Dynamic Stabilization of Syndesmosis Injuries Reduces Complications and Reoperations Compared to Screw Fixation: a Meta-Analysis of RCTs

Abstract

Background: Several devices to obtain a dynamic fixation of the syndesmosis have been introduced in the recent years, however their efficacy has been tested in few RCTs, without a clear benefit over the traditional static fixation with screws.

Purpose: To perform a Level I meta-analysis of RCTs to investigate the complications, subjective outcomes and functional results after dynamic or static fixation of acute syndesmotic injuries.

Methods: A systematic literature search of the MEDLINE/Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL) and EBSCOhost electronic databases and *clinicaltrials.gov* for unpublished studies was performed. Eligible studies were randomized controlled trials (RCTs) comparing dynamic fixation and the static fixation of acute syndesmosis injuries. A meta-analysis was performed, while bias and quality of evidences were rated according to the Cochrane Database questionnaire and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.

Results: Dynamic fixation has a significantly decreased RR (0.55, p=0.003) of complications, in particular the presence of inadequate reduction at the final follow-up (RR=0.36, p=0.0008) and the clinical diagnosis of recurrent diastasis or instability (RR=0.10, p=0.03). The effect was more evident compared to permanent screws (RR=0.10, p=0.0001). The reoperation rate was similar between the two groups (RR=0.64, p=0.07); however, the overall risk was reduced after dynamic fixation when compared to static fixation with permanent screws (RR=0.24, p=0.007). The AOFAS score was significantly higher in patients treated with dynamic fixation of 6.06 points (p=0.005) at 3 months, 5.21 points (p=0.03) at 12 months and 8.60 points (p<0.00001) at 24 months, while the Olerund-Morlander score was similar. VAS for pain was reduced at 6 months

(-0.73 points, p=0.003) and at 12 months (-0.52 points, p=0.005) and ankle ROM was increased of 4.36° (p=0.03) with dynamic fixation. The overall quality of evidence was from "moderate" to "very low" due to a substantial risk of bias, heterogeneity, indirectness of outcome reporting and evaluation of a limited number of patients.

Conclusion: Dynamic fixation of syndesmotic injuries was able to reduce the number of complications and improve clinical outcomes compared to static screw fixation, especially malreduction and clinical instability or diastasis, at a follow-up of 2 years. A lower risk of reoperation with dynamic fixation was found compared to static fixation with permanent screw. However, lack of patients or personnel blinding, treatment heterogeneity, small samples and short follow-up, limits the overall quality of these evidences.

Level of Evidence: Meta-analysis of randomized controlled trials (Level I)

Key words: Syndesmosis, ankle fracture, screw, suture button, complications, dynamic fixation, static fixation, Meta-analysis

What is known about the subject: Promising results have been reported with the use of dynamic fixation of syndesmotic injuries. However, only few RCTs are presents, with not consistent results in term of functional outcomes, reoperations and complication

What this study adds to existing knowledge: This meta-analysis of level I RCTs comparing dynamic with static fixation of tibio peroneal distal syndesmosis summarizes the highest level of evidences on this topic and provides information to clinicians regarding the performance of static fixation over standard treatment. The improved subjective clinical outcomes and the reduced number of complications and reoperations makes the dynamic fixation a good options for syndesmosis injury treatment, at least at short-term follow-up.

Introduction

Injuries to the distal tibio-peroneal syndesmosis could be present in isolation, or in approximately 13-20% of ankle fractures, caused by an injury mechanism of pronation and external rotation[7]. Concomitant stabilization of the syndesmosis is mandatory in addition to fracture fixation since its misdiagnosis or inadequate treatment could be responsible of persistent pain, functional impairment and early osteoarthritis[20, 27, 33, 35]. To obtain an accurate and stable syndesmosis reduction, the actual gold-standard in treatment is represented by screw fixation[34]. However, several complications are common with this treatment, such as screw loosening, breakage, local irritation and discomfort[8, 14, 36]. Moreover, when screw removal is planned to avoid implant problems, loss of reduction could occur[19, 37].

For these reasons, several devices to obtain a dynamic fixation of the syndesmosis have been introduced[6, 25, 30], with the rationale to possibility obtaining a more physiological movement of the syndesmosis during joint load while maintaining the required reduction. The result would be to allow early weight-bearing reducing the risk of implant loosening and breakage, avoid a second reoperation for eventual screw removal and reduce the risk of loss of reduction after implant removal[19, 28]. Several controlled studies comparing static screw fixation with various devices for dynamic fixation have been published and summarized in systematic reviews and meta-analyses [3, 14, 17, 25, 28, 31, 42] . However, the most recent meta-analysis by Chen et al.[3] which included 9 studies and 387 patients, was seriously biased by the overall limited quality due to the inclusion both prospective and retrospective studies, with only 3 RCTs[4, 18, 19]. The great interest on the treatment of syndesmotic injuries is confirmed by the fact that several new RCTs have been performed both in Europe[1, 5, 24], Canada[23] or Asia[41] in the last few years.

Due to the increased amount of high-level literature, there is the need to evaluate and summarize the Level I evidence regarding the static or dynamic fixation of syndesmotic injuries, in order to determine the most performant strategy in terms of patient's satisfaction, functional results and complications.

The aim of the present study was therefore to perform a Level I meta-analysis of RCTs to investigate the complications, subjective outcomes and functional results after dynamic or static fixation of acute syndesmotic injuries. The hypothesis was that dynamic and static syndesmosis fixation would present similar functional outcomes, complications and reoperations.

Material and Methods

Literature search

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines[22]. A systematic electronic search of the following databases was performed in March 2018; Pubmed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL); the website *clinicaltrials.gov* for unpublished studies. The key words were "syndesmosis OR syndsmotic OR syndesmoses OR high ankle" combined with "suture-button OR button OR endo-button OR tightrope OR arthrex OR dynamic OR wires OR fixation device". The full search strategy is provided in the Appendix 1. The electronic database search was supplemented by manual scanning of the reference lists of included articles and the ePublication lists of the leading orthopedic and sports medicine journals.

Article selection

Eligible studies were RCTs comparing screw fixation with dynamic fixation of syndesmotic injuries either with or without ankle fracture. Any device for dynamic stabilization was considered eligible for inclusion. Both published and unpublished studies in all languages were eligible. Biomechanical studies, *in-vitro* studies, review articles, surgical techniques, case reports, letters to the editor and editorials were excluded. There were no criteria for the technique used in the surgical procedure, study sample size or length of follow-up.

Two authors (X.X. and X.X) independently reviewed the title and abstract of each article from the literature search. The assessors were not blinded to the authors of the publications. The full text of an article was obtained and evaluated when eligibility could not be assessed from the first

screening. Any disagreements were resolved via a consensus discussion between the reviewers and a third reviewer was consulted if the disagreement could not be resolved.

Data extraction

An electronic piloted form was created for data extraction. Data on patient demographics, including patient gender and age at surgery, were extracted, as well as details of study design, such as level of evidence, inclusion and exclusion criteria, method of randomization and length of follow-up. Treatment factors, such as injury classification, surgical technique for syndesmotic injury and concomitant injuries or fractures were also collected. The piloted form also included columns for the extraction of all outcome measurements, which were defined prior to study start and it was compulsory for a study to present data on at least one of the outcomes to be included.

Outcomes definition

The outcomes of interest were: functional outcome measurements defined as the American Orthopedic Foot and Ankle Score (AOFAS), The Olerud-Molander score, the Visual Analogic Scale (VAS) for pain, joint range of motion (ROM) measured with dorsi-flexion and plantar-flexion, time to return to work and sport activity, and percentage of patients returning to the same pre-injury activity. Furthermore, complications and reoperations, as defined in each study, were collected. In particular, the inadequate reduction was considered intra or post-operatively when a correction of syndesmosis reduction was performed during surgery or the next day after CT scan; inadequate reduction was considered at final follow-up based on imaging criteria. Insufficient fixation was referred to inadequate reduction of fixation of concomitant fractures but not syndesmosis. Clinical recurrent diastasis or instability was based on clinical criteria defined in each study. Regarding reoperations, synthesis revision was considered when a reoperation was

performed to correct a concomitant fracture synthesis, but not syndesmosis; wound revision was considered when a reoperation was performed to address wound problems without removing the syndesmotic implant, otherwise it was considered as implant removal. For both syndesmotic implant and fracture hardware, only the not planned removal were accounted.

Due to the extreme heterogeneity of the possible complications, these were evaluated as: "overall complications" defined as all the complications reported in each study; "device-related complications" defined as those possibly caused by the device used to stabilize the syndesmosis, such as malreduction, recurrent instability, infection, irritation and discomfort, implant break, implant loosening, and "clinically significant complications" defined as all the previous ones except for implant loosening and implant break. Also reoperations were categorized as "overall" and "device-related"; the former were defined as syndesmosis refixation, wound revision and not planned implant removal.

Assessment of risk of bias and quality of evidence

The risk of bias was evaluated as "high risk", "low risk" and "unclear risk" according to the standardized Cochrane Database questionnaire[12]. Articles were not excluded on the basis of the assessment. The overall quality of evidence for each outcome was graded as "high", "moderate", "low" and "very low", based on study design, risk of bias, inconsistency, indirectness, imprecision and publication bias, according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines[2]. The risk of bias and GRADE evaluation was performed based on consensus by two authors (X.X. and X.X.). The intervention of a third reviewer was not needed because the authors reached consensus for all the items after discussion.

Statistical analysis

The meta-analysis was performed using RevMan V.5.0.18.33 (the Cochrane Collaboration, Copenhagen, Denmark). Continuous variables were extracted and analyzed as the mean ± standard deviation (SD). The corresponding author was contacted and asked to provide the data if the SD was not reported. In the event of no response, the SD was calculated from the available data, according to a previously validated formula; ((higher range value – lower range value)/4), of IQR/1.35)[10, 11]. If the SD could not be calculated using this approach, the highest SD was used. The mean difference (MD) and 95% confidence interval (CI) were calculated for continuous variables. The Relative Risk (RR) was calculated for dichotomous variables. The RR was defined as the ratio of the risk of an event in the two groups. It ranges from 0 to infinity, with values =1 indicating no differences of the risk between the groups, <1 indicating a lower risk in the "dynamic fixation" group (study group) and values >1 indicating an higher risk in the "dynamic fixation" group. We tested for heterogeneity using the x^2 and Higgins' I^2 tests[9]; according to Cochrane Guidelines, moderate heterogeneity was considered in the case of I^2 >30% or $p<0.05$. We adopted a conservative statistical approach applying a Mantel-Haenszel random-effects model in presence of moderate heterogeneity, and a fixed-effects model only when both I^2 and p-value were <30% and >0.05, respectively[9]. When possible, the meta-analysis of clinical scores was performed at the 3, 6, 12 and 24 months follow-up. A sensitivity analysis was performed analyzing separately patients with suture-buttons or other devices, patients that underwent systematic screw removal or screw retain, and patients that had a follow-up ≤12 months or >12 months. A p-value of < 0.05 was considered statistically significant in all the analyses.

Results

Article selection

The initial literature search yielded a total of 373 articles, and 18 were considered eligible for inclusion. Six of them were excluded because comparative studies without randomization, while 5 reports from clinicaltrials.gov were excluded because 1 RCT was still ongoing at the time of search, 1 was complete but with no report of the results, and 3 were referred to RCTs already completed and published. Therefore, after application of inclusion and exclusion criteria, 7 studies[1, 4, 5, 18, 19, 21, 41] were included in the final analysis (Figure 1).

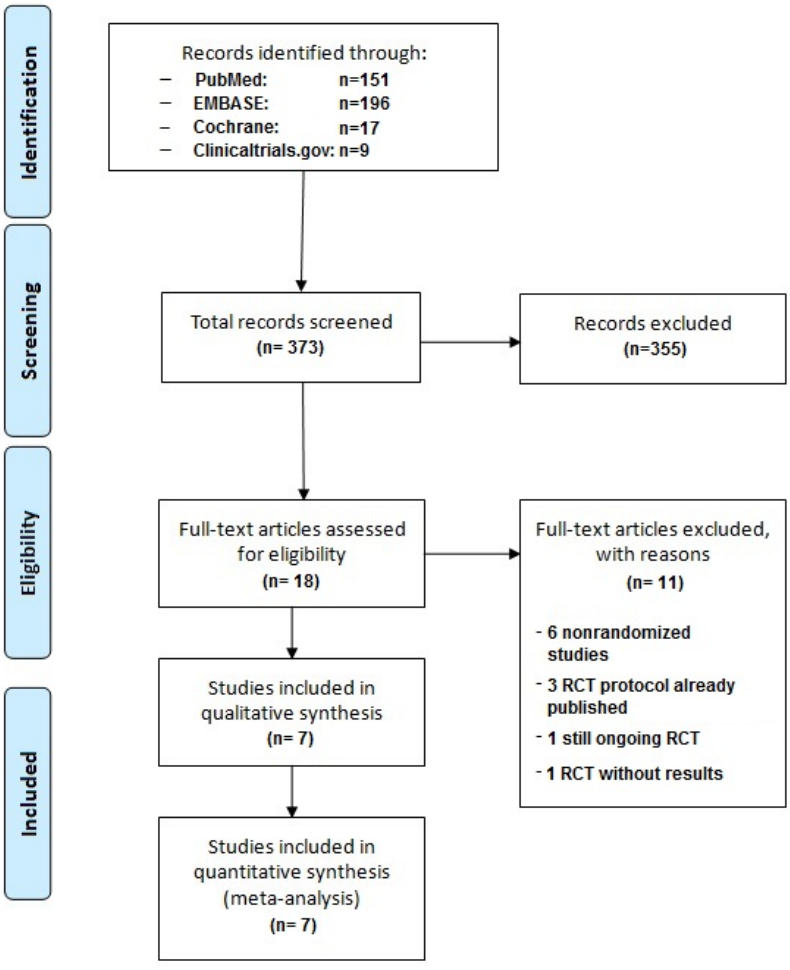

Figure 1: PRISMA flow-chart for study inclusion

Study characteristics

All of the included studies were level 1 RCTs. Well-defined exclusion criteria were specified by seven studies, which were mostly age >60 years, diabetes and open fractures (Appendix 2). A total of 168 patients were treated with dynamic fixation and 167 patients with static fixation. The mean age ranged from 32 to 48.2 years in the dynamic group and from 35 to 46.7 years in the static group. The mean follow-up time in the included studies ranged from 12 to 24 months (Table 1).

The dynamic fixations were performed with several devices: suture buttons (5 RCTs), wire cerclages (1 RCT) or elastic hook plates (1 RCT). The static fixation was performed with one or two 3.5 to 6.5 mm screws. Four studies performed intra or post operative imaging to detect syndesmosis malreduction and determine the need of syndesmosis refixation. Four studies had planned removal of the screws between 4 and 12 weeks. The postoperative rehabilitation protocol consisted in a cast up to 6 weeks and full weight-bearing at the 6^{th} week (Appendix 3). All the studies evaluated reoperations and complications, while the most used subjective clinical scores were the VAS for pain (5 studies), the AOFAS (4 studies) and the Olerud-Molander (4 studies) (Appendix 4).

Table I: Patients characteristics of the included studies														
				Patients enrolled		Patients evaluated		Age		Sex		Fracture types		Fracture anatomy	
Authors	Year	Patients secreened	Patients Randomized	Dynamic Fixation	Static Fixation	Dynamic Fixation	Static Fixation	Dynamic Fixation	Static Fixation	Dynamic Fixation	Static Fixation	Dynamic Fixation	Static Fixation	Dynamic Fixation	Static Fixation
Coetzee and Ebeling	**2009**	NA	NA	12	12	12	12	38 (18-55)	35 (18-53)	8M/4F	9M/3F	NA	NA	1 no fractures 4 Fibula 7 Fibula + MM	1 no fractures 6 Fibula 5 Fibula + MM
Massobrio et al.	**2011**	NA	NA	15	15	15	15	32 (16-62)	35 (15-73)	12M/3F	10M/5F	7 Weber B 5 Weber C 3 no fractures	9 Weber B 6 Weber C	3 no fractures 2 Fibula 1 PM 2 Fibula + MM 1 Fibula + MM + PM	8 Fibula 2 MM 4 Fibula + MM 1 Fibula + PM
Kortekangas et al.	**2015**	60	43	21	22	21	19	46.0 (14.8)	45.5 (15.7)	13M/8F	14M/8F	9 Maisonneuve 12 Weber C	9 Maisonneuve 12 Weber C	13 Fibula 1 Fibula + MM 2 Fibula + PM 5 Trimalleolar	9 Fibula 3 Fibula + MM 3 Fibula + PM 6 Trimalleolar
Laflamme et al.	**2015**	823	70	34	36	33	32	40.1 (14.8)	39.3 (12.4)	25M/9F	26M/10F	5 44B 29 44C	7 44B 29 44C	29 Fibula 4 Fibula + MM 1 Fibula + PM	30 Fibula 5 Fibula + MM 1 Fibula + PM
Andersen et al.	**2018**	196	97	48	49	48	49	46 (14.8)	43 (16.2)	34M/14F	30M/19F	15 Maisonneuve 33 Other	14 Maisonneuve 35 Other	NA	NA
Colcuc et al.	**2018**	110	62	32	30	26	28	35 (18-60)	39 (18-60)	19M/7F	22M/6F	5 Weber B 3 Weber C 5 Maisonneuve 13 Isolated	6 Weber B 4 Weber C 7 Maisonneuve 11 Isolated	NA	NA
Xian et al.	**2018**	96	32	16	16	13	12	48.2 (11.1	46.7 (12.1)	6M/7F	8M/4F	3 SER 3 7 SER 4 3 PER 4	2 SER 3 6 SER 4 4 PER 4	NA	NA

Table 2: Demographic characteristics and injury details of the patients included in the meta-analysis. SER, Supination External Rotation; PER, Pronation External Rotation; MM, Medial Malleolus; PM, Posterior Malleolus; M, Male; F, Female; NA, Not Assessed

Complications

Overall complications: The random-effect meta-analysis for overall complications revealed a significantly decreased risk (RR=0.55, p=0.003) in the patients treated with dynamic fixation, in particular the presence of inadequate reduction at the final follow-up (RR=0.36, p=0.0008) (Figure 2b) and the clinical diagnosis of recurrent diastasis or instability (RR=0.10, p=0.03). Also the occurrence of implant break (RR=0.13, p=0.0002) or loosening (RR=0.06, p=0.006) was significantly reduced by the use of dynamic fixation devices. Differently, the rates of inadequate post-operative reduction (figure 2a), insufficient fracture fixation, development of osteoarthritis or syndesmotic ossification, infection or irritation were similar between patient treated with dynamic and static fixation (Table 5).

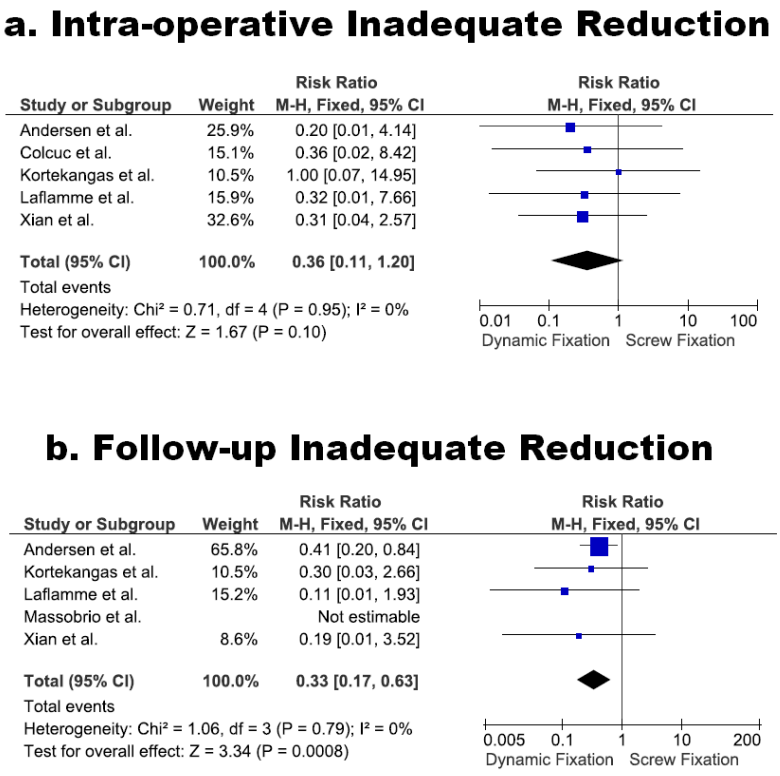

Figure 2: Forest-plots showing the incidence of inadequate intra-operative syndesmosis reduction (a) and inadequate reduction at final follow-up (b) in patients treated with Dynamic Fixation or Static Fixation.

Table V: Meta-analysis of Complications and Re-operations									
Outcome	**Patients**			**Risk Ratio (RR)**					
	Dynamic Fixation	**Screw Fixation**	**Studies**	**Model**	**ES**	**95% CI**	**p-val**	**I2**	**p-val**
Overall complications	168	167	7	RE	0.55	(0.37, 0.81)	**0.003***	39%	0.13
Inadequate reduction (intra\post operative)	141	142	5	FE	0.36	(0.11, 1.20)	0.10	0%	0.95
Inadequate reduction (follow-up)	130	127	5	FE	0.36	(0.17, 0.63)	**0.0008***	0%	0.79
Insufficient fixation	168	167	7	FE	0.60	(0.08, 4.40)	0.61	0%	0.59
Clinical recurrent diastasis\instability	74	77	2	FE	0.10	(0.01, 0.79)	**0.03***	0%	0.58
Osteoarthritis	84	83	3	FE	0.78	(0.52, 1.17)	0.23	17%	0.30
Syndesmosis ossification	81	81	2	FE	1.18	(0.42, 3.32)	0.75	0%	0.88
Infection	168	167	7	FE	0.99	(0.36, 2.69)	0.98	0%	0.58
Irritation and discomfort	168	167	7	RE	0.75	(0.12, 4.66)	0.76	56%	0.05
Implant break	168	167	7	FE	0.13	(0.04, 0.38)	**0.0002***	0%	0.92
Implant loosening	168	167	7	FE	0.06	(0.01, 0.44)	**0.006***	22%	0.26
Overall-reoperations	168	167	7	FE	0.64	(0.40, 1.03)	0.07	30%	0.21
Synthesis revision	168	167	7	FE	0.60	(0.08, 4.40)	0.61	0%	0.59
Syndesmosis refixation	168	167	7	FE	0.11	(0.01, 2.05)	0.22	NA	NA
Wound revision	168	167	7	FE	0.65	(0.11, 3.76)	0.63	0%	0.74
Hardware removal (not planned)	168	167	7	FE	1.02	(0.35, 2.94)	0.97	NA	NA
Implant removal (not planned)	168	167	7	RE	0.70	(0.21, 2.36)	0.56	48%	0.10
Arthrodesis	168	167	7	FE	3.06	(0.13, 73.34)	0.49	NA	NA
Implant-related complications (overall)	168	167	7	RE	0.28	(0.09, 0.88)	**0.03***	65%	0.008
Implant-related complications (clinically relevant)	168	167	7	RE	0.66	(0.22, 1.98)	0.46	43%	0.12
Implant-related reoperations	168	167	7	FE	0.64	(0.38, 1.06)	0.08	20%	0.28

Table 5: Meta-analysis of the dichotomous outcomes complications and reoperations. P-val; p-value; ES, Effect Size; RE, Random-Effect; FE, Fixed-Effect, NA, Not Assessed.

The risk of overall complications was reduced in patients treated with dynamic fixation independently from the device used, the screw removal or retain and the follow-up ≤12 or >12 months.

Implant-related complications: Considering only the complication strictly related to the device used for syndesmosis stabilization, a decreased risk (RR=0.28, p=0.03) was reported in the

dynamic fixation group compared to the static fixation group (Table 5), especially with the use of a suture-button device for dynamic fixation (RR=0.22, p=0.001), or when static fixation was performed with permanent screws (0.10, p=0.0001). Differently, a similar risk between static and dynamic fixation was found when using other devices than suture-buttons (RR=0.32, p=0.20), or when syindesmotic screws were systematically removed (RR=0.83, p=0.66). The length of follow-up had no impact on this outcome.

Clinically relevant implant-related complications: When further limiting the analysis to the complications with a clinical relevance, no differences were found between the two groups (Table 5). However, a lower risk was reported after dynamic fixation when compared only to static fixation with permanent screws (RR=0.26, p=0.01) (Figure 3), or considering only the studies with follow-up ≤12 months (RR=0.30, p=0.03).

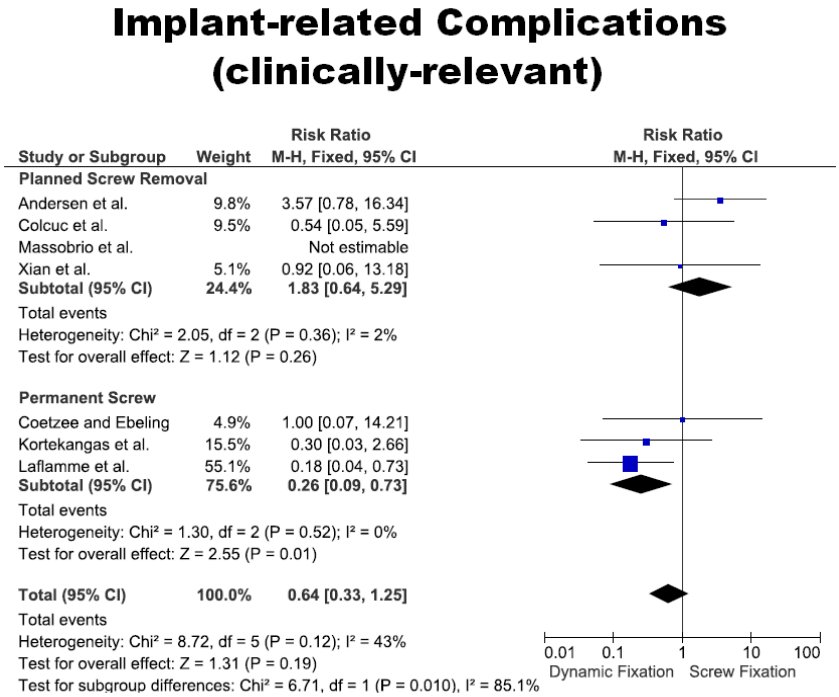

Figure 3: Forest-plots showing the incidence of clinically-relevant complications in patients treated with Dynamic Fixation or Static Fixation, stratified based on planned screw removal or permanent screw.

Reoperations

Overall reoperation: The overall reoperation rate was similar between the two groups (RR=0.64, p=0.07) (Table 5). However, the overall risk was reduced after dynamic fixation when compared to static fixation only with permanent screws (RR=0.24, p=0.007) (Figure 4). The type of device and the follow-up length had no impact on this outcome.

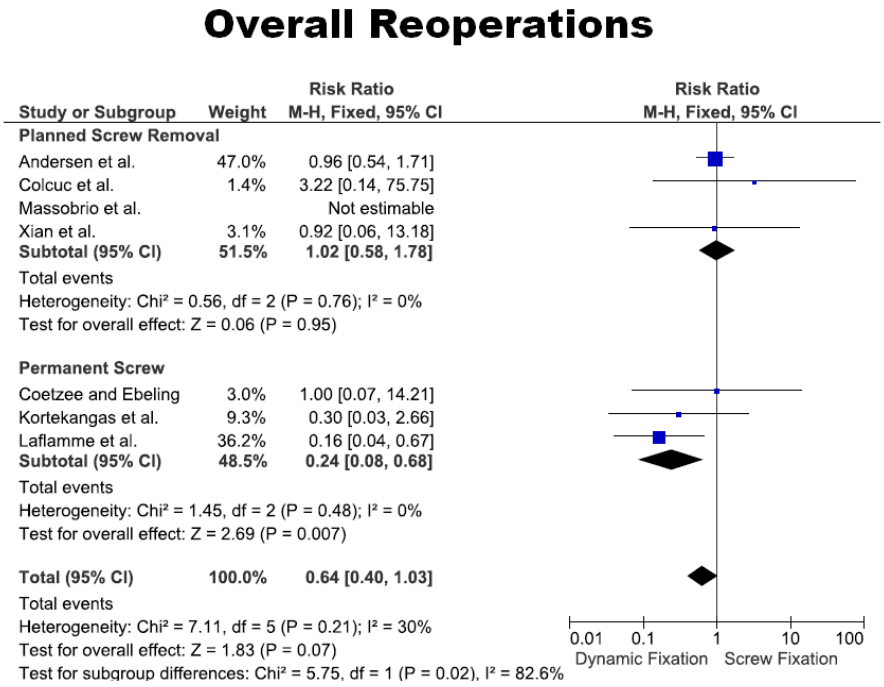

Figure 4: Forest-plots showing the incidence of overall reoperations in patients treated with Dynamic Fixation or Static Fixation, stratified based on planned screw removal or permanent screw.

Implant-related reoperations: There were no differences also for the implant-related reoperations (RR=0.64, p=0.08) and for each of the considered type of reoperation (Table 5). However, the risk was lower in dynamic fixation when compared with static fixation with permanent screws (RR=0.26, p=0.01). Also in this case, the type of device and the follow-up length had no impact.

Functional and subjective outcome measurements

Olerud-Morlander score: The random-effect meta-analysis revealed no differences between the two groups for the Olerud-Molander score at the 3, 6, 12 and 24 months follow-up (Figure 5).

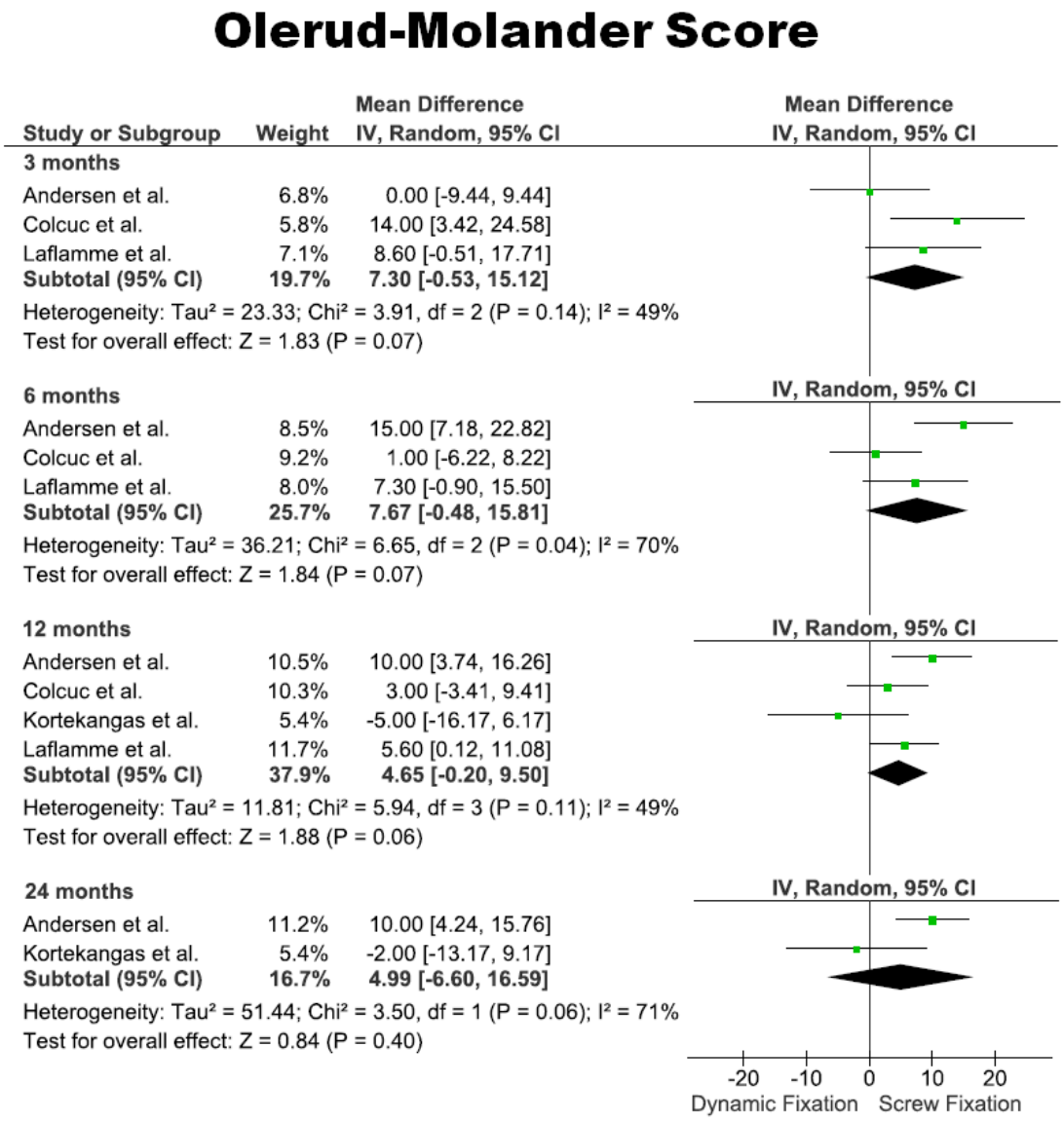

Figure 5: Forest-plots showing the mean difference of the Olerund-Molander score between patients treated with Dynamic Fixation or Static Fixation at 3 months, 6 months, 12 months and 24 months follow-up.

AOFAS score: Differently, the AOFAS score was 6.06 points higher in patients treated with dynamic fixation respect to static fixation at 3 months (p=0.005), 5.21 points higher (p=0.03) at 12 months and 8.60 points higher (p<0.00001) at 24 months (Figure 6).

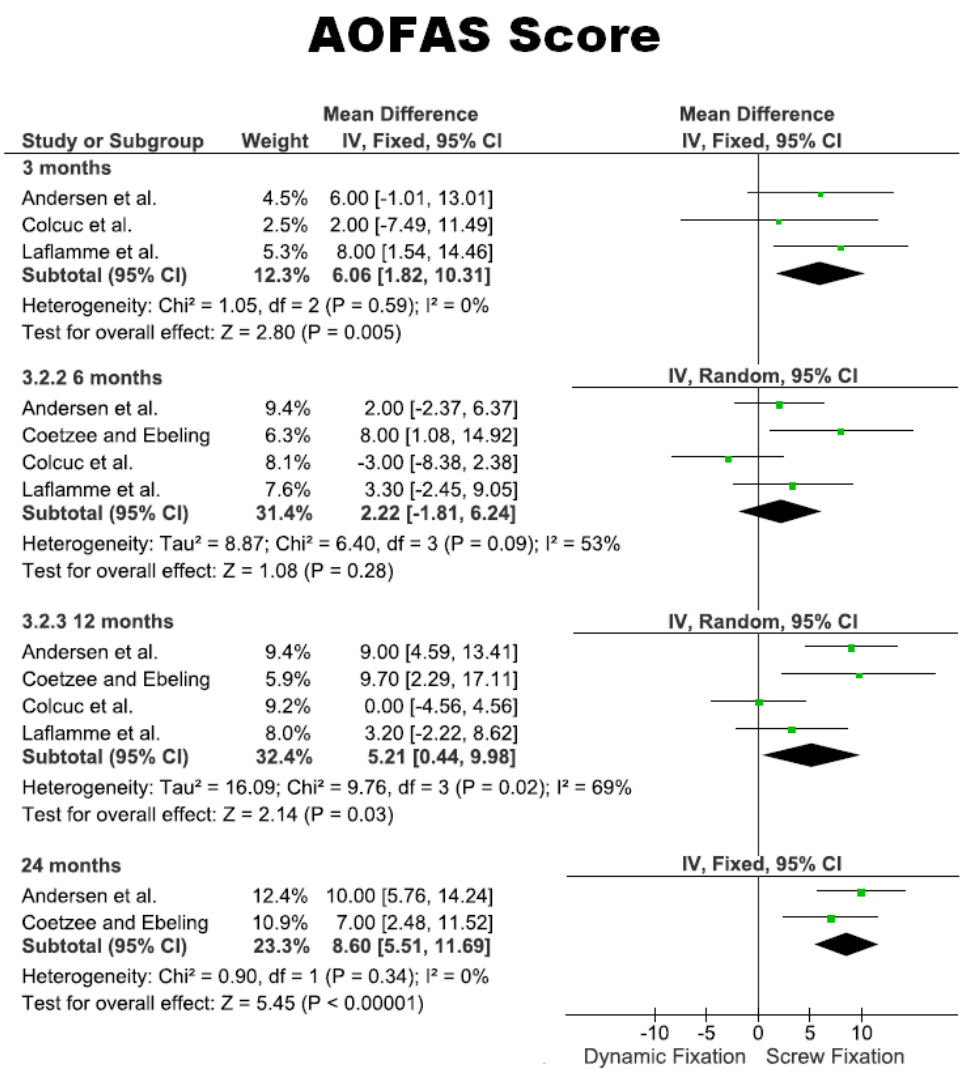

Figure 6: Forest-plots showing the mean difference of the AOFAS Score score between patients treated with Dynamic Fixation or Static Fixation at 3 months, 6 months, 12 months and 24 months follow-up.

VAS for pain score: Also, the VAS for pain was lower in those undergoing syndesmosis repair with dynamic devices respect to static screws at 6 months (-0.73 points, p=0.003) and at 12 months (-0.52 points, p=0.005) (Figure 7).

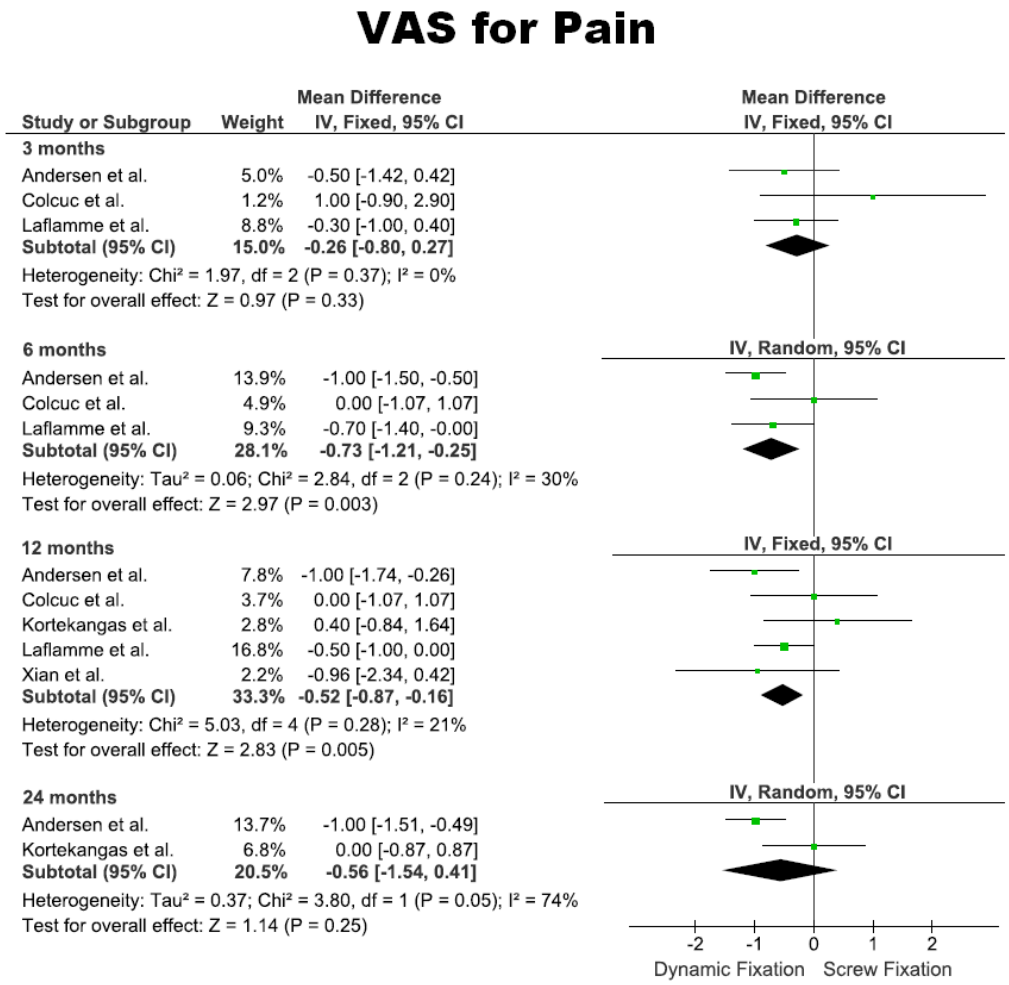

Figure 7: Forest-plots showing the mean difference of the VAS for pain score between patients treated with Dynamic Fixation or Static Fixation at 3 months, 6 months, 12 months and 24 months follow-up.

Ankle range of motion: Regarding the range of motion, the dorsi-flexion was significantly increase of 4.36° (p=0.03) in the dynamic fixation group, while the plantar-flexion was similar between the two (Figure 8).

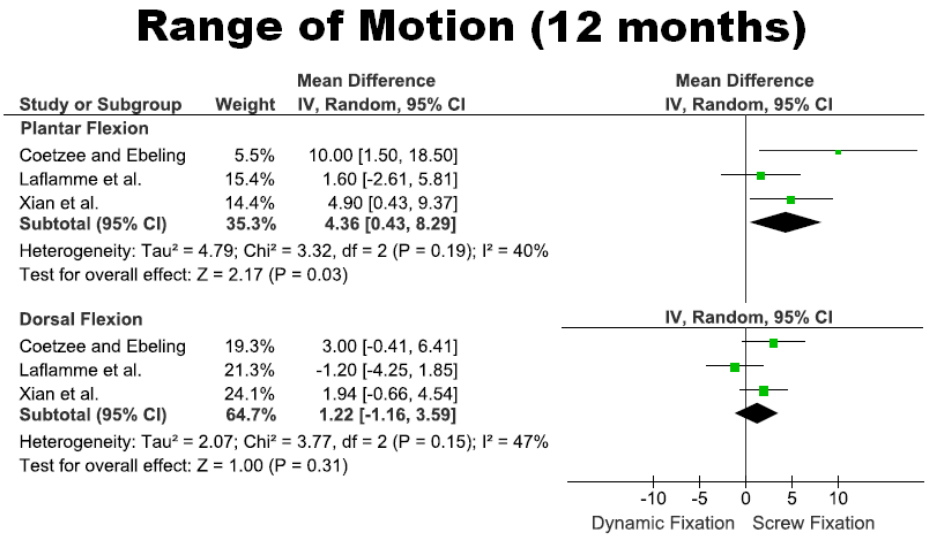

Figure 8: Forest-plots showing the mean difference of the plantar flexion (a) or dorsal flexion (b) range of motion between patients treated with Dynamic Fixation or Static Fixation.

Return to activity: Finally, the time to return to work and sport were significantly shorter after dynamic fixation, despite only being evaluated in 2 studies and 1 study, respectively (Table 6). However, no data regarding the type of work, sport or level were provided within the included studies.

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Table VI: Meta-analysis of Functional Outcomes

Outcome	Patients			Mean Difference (MD)					
	Dynamic Fixation	Screw Fixation	Studies	Model	ES	95% CI	p-val	I2	p-val
Olerud-Molander									
3 months	103	105	3	RE	7.30	(-0.53, 15.12)	0.07	45%	0.14
6 months	103	103	3	RE	7.67	(-0.48, 15.41)	0.07	70%	0.04
12 months	126	118	4	RE	4.65	(-0.20, 9.50)	0.06	49%	0.11
24 months	67	60	2	RE	4.99	(-6.60, 16.59)	0.40	71%	0.04
AOFAS									
3 months	105	105	3	FE	6.06	(1.82, 10.31)	**0.005***	0%	0.59
6 months	115	115	4	RE	2.22	(-1.81, 6.24)	0.28	53%	0.09
12 months	117	111	4	RE	5.21	(0.44, 9.98)	**0.03***	69%	0.02
24 months	53	50	2	FE	8.60	(5.51, 11.69)	**0.00001***	0%	0.34
VAS for Pain									
3 months	104	103	3	FE	-0.26	(-0.80. 0.27)	0.33	0%	0.37
6 months	102	103	3	RE	-0.73	(-1.21, -0.25)	**0.003***	30%	0.24
12 months	139	128	4	FE	-0.52	(-0.87, -0.16)	**0.005***	21%	0.28
24 months	67	60	2	RE	-0.56	(-1.54, 0.41)	0.25	75%	0.05
Range of Motion (12 months)									
Dorsi-Flexion	58	56	3	RE	4.36	(0.43, 8.29)	**0.03***	40%	0.19
Plantar-Flexion	58	56	3	RE	1.22	(-1.16, 3.59)	0.31	47%	0.15
Time to return to Activity									
Work	39	40	2	FE	-1.95	(-2.97, -0.94)	**0.0002***	0%	0.96
Sport	26	28	1	FE	-5.00	(-8.74, -1.26)	**0.009***	NA	NA

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302 **Table 6:** Meta-analysis of the continuous subjective and functional outcomes. P-val; p-value; ES, Effect Size; RE,

303 Random-Effect; FE, Fixed-Effect, NA, Not Assessed.

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Summary of outcomes and sensitivity analysis

The risk of overall complications, inadequate reduction at follow-up, clinical recurrent diastasis or instability, implant break, implant loosening and the risk of implant-related complications were reduced with the use of dynamic fixation. When the dynamic fixation was not performed with a suture button, the risk of implant related complications was similar between the static and dynamic fixation. When static fixation was performed with permanent screws, the RR of implant related complications, clinically relevant complications, reoperations and implant-related reoperations were reduced in the dynamic fixation group. Follow-up length had a limited impact only on clinically relevant implant-related complication (Table 7). The AOFAS score, VAS for pain score, range of motion and return to activity were improved after dynamic fixation compared to static fixation.

Table VII: Sensitivity Analysis of Complications and Re-operations

Dichotomic Outcomes	Overall complications			Overall-reoperations			Implant-related complications (overall)			Implant-related complications (clinically relevant)			Implant-related reoperations		
	ES	95% CI	p-val	ES	95% CI	p-val	ES	95% CI	p-val	ES	95% CI	p-val	ES	95% CI	p-val
Tightrope (n=5)	0.56	(0.35, 0.90)	**0.02***	0.58	(0.22, 1.55)	0.28	0.22	(0.13, 0.40)	**0.001***	0.63	(0.18, 2.27)	0.48	0.63	(0.37, 1.05)	0.08
Other devices (n=2)	0.41	(0.17, 0.97)	**0.04***	0.92	(0.06, 13.18)	0.95	0.32	(0.05, 1.83)	0.20	0.92	(0.06, 13.18)	0.95	0.92	(0.06, 13.18)	0.95
Permanent screw (n=3)	0.47	(0.33, 0.66)	**0.0001***	0.24	(0.08, 0.68)	**0.007***	0.10	(0.04, 0.24)	**0.0001***	0.26	(0.09, 0.73)	**0.01***	0.26	(0.09, 0.73)	**0.01***
Planned screw removal (n=4)	0.64	(0.44, 0.94)	**0.02***	1.02	(0.58, 1.78)	0.95	0.83	(0.36, 1.92)	0.66	1.83	(0.64, 5.29)	0.26	1.02	(0.55, 1.87)	0.96
Follow-up >12 months (n=3)	0.72	(0.56, 0.94)	**0.02***	0.86	(0.50, 1.48)	0.58	0.36	(0.18, 0.71)	**0.03***	1.22	(0.26, 5.80)	0.80	0.84	(0.46, 1.52)	0.56
Follow-up ≤12 months (n=4)	0.27	(0.14, 0.52)	**0.001***	0.51	(0.09, 2.99)	0.45	0.13	(0.05, 0.33)	**0.0001***	0.30	(0.10, 0.91)	**0.03***	0.51	(0.09, 2.81)	0.44

Table 7: Results of sensitivity analysis for complications and reoperations, based on type of dynamic fixation, permanent or removed screw, and length of follow-up. P-val; p-value; ES, Effect Size.

Risk of bias assessment

All the studies presented at least one domain of the Cochrane Risk of Bias Tool at unclear or high risk of bias (Figure 9).

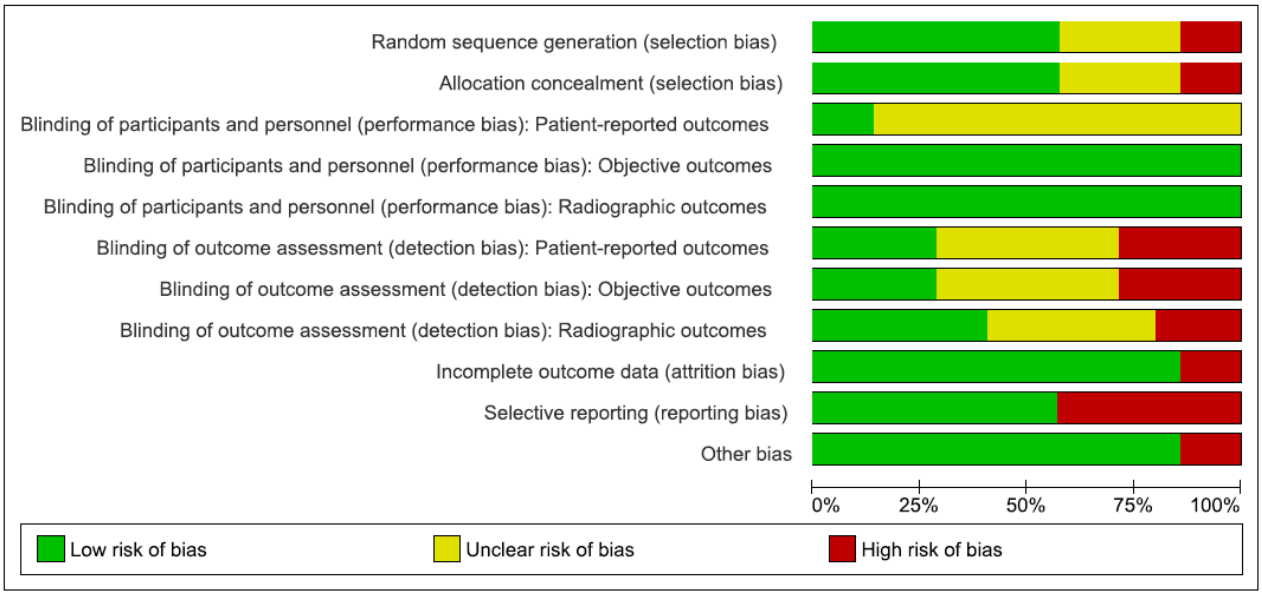

Figure 9: Risk of bias of each study: high-risk (red circle), low-risk (green circle) and unclear-risk (yellow circle)

Selection bias was high due to the inconsistent reporting of randomization and concealment methods in the included studies. Although the patients were not blinded to the allocated treatment, the risk of performance bias for objective outcomes such as complications and reoperations, and for radiographic outcomes was considered low, since those were not likely to be influenced by the patient's knowledge of a specific treatment. Differently, performance bias was considered at high risk for subjective outcomes due to the lack of patients blinding. The detection bias was considered at high risk as well, since most of the outcomes were assessed by investigators with inadequate or unknown blinding to treatments. Attrition bias and reporting bias were considered to be low risk, since the drop-out rates were minimal and all the studies

reported the result of all the outcomes described in the methods. One study was considered at high risk of bias because had different rehabilitation protocols between the two groups (Figure 10).

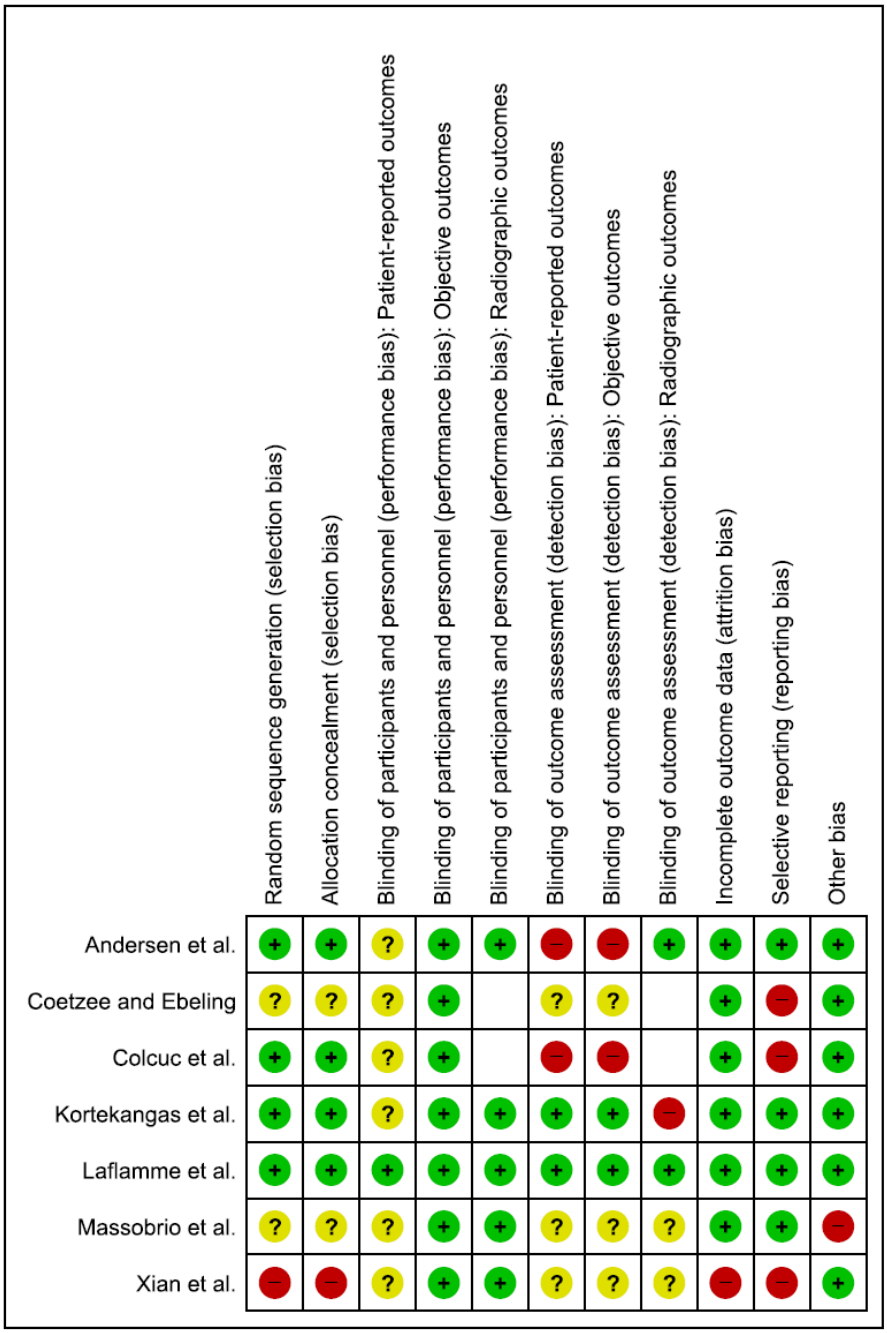

Figure 10: Summary table for the risk of bias across the included studies.

Quality assessment

The quality of evidence regarding the dynamic or static fixation of acute syndesmotic injury was generally “low” or “very low”, especially for reoperations and subjective or functional outcomes. The factors that lowered the quality according to the GRADE were the high risk of selection and performance bias, the high statistical heterogeneity and the limited number of included studies. Moreover, the indirectness of measurements, the imprecision due to small amount of changes, or the presence of discordant results based on sensitivity analysis further affected the quality. The highest level was “moderate”, and was reported for the compilation, both overall and implant-related”, especially considering a more evident effect of treatment when controlling for the confounding variables through the sensitivity analysis (Figure 11).

Summary of findings:

Dynamic Fixation compared to Static Fixation for Acute syndesmotic Injury

Patient or population: Acute syndesmotic Injury
Setting:
Intervention: Dynamic Fixation
Comparison: Static Fixation

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
Complications (overall) № of participants: 335 (7 RCTs)	**RR 0.55** (0.37 to 0.81)	49.7%	**27.3%** (18.4 to 40.3)	**22.4% fewer** (31,3 fewer to 9,4 fewer)	⨁⨁⨁◯ MODERATE a,b,c	RR=0.36 for inadequate follow-up reduction; RR= 0.10 for recurrent clinical instability\diastasis. No impact of device, screws retain, follow-up
Complications (implant-related) № of participants: 335 (7 RCTs)	**RR 0.28** (0.09 to 0.88)	34.7%	**9.7%** (3.1 to 30.6)	**25.0% fewer** (31,6 fewer to 4,2 fewer)	⨁⨁⨁◯ MODERATE a,b,c	Non significant RR using non suture button devices, or removing screw.
Complications (clinically relevant implant-related) № of participants: 335 (7 RCTs)	Non significant RR. Similar results with DF and SF				⨁◯◯◯ VERY LOW a,b,d,e	RR=0.26 in favour of DF compared fo permanent screws; RR=0.30 in favour of DF when follow-up ≤12 months
Reoperations (overall) № of participants: 335 (7 RCTs)	Non significant RR. Similar results with DF and SF				⨁⨁◯◯ LOW a,e	RR=0.24 in favour of DF compared fo permanent screws
Reoperations (implant-related) № of participants: 335 (7 RCTs)	Non significant RR. Similar results with DF and SF [a]				⨁⨁◯◯ LOW a,e	RR=0.26 in favour of DF compared fo permanent screws
AOFAS score follow up: mean 12 months № of participants: 244 (4 RCTs)	-		-	MD **5.21 points higher** (0.44 higher to 9.98 higher)	⨁⨁◯◯ LOW b,f	SM=6.60 higher in DF at 3 months; SM=8.60 higher at 24 months; No significant SM at 6 months
VAS for pain score follow up: mean 12 months № of participants: 267 (4 RCTs)	-		-	MD **0.57 points lower** (0.87 lower to 0.16 lower)	⨁⨁◯◯ LOW f,g	SM=0.73 lower in DF at 6 months; no significant SM at 3 months and 24 months
Olerud-Morlander score follow up: mean 12 months № of participants: 244 (4 RCTs)	Non significant RR. Similar results with DF and SF				⨁⨁◯◯ LOW b,f	No significant SM also at 3, 6 and 24 months.
Ankle dorsal flexion № of participants: 114 (3 RCTs)	-		-	MD **4.36 ° higher** (0.43 higher to 8.29 higher)	⨁◯◯◯ VERY LOW b,h,i,j	
Ankle plantar flexion № of participants: 114 (3 RCTs)	No signinifcant MD. Similar results with DF and SF				⨁◯◯◯ VERY LOW a,b,h,i,j	
Return to work № of participants: 79 (2 RCTs)	-		-	MD **1.95 weeks lower** (2.97 lower to 0.94 lower)	⨁◯◯◯ VERY LOW j,k	
Return to sport № of participants: 54 (1 RCT)	-		-	mean **5 weeks lower** (8.74 lower to 1.26 lower)	⨁◯◯◯ VERY LOW j,k	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. High risk of selection bias due to inappropriate or unclear randomization and concealement
b. High heterogeneity of the meta-analysis
c. Reduced RR according to sensityvity analysis
d. Arbitrary definition of clinical significance
e. Discordant results according to sensitivity analysis
f. High risk of berformance bias due to inadequate patients blinding
g. Small amount of differences and discordant results based on follow-up
h. High risk of detection bias due to inadequate clinicans blinding
i. Limitations in manual measurements methods
j. Limited number of studies

Figure 11: Summary table of the quality of evidence according to the GRADE for the outcomes after Dynamic Fixation or Static Fixation.

Discussion

The most important finding of the present meta-analysis of RCTs was that the use of dynamic fixation for the treatment of syndesmotic injuries was able to reduce the number of complications and improve clinical outcomes compared to static screw fixation, thus rejecting the initial hypothesis. The inclusion of 7 Level 1 RCTs with 335 patients represents the meta-analysis on this topic with the highest level of evidence and the widest sample size.

Several considerations should be made regarding the management of syndesmotic injuries based on the present results and the available highest-level literature. First of all, most of the reported complications such as implant loosening or breakage could be considered clinically irrelevant, thus limiting the enthusiastic appeal of dynamic fixation. For this reason, we performed a further analysis excluding such events, reporting in fact similar results between static and dynamic fixation. However, when considering only the studies using permanent screws, a higher risk of clinically relevant complications in static fixation was found. Therefore, based on these results, dynamic fixation should be considered superior to screw fixation only when screws are retained. On the other hand, screw removal should not be considered totally harmless. Laflamme et al.[19], which did not performed routine screw removal, reported 3 case of loss of reduction when the screw was removed due to unplanned reasons. Similarly, Andersen et al.[1] reported the doubling of the patients with malreduced syndesmosis during the first year after surgery using serial CT, attributing this finding to loss of reduction occurred after routine screw removal. Therefore, late tibio-peroneal diastasis can be considered a common finding after screw removal, as already described by other authors[29] and, as a consequence, recurrent diastasis or instability could occur[1, 5].

Another relevant issue is the economic burden of syndesmotic injuries management. In fact, when screw removal is planned, the expense for the healthcare system is increased due to the need of a second operation, while in the case of screw retention the procedure remains cost-effective only if re-operation rate is maintained below 17.5% of cases[26]. When evaluating reoperations in our meta-analysis, we found an almost 4-fold increase of implant-related reoperation when comparing dynamic fixation to permanent screw fixation.

Regarding clinical outcomes, dynamic fixation showed better results in terms of ankle pain from 6 to 12 months and ankle function from 12 to 24 months. The increased plantar flexion could have contributed to the more satisfactory outcomes as well, even if the difference of less than 5° could fall within the measurement error or could not considered clinically significant. The clinical superiority of dynamic fixation compared to static fixation can be explained by the biomechanical characteristics of the construct. The restoration of a more physiological movements of the syndesmosis obtained with dynamic devices could have contributed to faster healing and clinical recovery[16]. In fact, a shorter time to return to work and sport activity was reported in 2 studies[5, 19], even considering that a standardized rehabilitation protocols was used in the two groups (despite the possibility of early weight-bearing in the case of dynamic fixation). Another theoretical advantage of dynamic fixation, especially with suture-buttons, is that it may allow more motion and better self-centering of the syndesmosis, thus making anatomic reduction easier to accomplish[39]. In fact, Westermann et al.[39] demonstrated in a cadaveric model the suture button's ability to allow for natural correction of deliberate malreduction, especially with posterior off-axis clamping. The authors postulated that suture-button syndesmotic fixation appeared to take advantage of ankle anatomy by seating the fibula within the tibial incisura fibularis as the construct was tensioned, resulting in superior reduction compared with rigid

screw placement. The detrimental effects of syndesmotic malreduction has been pointed out in clinical studies, since it has been identified as the most important predictor of functional outcome following surgery to treat an ankle fracture[25, 38]. In this regard, an interesting consideration on the use of suture-buttons was highlighted by Kortekangas et al.[18], which performed intra-operative bilateral CT scan to assess syndesmotic reduction. The authors noted a relevant number of patients with syndesmosis considered malreduced after suture button fixation. However, in all cases the syndesmoses were found to be well reduced after open exploration if the ankle was at 90° of dorsiflexion, thus not requiring re-fixation. The correct reduction was confirmed on postoperative CT, with the ankle at 90° of dorsiflexion in a below-knee cast. Therefore, they attributed the high rate of false positive findings in the intraoperative CT to the less rigid fixation of the suture button device, which could allow fibular rotation and posterior slide when the lower limb is in a free position.

Beside the results of statistical analysis, there are also important methodological considerations. The most important is the high risk of bias, which impairs the overall quality of the evidences, despite derived only from RCTs. The main bias and limitations are those typical of surgical RCTs, such as inadequate blinding, small sample and heterogeneity in treatments. Regarding the latter point, we performed a subgroup-analysis considering only patients treated with suture-button, without reporting higher risk of complications like stitch abscess or osteomyelitis, painful aseptic osteolysis and failed stabilization, as suggested is several series[13, 32, 40]. Several technical tips has been in fact suggested to avoid complications and implant removal, such as cutting the FiberWire 1 cm beyond knot and burying end adjacent to fibula, performing a small medial incision to position the button abutting tibial cortex and always applying the button through

the fibular plate[32]. In fact, applying these cautions, Storey et al.[32] reported implant removal in only 8 out of 102 consecutive cases (7.8%).

Beside the high risk of performance and detection bias, the level of evidence for most of the outcomes was rated as "low" or "very low" according to the GRADE. The highest level ("moderate") was reported for the lower risk of overall and implant-related complications. However, this could be questioned due to the inclusion of clinically irrelevant complications as well. Regarding the PROMs employed in the meta-analysis, a 5 to 8 points significant difference in the AOFAS score was found. Despite a minimal clinically important difference in AOFAS score has not been defined for the evaluation of ankle fractures, Andersen et al.[1] proposed a value of 6 points, thus suggesting a real clinical effect of the treatment. Another criticism to the AOFAS is represented by its limited precision, lack of responsiveness, and inclusion of measures obtained by the examiner, thus prone to detection bias[1, 15]. Another limitation is due to the fact that, in order to be as much as conservative as possible in our analysis, we did not take into account the planned screw removal as reoperation. Moreover, the 2-years follow-up does not allow to confirm the results at long-term, thus caution should be used when interpreting the results and the safety of the dynamic fixation. Finally, the strict inclusion criteria mostly to closed Weber B and C fracture in middle-aged patients limits the external validity of the treatment to this subset of patients. Therefore further studies are required to confirm the encouraging results also in younger and athletic populations.

Conclusion

Dynamic fixation of syndesmotic injuries was able to reduce the number of complications and improve clinical outcomes compared to static screw fixation, especially malreduction and

clinical instability or diastasis, at a follow-up of 2 years. A lower risk of reoperation with dynamic fixation was found compared to static fixation with permanent screw. However, lack of patients or personnel blinding, treatment heterogeneity, small samples and short follow-up, limits the overall quality of these evidences.

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