

VIII CONGRESSO NAZIONALE PIEDE DIABETICO INTERASSOCIATIVO SID-AMD

Focus sul piede nella
gestione del diabete

Il piede infetto e Medicazioni e terapie adiuvanti Matteo Monami

*AOU-Careggi
Firenze*

16.00-18.30

I SESSIONE: Linee Guida sulla diagnosi e terapia del piede diabetico

Panel: Cesare Miranda, Matteo Monami, Luca Monge, Alessia Scatena, Luigi Uccioli, Cristiana Vermigli

Moderatori: Roberto Anichini, Enrico Brocco

Introduce: Cristiana Vermigli

1. Criteri per un team multidisciplinare
2. Piede neuropatico
3. Piede infetto
4. Piede Ischemico
5. Medicazioni e terapia adiuvante

DICHIARAZIONE DI CONFLITTO DI INTERESSI

Dichiaro di:

☐ NON avere avuto negli ultimi due anni alcun rapporto di natura finanziaria con soggetti portatori di interessi commerciali in ambito sanitario

☒ AVERE avuto negli ultimi due anni rapporti di natura finanziaria con soggetti portatori di interessi commerciali in ambito sanitario, come di seguito indicato:

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Il piede infetto

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PICO 18 – Debridement della lesione vs nessun debridement

Nei pazienti con diabete e infezione del piede moderata - severa (IDSA grado 3 con osteomielite o 4), il debridement chirurgico della lesione è preferibile a nessun debridement per ridurre il rischio di eventi avversi?

Indicazione di buona pratica basata su una qualità non valutabile delle prove

PICO 22 – Terapia antibiotica locale rispetto a terapia antibiotica sistemica

Nei pazienti con piede diabetico infetto, l'utilizzo della terapia antibiotica locale è preferibile rispetto alla terapia antibiotica sistemica per ridurre il rischio di eventi avversi?

Per terapia antibiotica topica si intende un trattamento che prevede l'applicazione locale di un antibiotico (non di un antisettico), sotto forma di creme o gel, direttamente sulla superficie di un'ulcera.

Indicazione di buona pratica basata su una qualità non valutabile delle prove

PICO 20 – Terapia antibiotica empirica vs terapia antibiotica mirata

Nei pazienti con piede diabetico infetto con mancata remissione, la terapia antibiotica mirata è preferibile rispetto alla terapia antibiotica empirica per ridurre il rischio di eventi avversi?

Indicazione di buona pratica basata su una qualità non valutabile delle prove

4 PICO 19 – Terapia conservativa con approccio chirurgico vs trattamento antibiotico sistemico

Nei pazienti con diabete e osteomielite cronica del piede, l'approccio chirurgico è preferibile rispetto alla sola terapia conservativa con trattamento antibiotico sistemico al fine di ridurre gli esiti avversi?

In letteratura è disponibile un unico RCT che confronta un trattamento antibiotico sistemico versus un intervento chirurgico (conservativo) con trattamenti antibiotico post-chirurgico. Il gruppo trattamento antibiotico (AG) è stato trattato per un periodo di 12 settimane; mentre i pazienti del gruppo di trattamento chirurgico (SG) hanno effettuato un trattamento antibiotico post-operatorio di 10 giorni. Nessuna differenza

PICO 21 – Terapia antibiotica sistemica per un periodo di almeno sei settimane vs altri schemi di trattamento antibiotico sistemico di differente durata.

Nei pazienti con diabete mellito e osteomielite del piede non trattata chirurgicamente, una terapia antibiotica sistemica di almeno sei settimane è preferibile rispetto a schemi di trattamento antibiotico di differente durata, al fine di ridurre esiti avversi?

Figura 1 – Probabilità di guarigione con terapia antibiotica effettuate per 6 settimane vs 12 settimane.

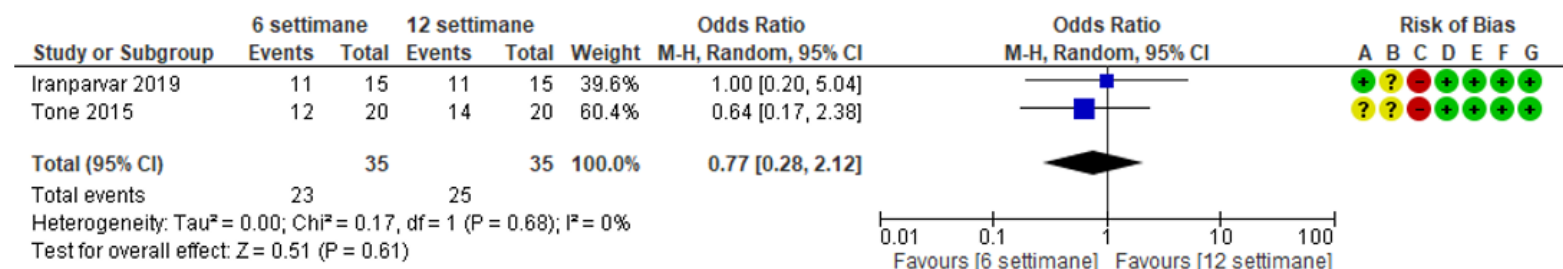
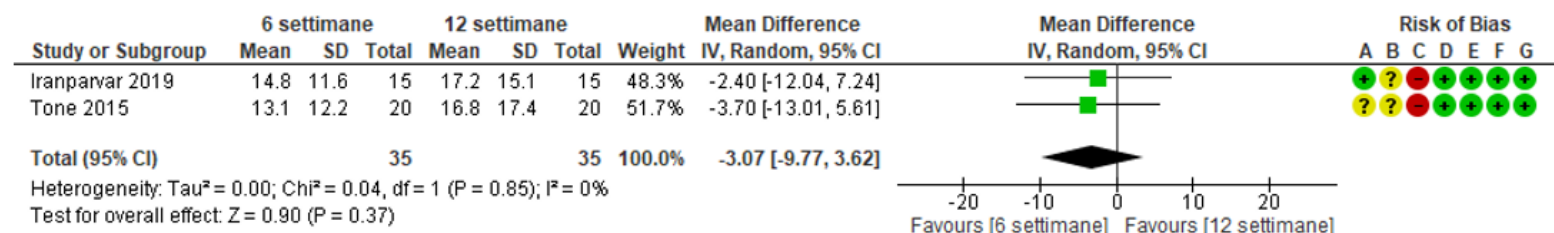
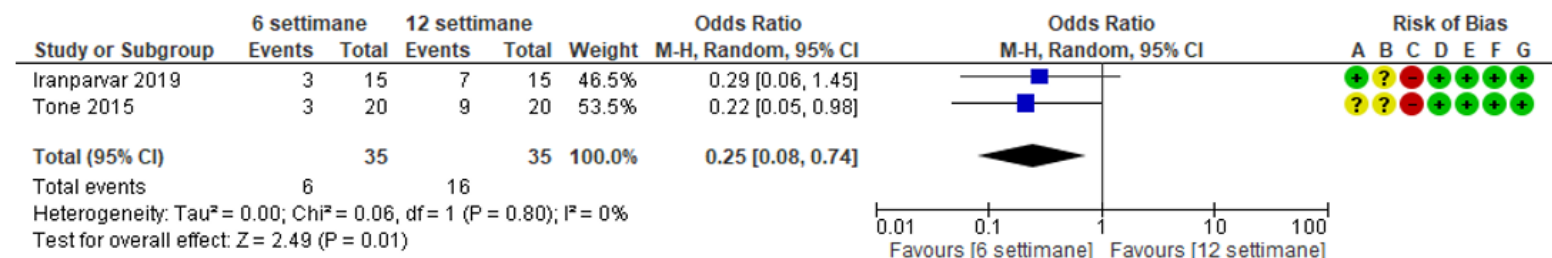


Figura 2 – Tempi di guarigione con terapia antibiotica effettuate per 6 settimane vs 12 settimane.



Minori costi

Figura 3 – Effetti avversi gastrointestinali nei soggetti trattati con terapia antibiotica per 6 settimane vs 12 settimane.



▣ PICO 23 – Biopsia vs tampone

Nei pazienti con diabete e ulcere infette del piede, la biopsia di tessuto profondo/osso è preferibile al tampone superficiale per individuare i patogeni responsabili dell'infezione?

Effetti favorevoli		
Di quale entità sono gli effetti favorevoli dell'intervento?		
Giudizio	Prove a supporto (vedi "Evidenze Supporto")	Considerazioni aggiuntive (vedi "Evidenze Supporto")
Piccoli	In letteratura sono disponibili due RCT^{25,26} che confrontano le performance della biopsia tissutale e quella del tampone superficiale. <i>Guarigione e tempi di guarigione</i> Solo lo studio CODIFI²⁵ riporta il dato senza mostrare differenze tra i due gruppi significative (tassi guarigione: 45.3% (33.5%–56.4%) vs 44.6% (33.0–55.6%); HR biopsia vs. tampone: 1.01 (95% CI 0.65–1.55). <i>Identificazione del patogeno</i> Nello studio CODIFI²⁶, l'identificazione di almeno un patogeno potenziale è stato riportato nel 70.1% dei tamponi contro l'86.1% delle biopsie (p<0.001), con un numero significativamente più basso di agenti contaminanti a favore delle biopsie. Tutti gli altri outcome critici non sono stati considerati nei due trial presi in esame.	

Effetti sfavorevoli		
Di quale entità sono gli effetti sfavorevoli dell'intervento?		
Giudizio	Prove a supporto	Considerazioni aggiuntive
Piccoli	<i>Dolore</i> Biopsia vs tampone: 9.3% vs 1.3%²⁵. <i>Sanguinamenti</i> Biopsia vs tampone: 6.8% vs 1.5%²⁵.	

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IWGDF

3. Dressing/application for enhancing wound healing

1. Dressings should be selected principally on the basis of exudate control, comfort, and cost (**strong; low**).
2. Do not use dressings/applications containing surface antimicrobial agents with the sole aim of accelerating healing of an ulcer (honey, iodine, silver, polyhexamethylene; **strong; low**).
3. Consider the use of the sucrose-octasulfate–impregnated dressing as an adjunctive treatment, in addition to best standard of care, in noninfected, neuro-ischaemic diabetic foot ulcers that are difficult to heal (**weak; moderate**).

The evidence to support the adoption of any of these dressings or application above any other is poor because the available studies are small, usually of short duration of follow-up and are at a high risk of bias.

IWGDF

EXPLORER TRIAL: sucrose-octasulfate-impregnate dressing

	Control dressing group	Sucrose octasulfate dressing group	Adjusted odds ratio (95% CI; p value) or p value
Primary efficacy outcome (ITT cohort)			
Wound closure, confirmed by the investigator	34/114 (30%)	60/126 (48%)	2.60 (1.43–4.73; p=0.002)
Secondary efficacy outcomes (ITT cohort)			
Kaplan-Meier-estimated time to closure (days); mean (95% CI)	180 (163–198)	120 (110–129)	p=0.029
Extrapolated instantaneous Gilman parameter at week 20 (mm per week)	..	..	
Mean (SD)	0.3 (1.1)	0.5 (0.8)	NA
Median (IQR)	0.2 (0.0–0.5)	0.4 (0.0–0.8)	p=0.021 for median comparison
Absolute wound area reduction from day 0 to week 20 (cm ²)	..	..	NA
Mean (SD)	2.3 (5.5)	3.2 (5.2)	NA
Median (IQR)	1.2 (0.6–2.4)	1.8 (0.9–3.8)	p=0.022 for median comparison
Relative wound area reduction from day 0 to week 20 (%)	..	..	
Mean (SD)	42 (115)	72 (47)	NA
Median (IQR)	90 (29–100)	98 (58–100)	p=0.024 for median comparison

Effectiveness of different advanced wound dressings versus standard of care for the management of diabetic foot ulcers: a meta-analysis of randomized controlled trials for the development of the Italian guidelines for the treatment of diabetic foot syndrome

Matteo Monami^{1,8}  · Benedetta Ragghianti¹ · Alessia Scatena² · Cesare Miranda³ · Luca Monge⁴ · Luigi Uccioli⁵ · Laura Stefanon⁶ · Cristina Cappella⁷ · Antonio Silverii¹ · Cristiana Vermigli⁷ · for the Panel of the Italian Guidelines for the Treatment of Diabetic Foot Syndrome and on behalf of SID and AMD

"In patients with neuropathic (non-ischemic and non-infected) foot ulcers, is the use of an active dressing preferable to standard of care, to reduce adverse outcomes and increase the chance of ulcer healing" (PICO #9 [9])?

Effectiveness of different advanced wound dressings versus standard of care for the management of diabetic foot ulcers: a meta-analysis of randomized controlled trials for the development of the Italian guidelines for the treatment of diabetic foot syndrome

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- (1) Alginate dressings: highly absorbent calcium alginate or calcium sodium alginate which can be combined with collagen. The alginate forms a gel at the wound surface level, which can increase absorbency.
- (2) Foam dressings: polyurethane foam dressings designed to absorb ulcer exudate and maintain moist wound surface.
- (3) Hemoglobin spray: topically application of hemoglobin to the wound bed to promote oxygen diffusion and increase granulation tissue formation.
- (4) Hydrocolloids: are occlusive dressings usually composed of a hydrocolloid matrix. This matrix forms a gel to provide a moist environment. Fibrous hydrocolloids have been developed for being more absorbent than standard hydrocolloid dressings.
- (5) Hydrogels: dressing made of insoluble polymers and designed to absorb wound exudate or rehydrate a wound. Hydrogels are supplied in either flat sheets or as beads.
- (6) Hyaluronic acid: is a naturally occurring, non-immunogenic, biodegradable polysaccharide acting with fibrin to support the influx of fibroblasts and endothelial cells into the wound site and the subsequent formation of granulation tissue. Interventions assessed: HA-impregnated inert pads, HA gel, or cream; pad or matrix composed entirely of HA.
- (7) Protease-modulating matrix dressings: capable of regulating the activity of proteolytic enzymes in chronic wounds.
- (8) Sucrose octasulfate-impregnated dressings (Technology Lipido-Colloid-Nano-OligoSaccharide Factor): the potassium salt contained in the sucrose octasulfate inhibits the excess of matrix metalloproteinase and interacts with growth factors promoting the restoration of their biological functions and contributing to new tissue formation.
- (9) Silver-impregnated dressings: different types (foam, hydrocolloids, etc.) of dressing containing silver ions usually used for treating infected ulcers.
- (10) Honey-impregnated dressings: medical-grade honey dressings proposed as an antimicrobial/anti-inflammatory local treatment which can be used both for acute and chronic ulcers.
- (11) Microorganism-binding dressings: are capable of binding microorganisms in a two water-repellent surfaces and subsequently removed at dressing change.

Dressings with antimicrobial properties

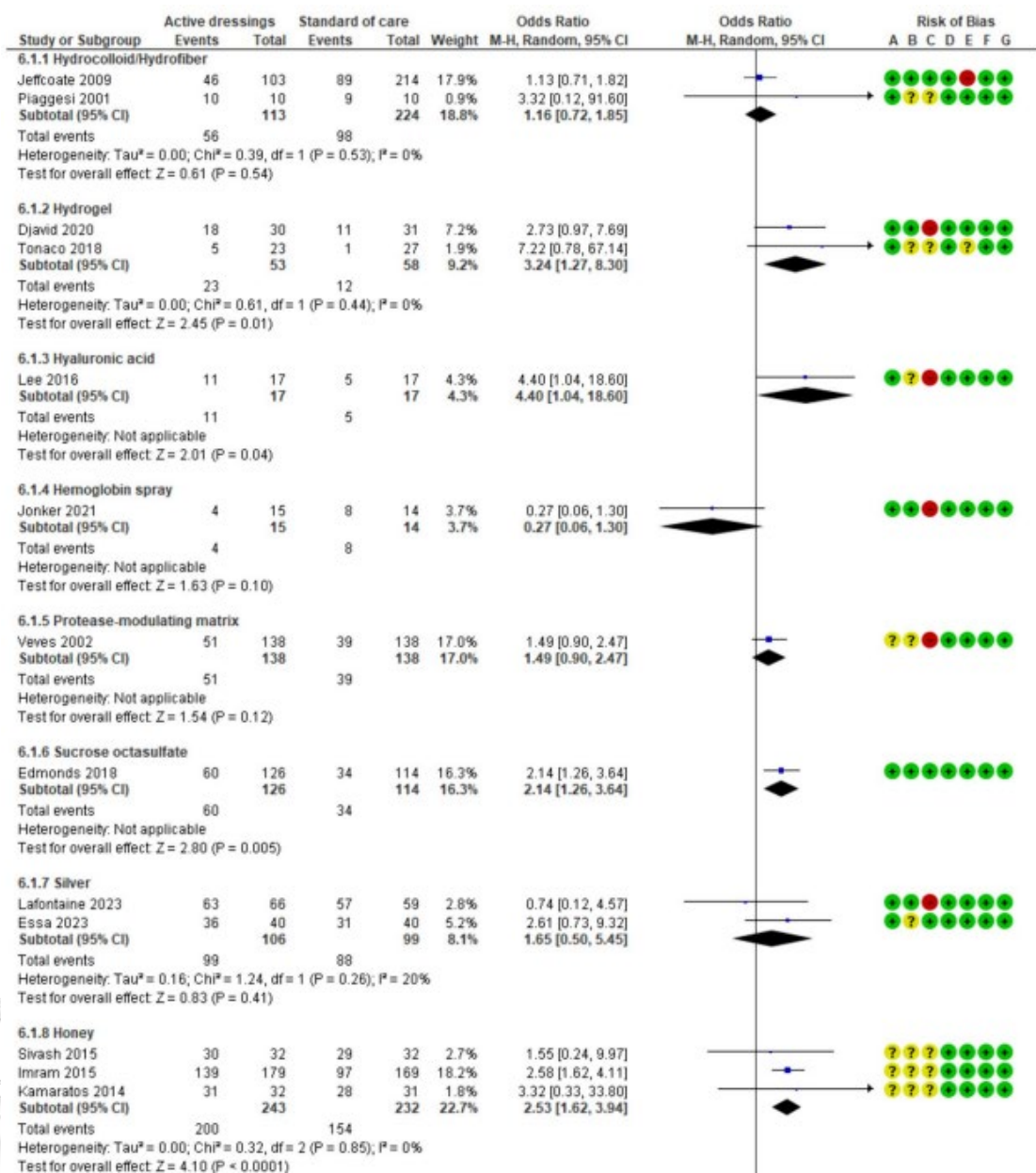
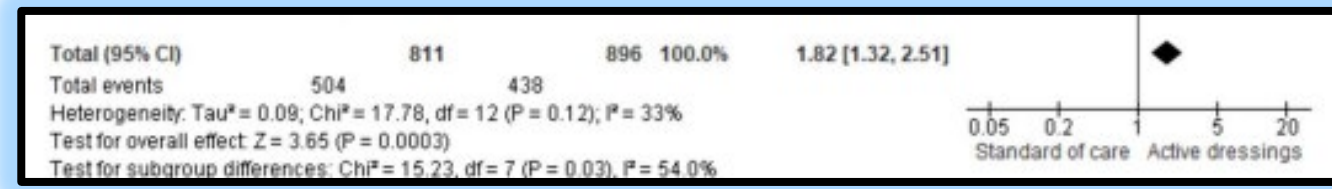


Fig.1 Effects of active dressings on ulcer healing in comparison with standard therapy/placebo (control)



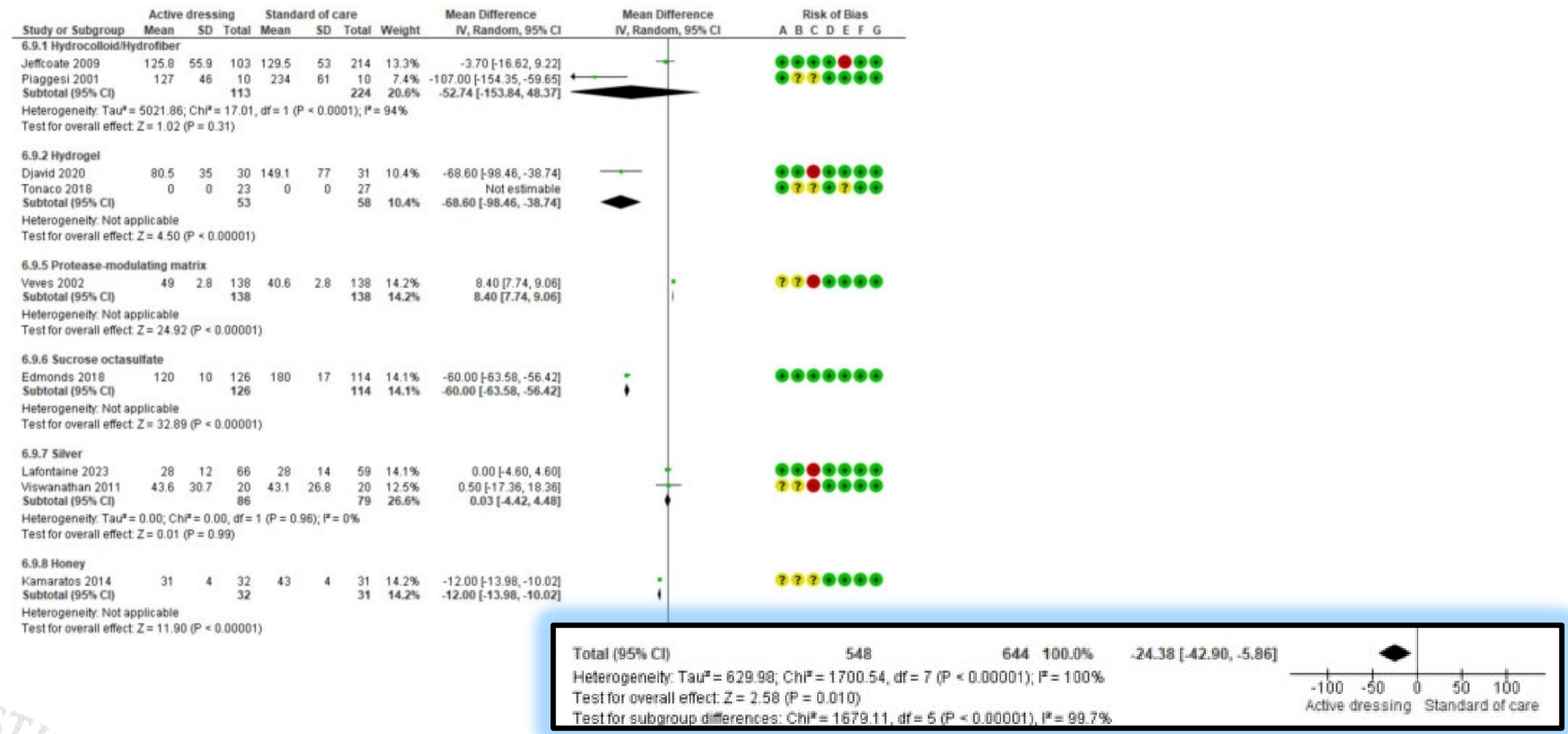


Fig. 2 Effects of active dressings on the ulcer time-to-healing in comparison with standard therapy/placebo (control)

Effectiveness of most common adjuvant wound treatments (skin substitutes, negative pressure wound therapy, hyperbaric oxygen therapy, platelet-rich plasma/fibrin, and growth factors) for the management of hard-to-heal diabetic foot ulcers: a meta-analysis of randomized controlled trials for the development of the Italian Guidelines for the Treatment of Diabetic Foot Syndrome.

Matteo Monami¹, Alessia Scatena², Benedetta Ragghianti¹, Cesare Miranda³, Luca Monge⁴, Antonio Silverii¹, Luigi Uccioli⁵, Cristiana Vermigli⁸, for the Panel of the Italian Guidelines for the Treatment of Diabetic Foot Syndrome *and on behalf of SID and AMD.*

"In patients with diabetes and recalcitrant foot ulcers, is EMA-approved adjuvant local or systemic therapy preferable to the standard of care to reduce adverse outcomes" (PICO #28)²⁵?

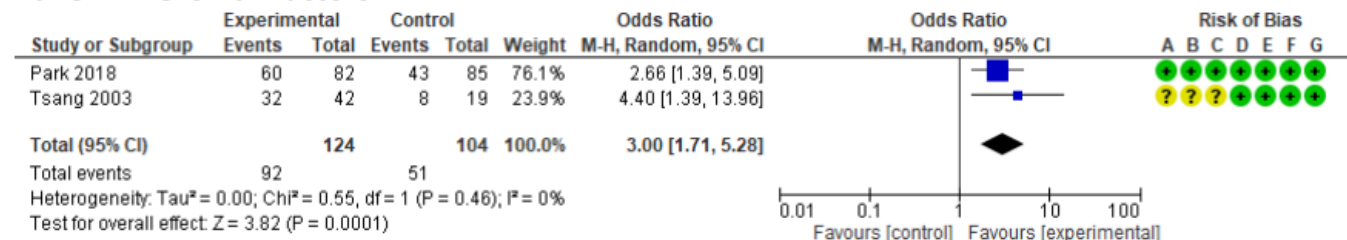
Effectiveness of most common adjuvant wound treatments (skin substitutes, negative pressure wound therapy, hyperbaric oxygen therapy, platelet-rich plasma/fibrin, and growth factors) for the management of hard-to-heal diabetic foot ulcers: a meta-analysis of randomized controlled trials for the development of the Italian Guidelines for the Treatment of Diabetic Foot Syndrome.

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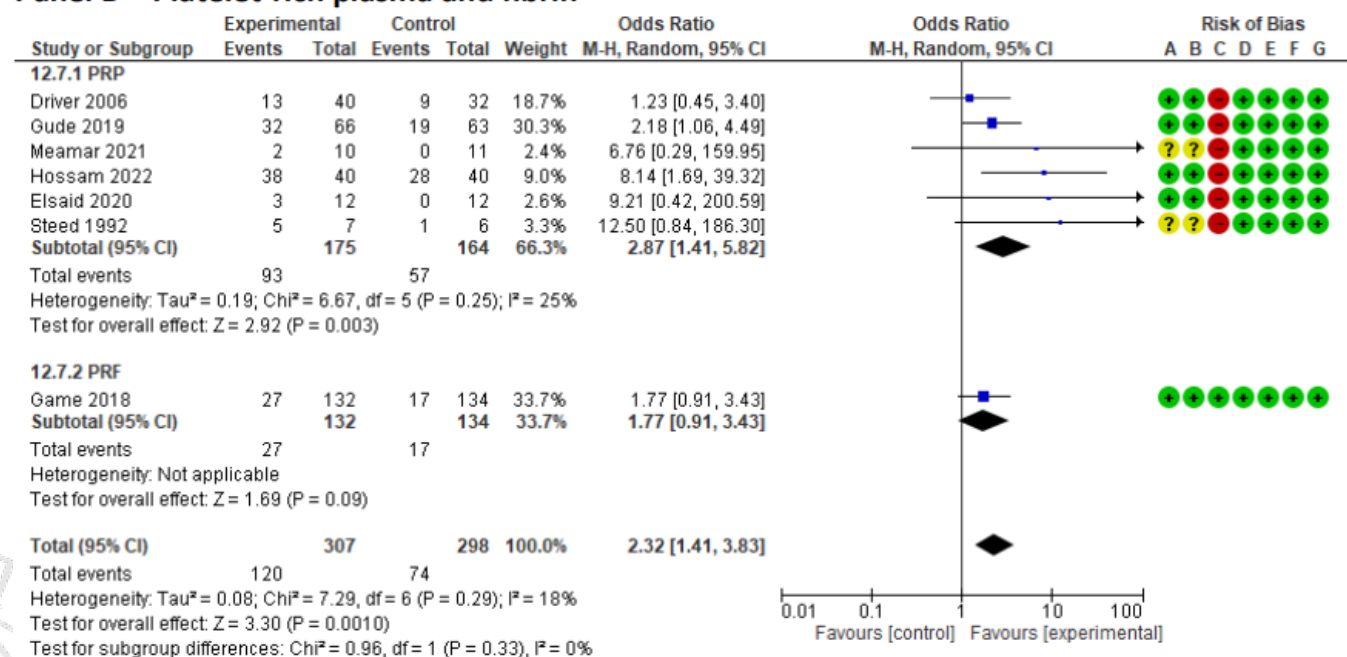
- 1) Growth factors (GF): platelet-derived, endothelium-derived, or macrophage-derived growth factors including granulocyte colony-stimulating factor, platelet-derived growth factor, epidermal growth factor, transforming growth factor, fibroblast growth factor, vascular endothelial growth factor, insulin-like growth factor, and keratinocyte growth factor.
- 2) Platelet-rich plasma and fibrin dressings (PRP/F): autologous or allogeneic platelet-rich plasma or fibrin dressings. Cytokines, growth factors, and chemokines can stimulate and promote the healing process.
- 3) Skin substitutes (SS): bioengineered or artificial skin (autografts, allografts, or xenografts) which can be of help in repairing skin defects. Skin substitutes were divided into three main subgroups: placental-based tissue products (PTP), skin substitutes with living cells (SWLC) (e.g., Hyalograft, Apligraf), and acellular skin substitutes (AS) (e.g., Graftjacket, Integra).
- 4) Hyperbaric oxygen therapy (HBOT): the topical or systemic administration of oxygen can increase the healing rate since oxygen is an essential component in the wound-healing cascade (e.g., angiogenesis, antioxidant generation, collagen synthesis, etc.).
- 5) Negative pressure wound therapy (NPWT): involves the application of a wound dressing attached to a vacuum suction machine, which can collect high volumes of wound exudate, thus reducing the frequency of dressing changes. The application of mechanical force to the wound bed could promote wound healing by increasing local perfusion and removing infected material and exudate.

Figure 1 – Effects of individual adjuvant therapy on the chance of ulcer healing versus standard therapy/placebo (control). A: Random sequence generation; B: Allocation concealment; C: Blinding of participants and personnel; D: Blinding of outcome assessment; E: Incomplete outcome data; F: Selective reporting; G: Other bias. PRP: Plasma-Rich Platelet; PRF: Plasma-Rich Fibrin.

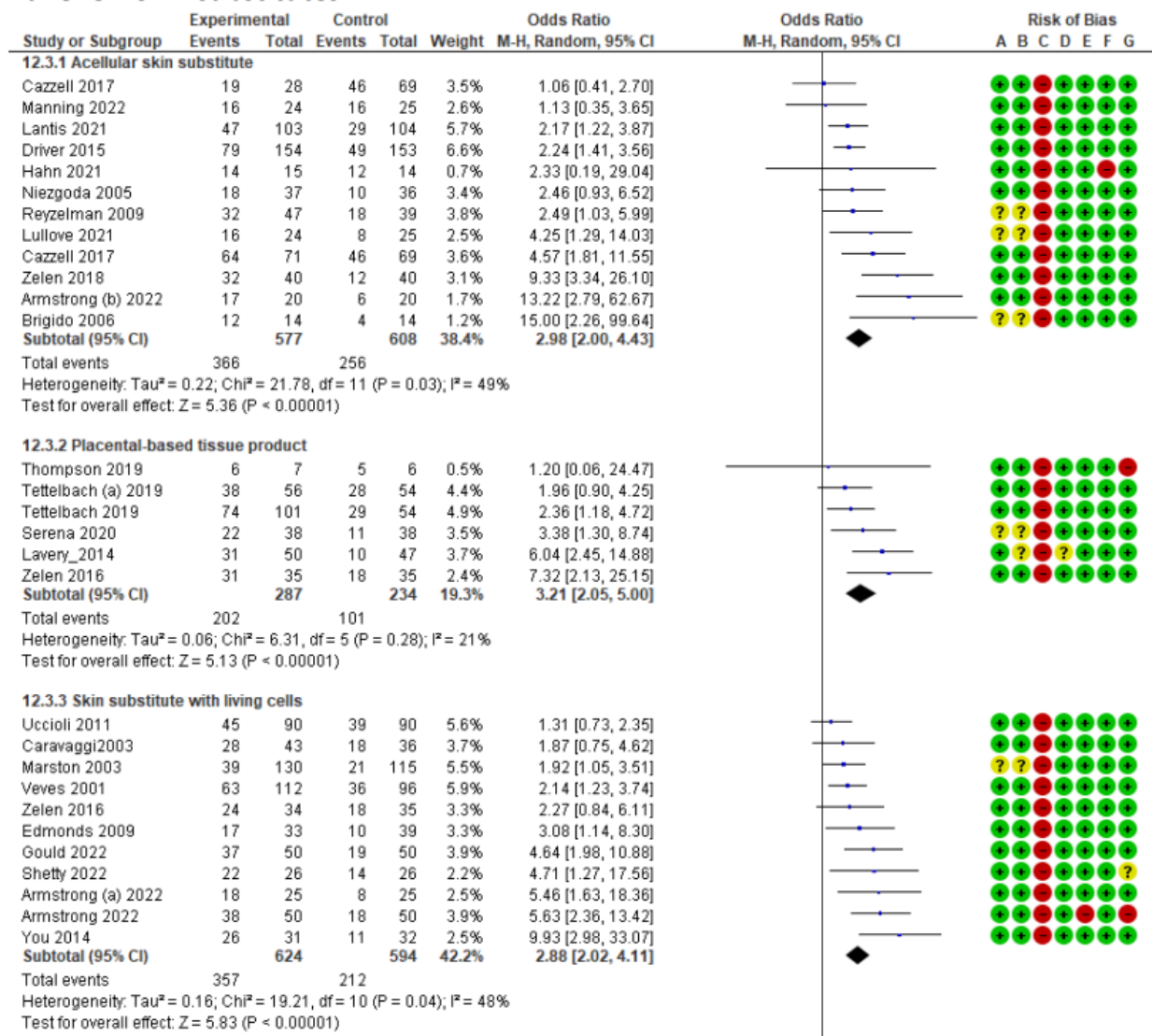
Panel A – Growth Factors



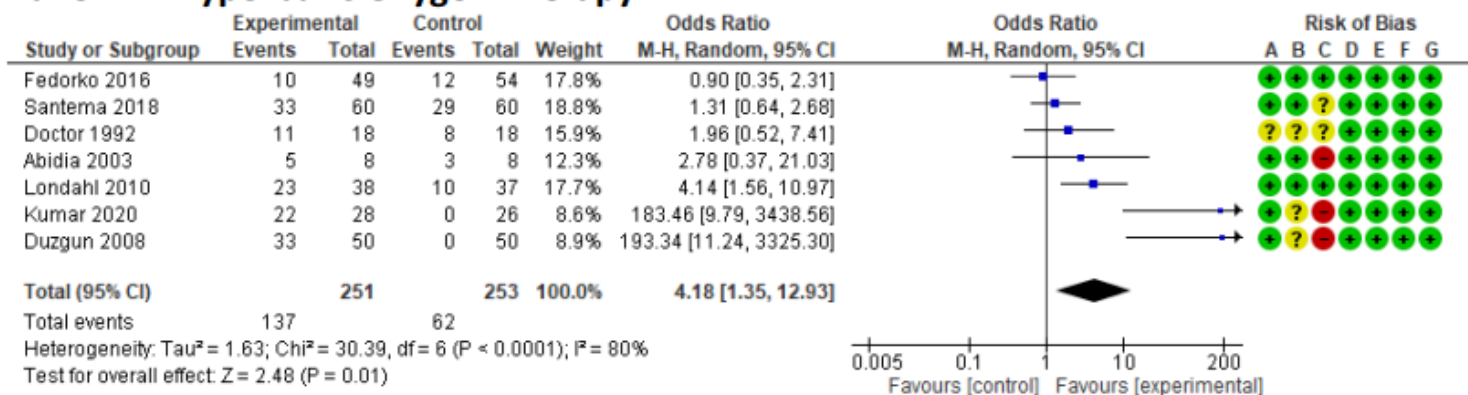
Panel B – Platelet-rich plasma and fibrin



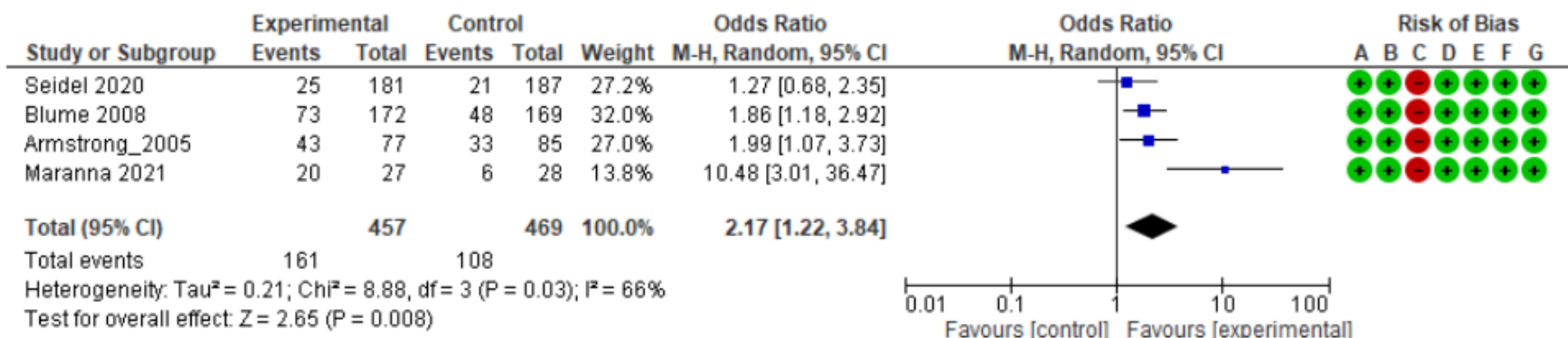
Panel C – Skin substitutes



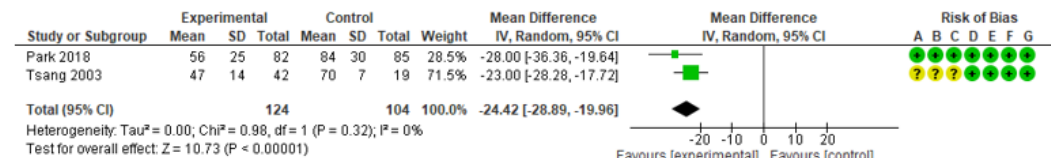
Panel D – Hyperbaric Oxygen Therapy



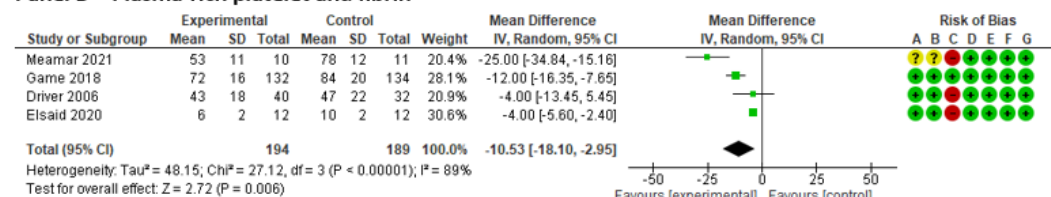
Panel E – Negative pressure wound therapy



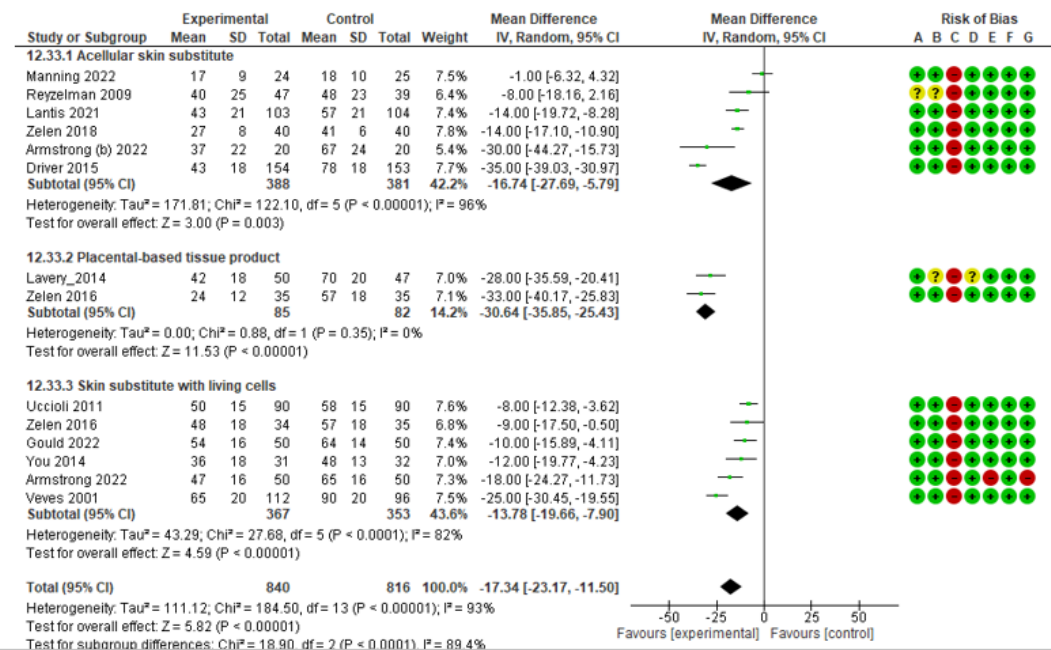
Panel A – Growth factors



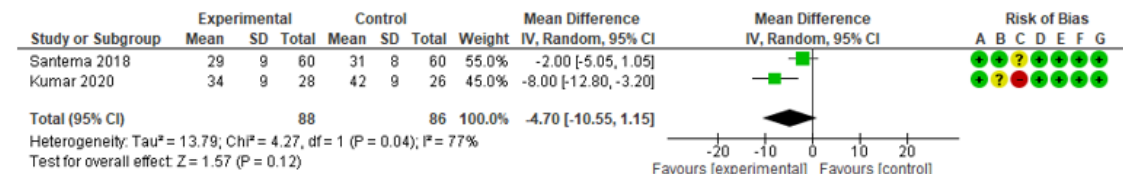
Panel B – Plasma-rich platelet and fibrin



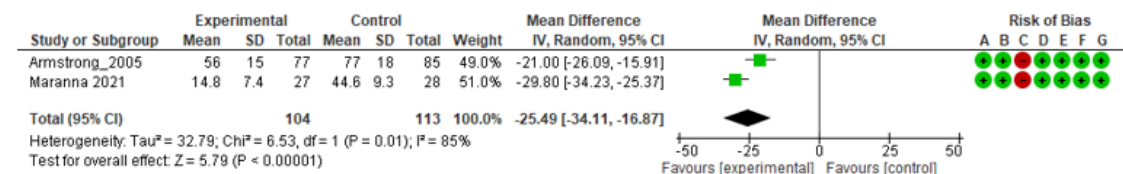
Panel C – Skin substitutes



Panel D – Hyperbaric Oxygen Therapy



Panel E – Negative Pressure Wound Therapy



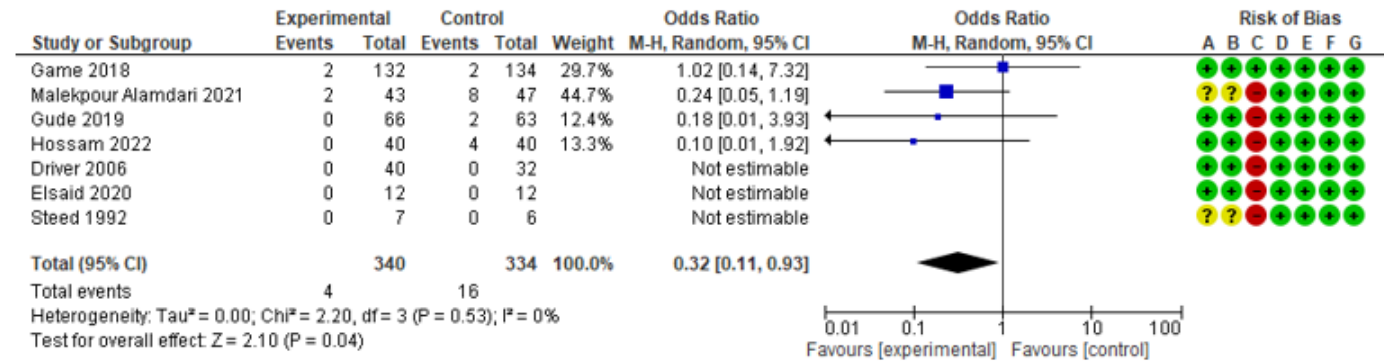
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

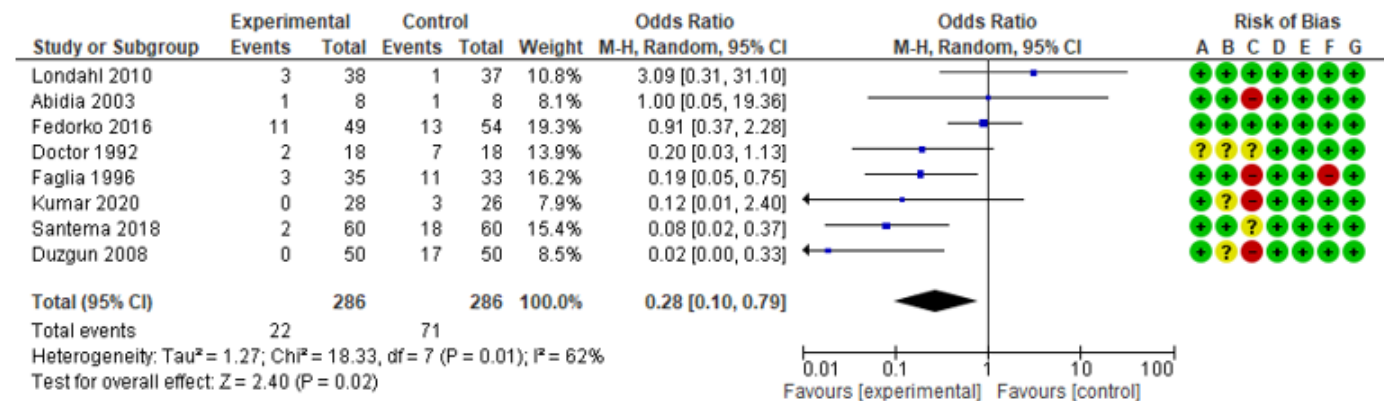
Figure 3S – Effects of adjuvant therapies on time-to-healing, in comparison with placebo/standard of care. A: Random sequence generation; B: Allocation concealment; C: Blinding of participants and personnel; D: Blinding of outcome assessment; E: Incomplete outcome data; F: Selective reporting; G: Other bias.

Figure 5S – Effects of adjuvant therapies on the risk of major amputations, in comparison with placebo/standard of care. A: Random sequence generation; B: Allocation concealment; C: Blinding of participants and personnel; D: Blinding of outcome assessment; E: Incomplete outcome data; F: Selective reporting; G: Other bias.

Panel A – Plasma-rich platelet and fibrin



Panel B – Hyperbaric Oxygen Therapy



La (in)sostenibilità dei costi del....piede

La (in)sostenibilità dei costi del piede



R.L., 62 years, male

RLP068 (Photodynamic therapy)+
Dermal substitute +
CO₂ laser +
PTA su ATA +
Local antibiotics+ (CaS beds)
Minor amputation
VAC therapy
Hyperbaric oxygen therapy
SOC

La (in)sostenibilità dei costi del piede

12 weeks



36 weeks – 4 years



R.L., 62 years, male

RLP068 (Photodynamic therapy)+
Dermal substitute +
CO2 laser +
PTA su ATA +
Local antibiotics+ (CaS beds)
Minor amputation
VAC therapy
Hyperbaric oxygen therapy
SOC

Total: **20,550 € (8 months)**

Major amputation: **21,065€** (including rehabilitation)
1 QALY = 30,825 € (per farmaco antitumorale 40-100,000€)