, Reza Firoozabadi , Michael J Bosse , Samuel Z Goldhaber, Debra Marvel, Renan L. Castillo. **Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture Major Extremity Trauma Research Consortium (METRC).** Engl J Med. 2023 Jan 19;388(3):203-213.doi: 10.1056/NEJMoa2205973

Background: Clinical guidelines recommend low-molecular-weight heparin for thromboprophylaxis in patients with fractures, but trials of its effectiveness as compared with Aspirin are lacking
Methods: In this pragmatic, multicenter, randomized, noninferiority trial, we enrolled patients 18 years of age or older who had a fracture of an extremity (anywhere from hip to midfoot or shoulder to wrist) that had been treated operatively or who had any pelvic or acetabular fracture. Patients were randomly assigned to receive low-molecular-weight heparin (enoxaparin) at a dose of 30 mg twice daily or aspirin at a dose of 81 mg twice daily while they were in the hospital. After hospital discharge, the patients continued to receive thromboprophylaxis according to the clinical protocols of each hospital. The primary outcome was death from any cause at 90 days. Secondary outcomes were nonfatal pulmonary embolism, deep-vein thrombosis, and bleeding complications.
Results: A total of 12,211 patients were randomly assigned to receive aspirin (6101 patients) or low-molecular-weight heparin (6110 patients). Patients had a mean (±SD) age of 44.6±17.8 years, 0.7% had a history of venous thromboembolism, and 2.5% had a history of cancer. Patients received a mean of 8.8±10.6 in-hospital thromboprophylaxis doses and were prescribed a median 21-day supply of thromboprophylaxis at discharge. Death occurred in 47 patients (0.78%) in the aspirin group and in 45 patients (0.73%) in the low-molecular-weight-heparin group (difference, 0.05 percentage points; 96.2% confidence interval, -0.27 to 0.38; P<0.001 for a noninferiority margin of 0.75 percentage points). Deep-vein thrombosis occurred in 2.51% of patients in the aspirin group and 1.71% in the low-molecular-weight-heparin group (difference, 0.80 percentage points; 95% CI, 0.28 to 1.31). The incidence of pulmonary embolism (1.49% in each group), bleeding complications, and other serious adverse events were similar in the two groups.
Conclusions: In patients with extremity fractures that had been treated operatively or with any pelvic or acetabular fracture, thromboprophylaxis with aspirin was noninferior to low-molecular-weight heparin in preventing death and was associated with low incidences of deep-vein thrombosis and pulmonary embolism and low 90-day mortality. (Funded by the Patient-Centered Outcomes Research Institute; PREVENT CLOT ClinicalTrials.gov number, NCT02984384.).

- Ricardo de Ávila Oliveira, Rachel Riera, Vladimir Vasconcelos, Jose Cc Baptista-Silva. **Injection sclerotherapy for Varicose Veins.** Cochrane Database Syst Rev 2021 Dec 10;12(12):CD001732.doi: 10.1002/14651858.CD001732.pub3.

Background: Varicose veins are enlarged and tortuous veins, affecting up to one-third of the world's population. They can be a cause of chronic venous insufficiency, which is characterised by oedema, pigmentation, eczema, lipodermatosclerosis, atrophie blanche, and healed or active venous ulcers. Injection sclerotherapy (liquid or foam) is widely used for treatment of varicose veins aiming to transform the varicose veins into a fibrous cord. However, there is limited evidence regarding its

effectiveness and safety, especially in patients with more severe disease. This is the second update of the review first published in 2002.

Objectives: To assess the effectiveness and safety of injection sclerotherapy for the treatment of varicose veins.

Search methods: For this update, the Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, AMED, CINAHL, and LILACS databases, and the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registries, on 20 July 2021.

Selection criteria: We included all randomised controlled trials (RCTs) (including cluster-randomised trials and first phase cross-over studies) that used injection sclerotherapy for the treatment of varicose veins.

Data collection and analysis: Two review authors independently assessed, selected and extracted data. Disagreements were cross-checked by a third review author. We used Cochrane's Risk of bias tool to assess the risk of bias. The outcomes of interest were cosmetic appearance, complications, residual varicose veins, quality of life (QoL), persistence of symptoms, and recurrent varicose veins. We calculated risk ratios (RRs) or mean difference (MD) with 95% confidence intervals (CIs). We used the worst-case-scenario for dichotomous data imputation for intention-to-treat analyses. For continuous outcomes, we used the 'last-observation-carried-forward' for data imputation if there was balanced loss to follow-up. We assessed the certainty of the evidence using the GRADE approach.

Main results: We included 23 new RCTs for this update, bringing the total to 28 studies involving 4278 participants. The studies differed in their design, and in which sclerotherapy method, agent or concentration was used. None of the included RCTs compared sclerotherapy to no intervention or to any pharmacological therapy. The certainty of the evidence was downgraded for risk of bias, low number of studies providing information for each outcome, low number of participants, clinical differences between the study participants, and wide CIs. Sclerotherapy versus placebo Foam sclerotherapy may improve cosmetic appearance as measured by IPR-V (independent photography review - visible varicose veins scores) compared to placebo (polidocanol 1%: mean difference (MD) -0.76, 95% CI -0.91 to -0.60; 2 studies, 223 participants; very low-certainty evidence); however, deep vein thrombosis (DVT) rates may be slightly increased in this intervention group (RR 5.10, 95% CI 1.30 to 20.01; 3 studies, 302 participants; very low-certainty evidence). Residual varicose vein rates may be decreased following polidocanol 1% compared to placebo (RR 0.19, 95% CI 0.13 to 0.29; 2 studies, 225 participants; very low-certainty evidence). Following polidocanol 1% use, there may be a possible improvement in QoL as assessed using the VEINES-QOL/Sym questionnaire (MD 12.41, 95% CI 9.56 to 15.26; 3 studies, 299 participants; very low-certainty evidence), and possible improvement in varicose vein symptoms as assessed using the Venous Clinical Severity Score (VCSS) (MD -3.25, 95% CI -3.90 to -2.60; 2 studies, 223 participants; low-certainty evidence). Recurrent varicose veins were not reported for this comparison. Foam sclerotherapy versus foam sclerotherapy with different concentrations Three individual RCTs reported no evidence of a difference in cosmetic appearance after comparing different concentrations of the intervention; data could not be pooled for two of the three studies (RR 1.11, 95% CI 0.84 to 1.47; 1 study, 80 participants; very low-certainty evidence). Similarly, there was no clear difference in rates of thromboembolic complications when comparing one foam concentration with another (RR 1.47, 95% CI 0.41 to 5.33; 3 studies, 371 participants; very low-certainty evidence). Three RCTs investigating higher concentrations of polidocanol foam indicated the rate of residual varicose veins may be slightly decreased in the polidocanol 3% foam group compared to 1% (RR 0.67, 95% CI 0.43 to 1.04; 3 studies, 371 participants; moderate-certainty

evidence). No clear improvement in QoL was detected. Two RCTs reported improved VCSS scores with increasing concentrations of foam. Persistence of symptoms were not reported for this comparison. There was no clear difference in recurrent varicose vein rates (RR 0.91, 95% CI 0.62 to 1.32; 1 study, 148 participants; low-certainty evidence). Foam sclerotherapy versus liquid sclerotherapy One RCT reported on cosmetic appearance with no evidence of a difference between foam or liquid sclerotherapy (patient satisfaction scale MD 0.2, 95% CI -0.27 to 0.67; 1 study, 126 participants; very low-certainty evidence). None of the RCTs investigated thromboembolic complications, QoL or persistence of symptoms. Six studies individually showed there may be a benefit to polidocanol 3% foam over liquid sclerotherapy in reducing residual varicose vein rate; pooling data from two studies showed a RR of 0.51, with 95% CI 0.41 to 0.65; 203 participants; very low-certainty evidence. One study reported no clear difference in recurrent varicose vein rates when comparing sodium tetradecyl sulphate (STS) foam or liquid (RR 1.10, 95% CI 0.86 to 1.42; 1 study, 286 participants; very low-certainty evidence). Sclerotherapy versus sclerotherapy with different substances Four RCTs compared sclerotherapy versus sclerotherapy with any other substance. We were unable to combine the data due to heterogeneity or assess the certainty of the evidence due to insufficient data.

Authors' conclusions: There is a very low to low-certainty evidence that, compared to placebo, sclerotherapy is an effective and safe treatment for varicose veins concerning cosmetic appearance, residual varicose veins, QoL, and persistence of symptoms. Rates of DVT may be slightly increased and there were no data concerning recurrent varicose veins. There was limited or no evidence for one concentration of foam compared to another; foam compared to liquid sclerotherapy; foam compared to any other substance; or one technique compared to another. There is a need for high-quality trials using standardised sclerosant doses, with clearly defined core outcome sets, and measurement time points to increase the certainty of the evidence.

Le conclusioni di questa pubblicazione Cochrane sono quanto meno discutibili. Comunque evidenziano degli aspetti sulla scleroterapia ben noti a tutti : la difficoltà di confrontare e standardizzare pazienti, concentrazioni di farmaci e dunque i risultati . Possiamo per altro concordare sulla necessità di studi di alta qualità con maggiore standardizzazione.

- Martinez-Zapata MJ, Vernooij RW, Simancas-Racines D, Uriona Tuma SM, Stein AT, Moreno Carriles RMM, Vargas E, Bonfill Cosp X. **Phlebotonics for venous insufficiency.** Cochrane Database Syst Rev. 2020 Nov 3;11(11):CD003229. doi: 10.1002/14651858.CD003229.pub4

Background: Chronic venous insufficiency (CVI) is a condition in which veins are unable to transport blood unidirectionally towards the heart. CVI usually occurs in the lower limbs. It might result in considerable discomfort, with symptoms such as pain, itchiness and tiredness in the legs. Patients with CVI may also experience swelling and ulcers. Phlebotonics are a class of drugs often used to treat CVI. This is the second update of a review first published in 2005.

Objectives: To assess the efficacy and safety of phlebotonics administered orally or topically for treatment of signs and symptoms of lower extremity CVI.

Search methods: The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL databases and the

World Health Organization International Clinical Trials Registry Platform and Clinicaltrials.gov trials register up to 12 November 2019. We searched the reference lists of the articles retrieved by electronic searches for additional citations. We also contacted authors of unpublished studies.

Selection criteria: We included randomised, double-blind, placebo-controlled trials (RCTs) assessing the efficacy of phlebotonics (rutosides, hidrosmine, diosmine, calcium dobesilate, chromocarbe, Centella asiatica, disodium flavodate, French maritime pine bark extract, grape seed extract and aminaftone) in patients with CVI at any stage of the disease.

Data collection and analysis: Two review authors independently extracted data and assessed the quality of included RCTs. We estimated the effects of treatment by using risk ratios (RRs), mean differences (MDs) and standardized mean differences (SMDs), according to the outcome assessed. We calculated 95% confidence intervals (CIs) and percentage of heterogeneity (I^2). Outcomes of interest were oedema, quality of life (QoL), assessment of CVI and adverse events. We used GRADE criteria to assess the certainty of the evidence.

Main results: We identified three new studies for this update. In total, 69 RCTs of oral phlebotonics were included, but only 56 studies (7690 participants, mean age 50 years) provided quantifiable data for the efficacy analysis. These studies used different phlebotonics (28 on rutosides, 11 on hidrosmine and diosmine, 10 on calcium dobesilate, two on Centella asiatica, two on aminaftone, two on French maritime pine bark extract and one on grape seed extract). No studies evaluating topical phlebotonics, chromocarbe, naftazone or disodium flavodate fulfilled the inclusion criteria. Moderate-certainty evidence suggests that phlebotonics probably reduce oedema slightly in the lower legs, compared with placebo (RR 0.70, 95% CI 0.63 to 0.78; 13 studies; 1245 participants); and probably reduce ankle circumference (MD -4.27 mm, 95% CI -5.61 to -2.93 mm; 15 studies; 2010 participants). Moderate-certainty evidence shows that phlebotonics probably make little or no difference in QoL compared with placebo (SMD -0.06, 95% CI -0.22 to 0.10; five studies; 1639 participants); and similarly, may have little or no effect on ulcer healing (RR 0.94, 95% CI 0.79 to 1.13; six studies; 461 participants; low-certainty evidence). Thirty-seven studies reported on adverse events. Pooled data suggest that phlebotonics probably increase adverse events slightly, compared to placebo (RR 1.14, 95% CI 1.02 to 1.27; 37 studies; 5789 participants; moderate-certainty evidence). Gastrointestinal disorders were the most frequently reported adverse events. We downgraded our certainty in the evidence from 'high' to 'moderate' because of risk of bias concerns, and further to 'low' because of imprecision.

Review sui farmaci Flebotonici proposta da Cochrane che evidenzia pochi studi validi e limitate evidenze scientifiche. Anche per i Flebotonici sarebbero necessari pubblicazioni più standardizzate e di maggiore qualità.
L'articolo completo sarà disponibile a breve nel SITO SIF -> Linee Guida Internazionali