

Evidence for Collagen/ORC Therapies- In vitro, Ex vivo and in Clinical Practice



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ABSTRACT

The selection of a treatment for chronic wounds should be based on good clinical practice, combined with an objective review of the various types of evidence that are available to support product use. While randomised clinical trials are deemed the ultimate statistical proof that a product is significantly better than another treatment, they are rarely undertaken with chronic wound therapies due to patient heterogeneity and cost. As a result many products rely on laboratory or animal data to support their use. The use of *in vitro* and *in vivo* data is scientifically acceptable, however to make such data useful in treatment selection, they must relate to the clinical situation.

In this study, we evaluated the effectiveness of collagen/ORC to control proteases. Our previous studies have shown that both matrix metalloproteinases (MMPs) and neutrophil-derived elastase predominate in the chronic wound environment. Therefore we tested the effect of collagen/ORC on both classes of proteases.

Our *in vitro* and *ex vivo* studies show that collagen/ORC significantly reduces MMP and elastase activities. The ability of collagen/ORC to reduce elastase levels has been attributed to the ORC component. Other collagen containing dressings tested *in vitro* showed less ability to reduce MMP levels, and limited effectiveness in reducing elastase activity. We confirmed the efficacy of collagen/ORC *in vitro* and *ex vivo* by measuring the level of protease activities in chronic wounds, after treatment with collagen/ORC.

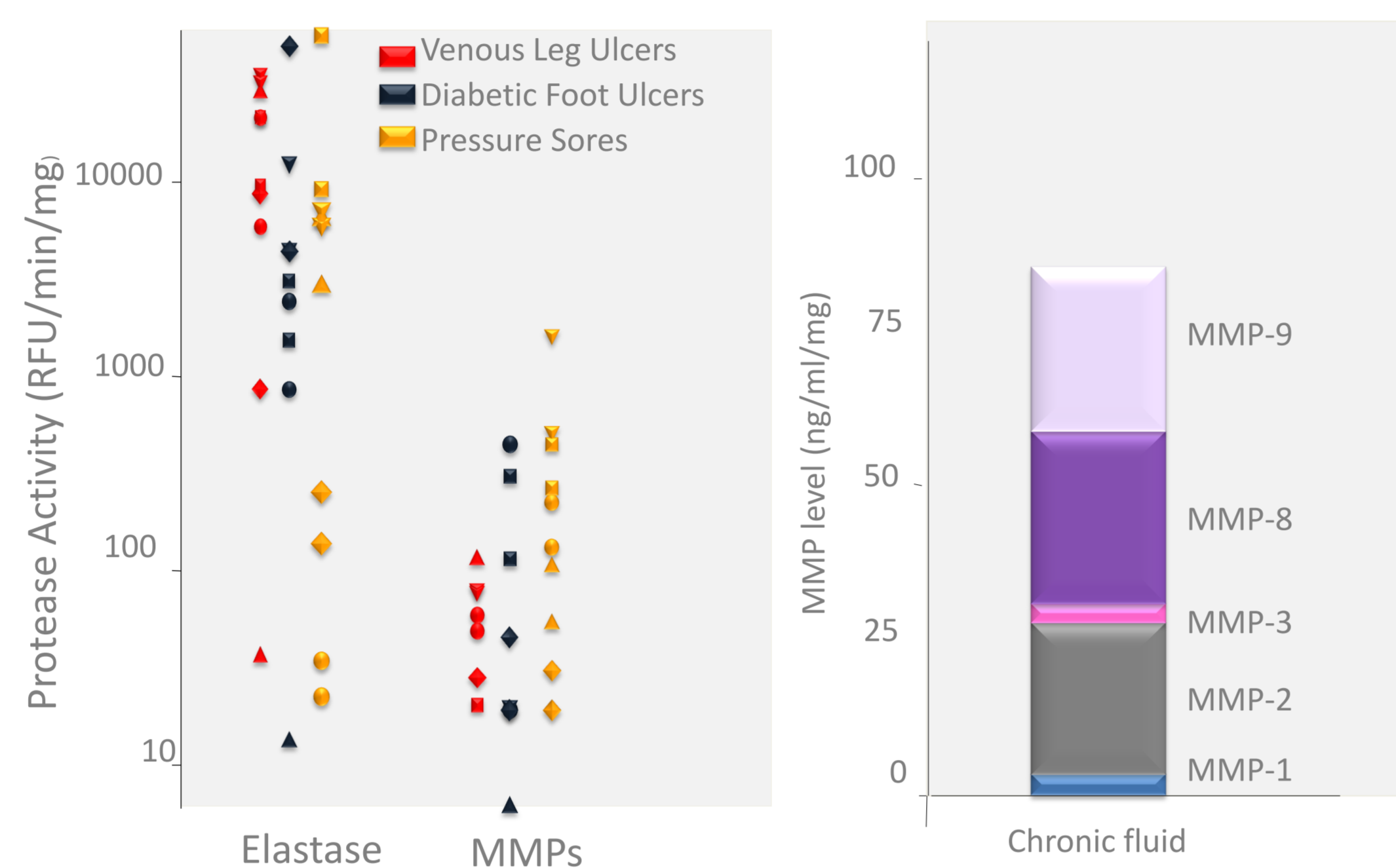
These clinical results validate our *in vitro* and *ex vivo* studies, showing that collagen/ORC binds and inactivates proteases. We believe that a combination of *in vitro*, *ex vivo* and in patient studies should be used to increase our confidence in product selection. This study provides multiple levels of evidence to support the selection and utilisation of collagen/ORC as a method of reducing the levels of protease activities in chronic wounds.

OBJECTIVES

- To examine the levels of evidence which exist to support the ability of Collagen/ORC therapies to reduce proteases in chronic wounds
- To determine if our *in vitro* and *ex vivo* test systems are clinically relevant

Inflammatory Proteases Elevated in Chronic Wounds

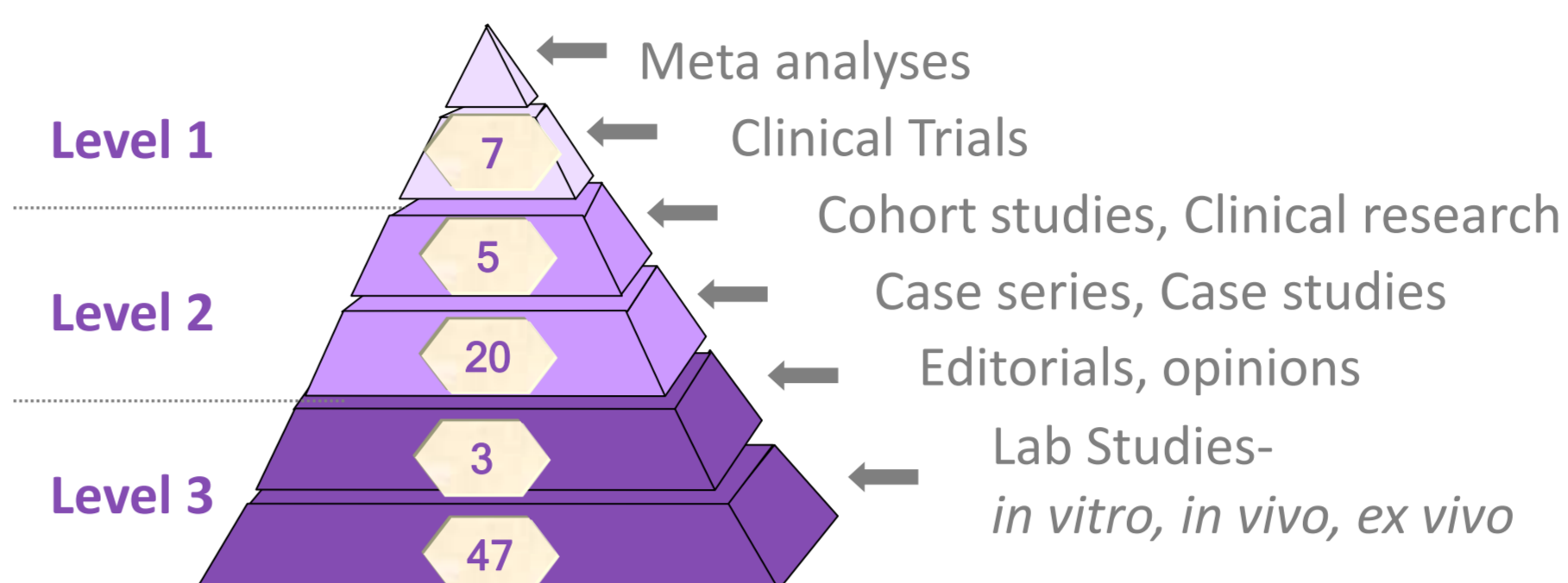
Published: Cullen, B. et al., (2002) Wound Rep Reg. 10: 16-25



This study demonstrates

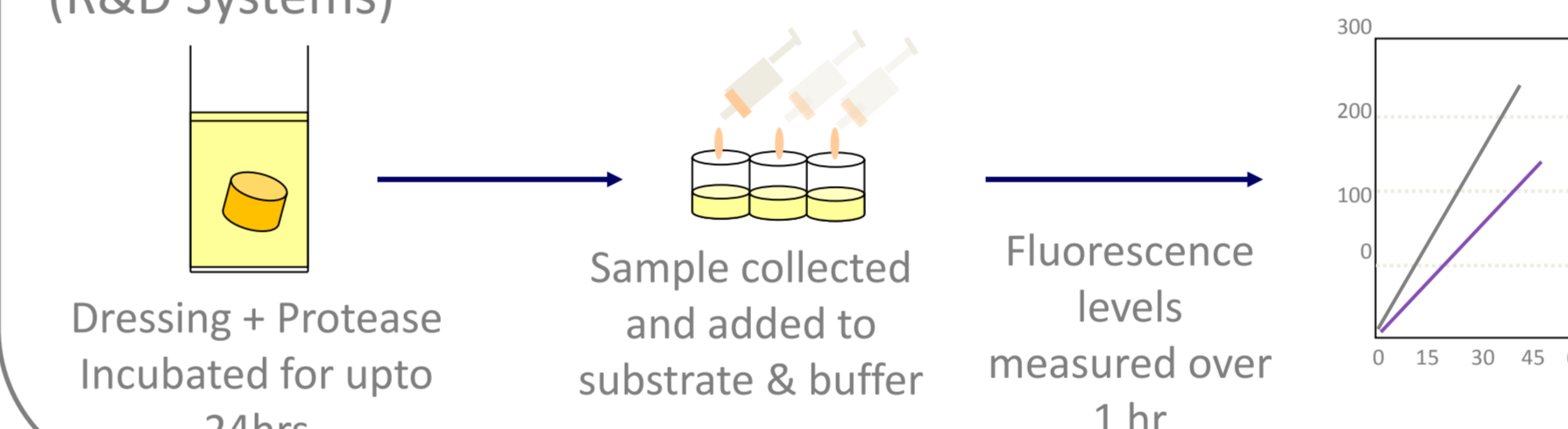
- Elastase is the predominate protease in chronic wound fluid
- MMPs were also found to be in excess in chronic wound fluid
- MMP-2, MMP-8 & MMP-9 are the main MMPs present in wound fluid

Evidence for Collagen/ORC Therapies



Inflammatory Proteases – Measurement Methods

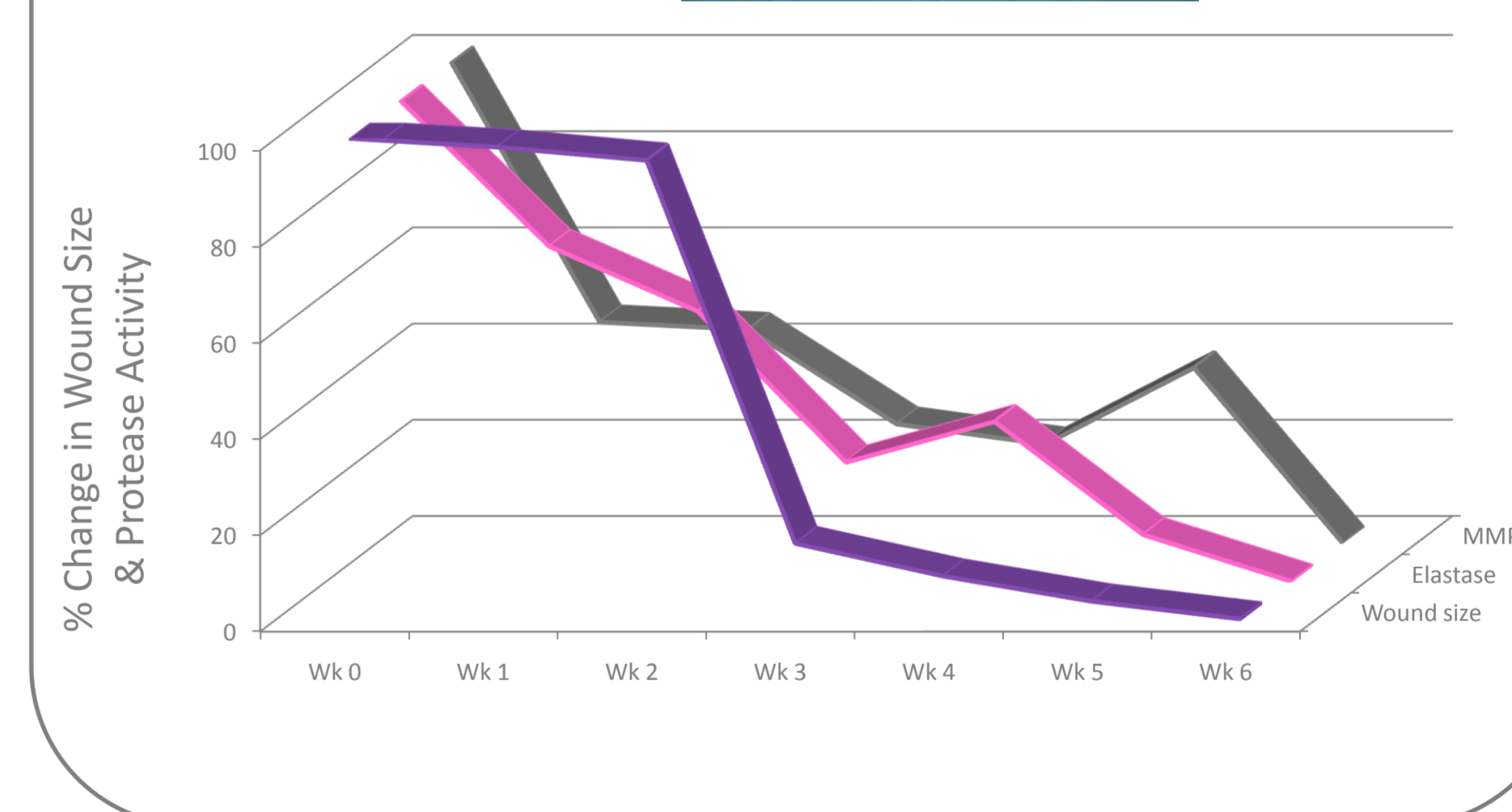
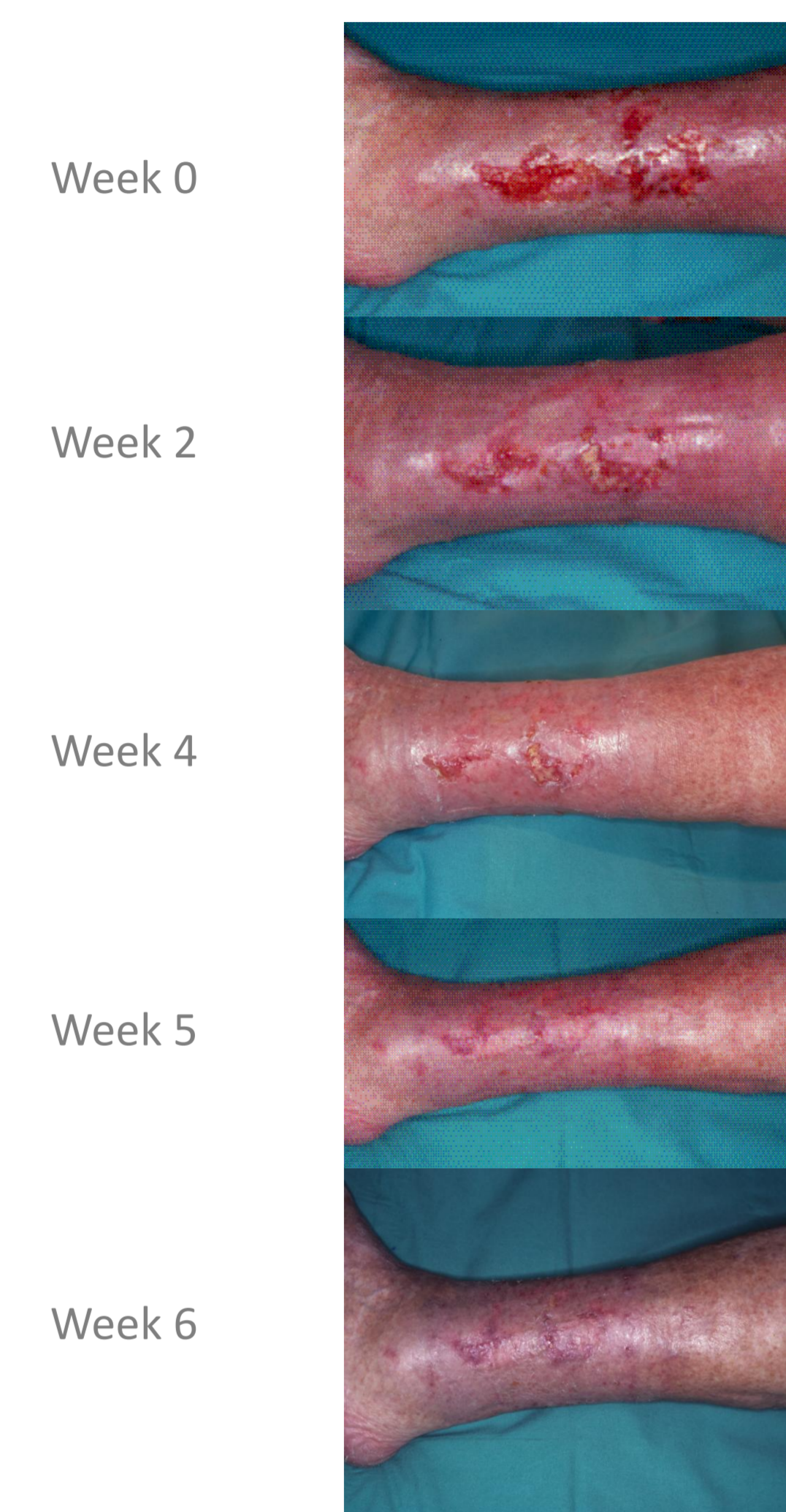
The effect of Collagen/ORC on protease levels was evaluated using protease activity assays. Clinically relevant levels of proteases, or chronic wound fluid was used in the assay. Peptide substrate with a fluorescent reporter groups (AMC) was used for the activity assays in combination with an appropriate buffer system. Neutrophil-derived elastase measured using a specific substrate and buffer system. 0.1M HEPES, pH 7.5, 0.5M NaCl, 10% DMSO. MMP8 & MMP 9 levels were measured using ELISA based activity assays (R&D Systems).



Level 2 Evidence - Effect in Patients

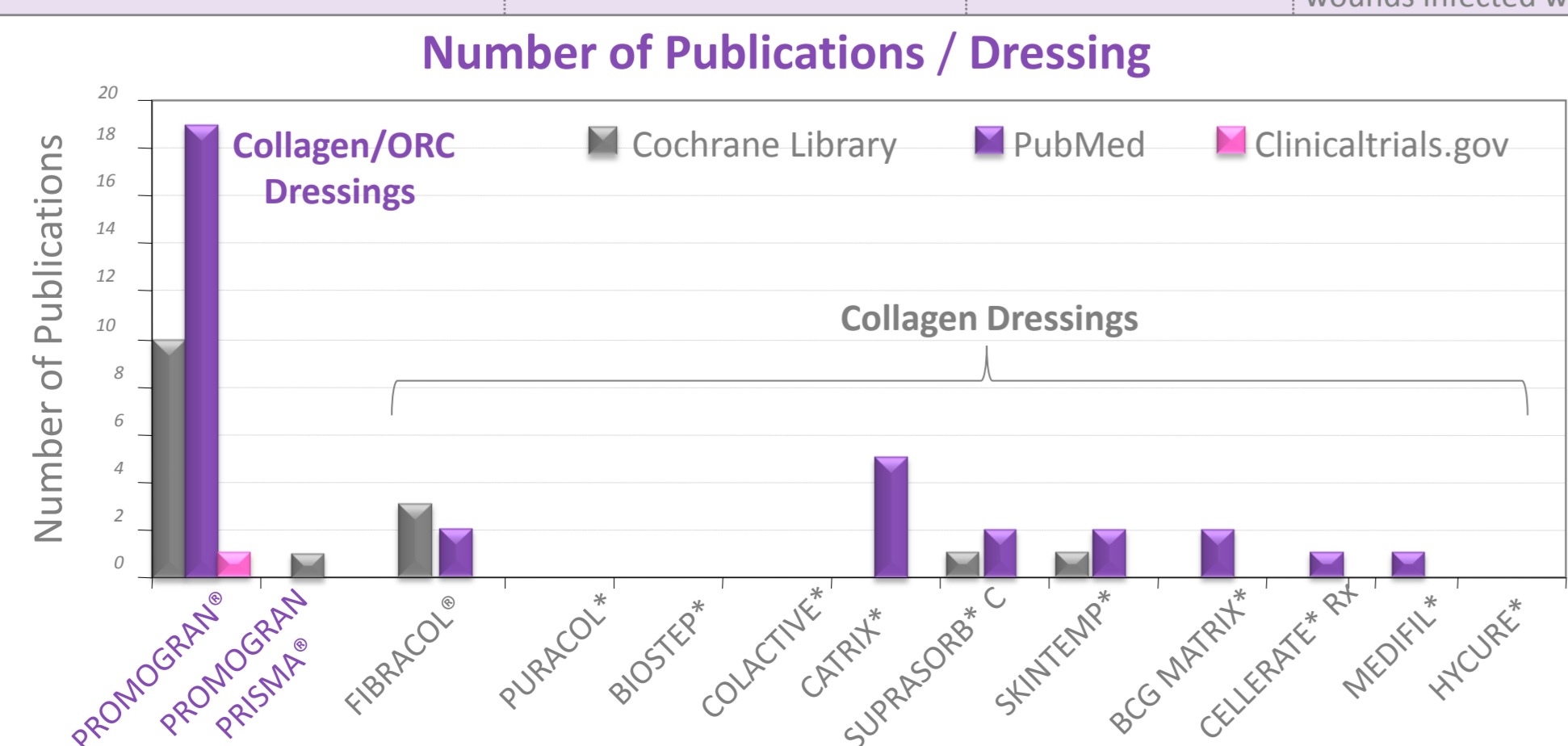
Patient Age: 80
Aetiology: venous-arterial mixed leg ulcer
Wound age: 6 months
Wound size: 34.5cm²

Wound healed after 6 weeks Collagen/ORC therapy



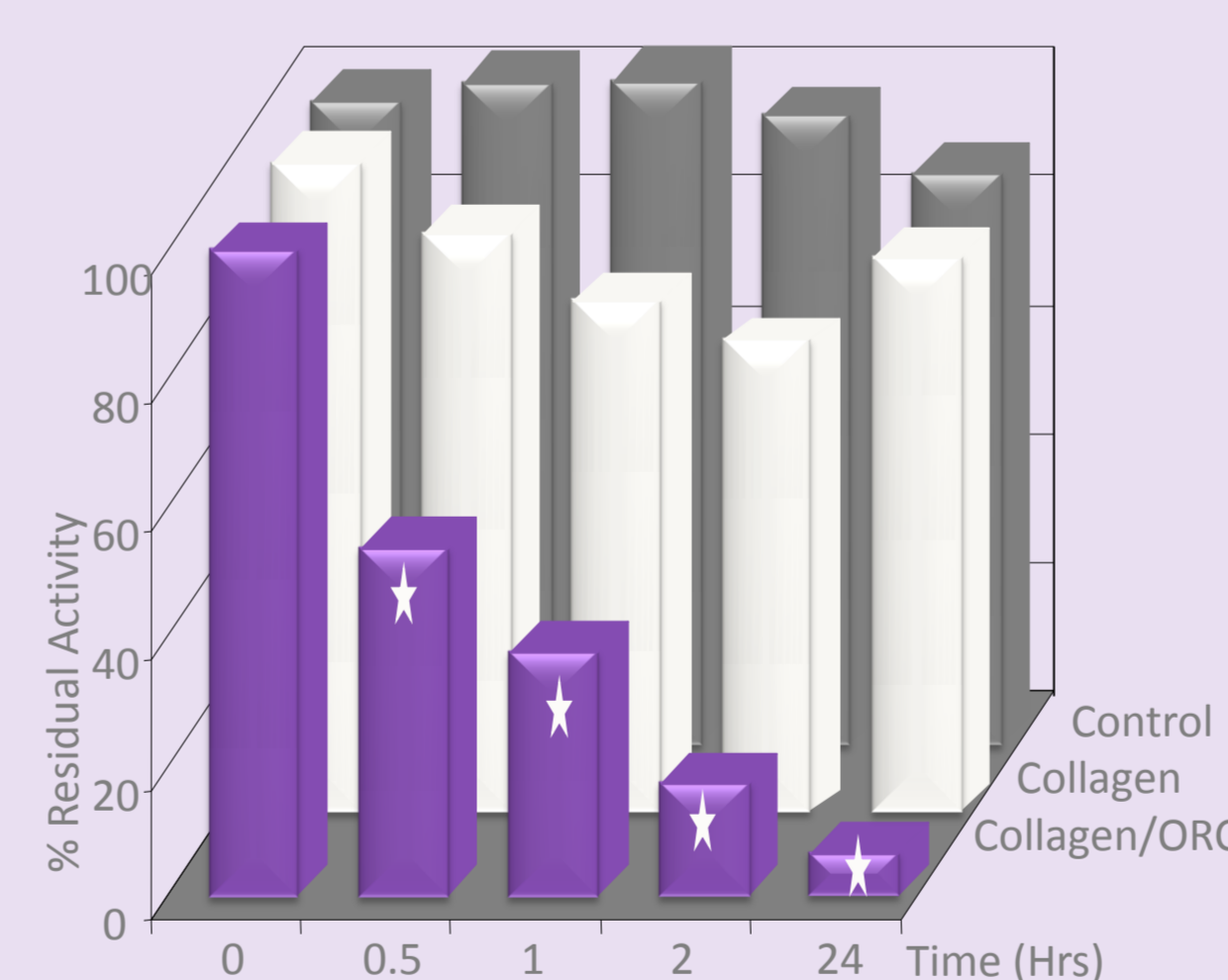
Level 1 Evidence for Collagen/ORC Therapies

Study Reference	Therapy	Design	Selection Criteria	Clinical Outcomes
Veves A, et al. Arch Surg 2002; 137(7): 822-7	PROMOGRAN® vs standard treatment (saline moistened gauze) for 12 weeks	Randomised prospective controlled multicenter clinical trial n=276	Diabetic foot ulcers	More wounds achieved complete healing with PROMOGRAN® treatment, especially in wounds <6 months duration (45% vs 33%, p=0.056)
Vin F, et al. J Wound Care 2002; 11(9): 335-341	PROMOGRAN®+ compression vs non-adherent + compression for 12 weeks	Randomised prospective controlled multicenter clinical trial n=73	Venous leg ulcers	PROMOGRAN® accelerates healing in venous leg ulcers; 20% more wounds were characterised as healing or improved in favour of PROMOGRAN® (p=0.0797). A significant reduction in wound area was achieved with PROMOGRAN® over compression alone (p<0.0001)
Nisi G, et al. Chir Ital 2005 ; 57(4) : 465-8	PROMOGRAN® vs moist wound healing	Randomised, prospective, controlled, clinical trial n=80	Pressure sores	More wounds achieved complete healing with PROMOGRAN® (90% vs 70%), within shorter healing times and proved more cost-effective
Lazaro-Martinez JL, et al, Circ Esp 2007; 82(1): 27-31	PROMOGRAN® vs moist wound healing for 6 weeks	Randomised, prospective, controlled, clinical trial n=40	Diabetic foot ulcers	Significantly more wounds achieved complete healing with PROMOGRAN®, 63% vs 15% (p<0.03). Healing time was significantly shorter with PROMOGRAN®, 23.3 vs 40 days (p<0.01)
Wollina U, et al, Int J low extrem Wounds 2005; 4(4): 214-24	PROMOGRAN® vs moist wound healing for 2 weeks	Randomised, prospective, controlled, clinical trial n=30 vs n=10	Venous leg ulcers	PROMOGRAN® treated wounds showed a significant improvement in quality of healing and pain levels, as early as 1-week post treatment. A significant reduction in ulcer area was measured 2-weeks post-treatment (p<0.05). Study showed improved wound microcirculation with PROMOGRAN® therapy
Lanzara S, et al. EWMA 2008	PROMOGRAN PRISMA® + compression vs best standard treatment (moist wound healing + compression) for 12 weeks	Randomised prospective controlled pilot study n=30	Venous leg ulcers	Patients were 4 times more likely to heal when treated with PROMOGRAN PRISMA® (OR=4.3; p<0.04). A significant reduction in wound size was achieved with PROMOGRAN PRISMA® (p<0.00005).
Gottrup F, et al. Presented at EWMA 2010	PROMOGRAN PRISMA® vs best standard of care for 14 weeks	Randomised prospective controlled clinical study n=25 vs n=15	Diabetic foot ulcers	PROMOGRAN PRISMA® stimulated healing while protecting the wound from infection. Significantly more wounds showed >50% reduction in wound area (Margolis Index) at week 4 (70% vs 43%, p=0.035), a trend which continued throughout the 14 weeks of treatment. Significantly more wounds infected in control group (33%) vs no wounds infected when PROMOGRAN PRISMA® was used (p=0.012).

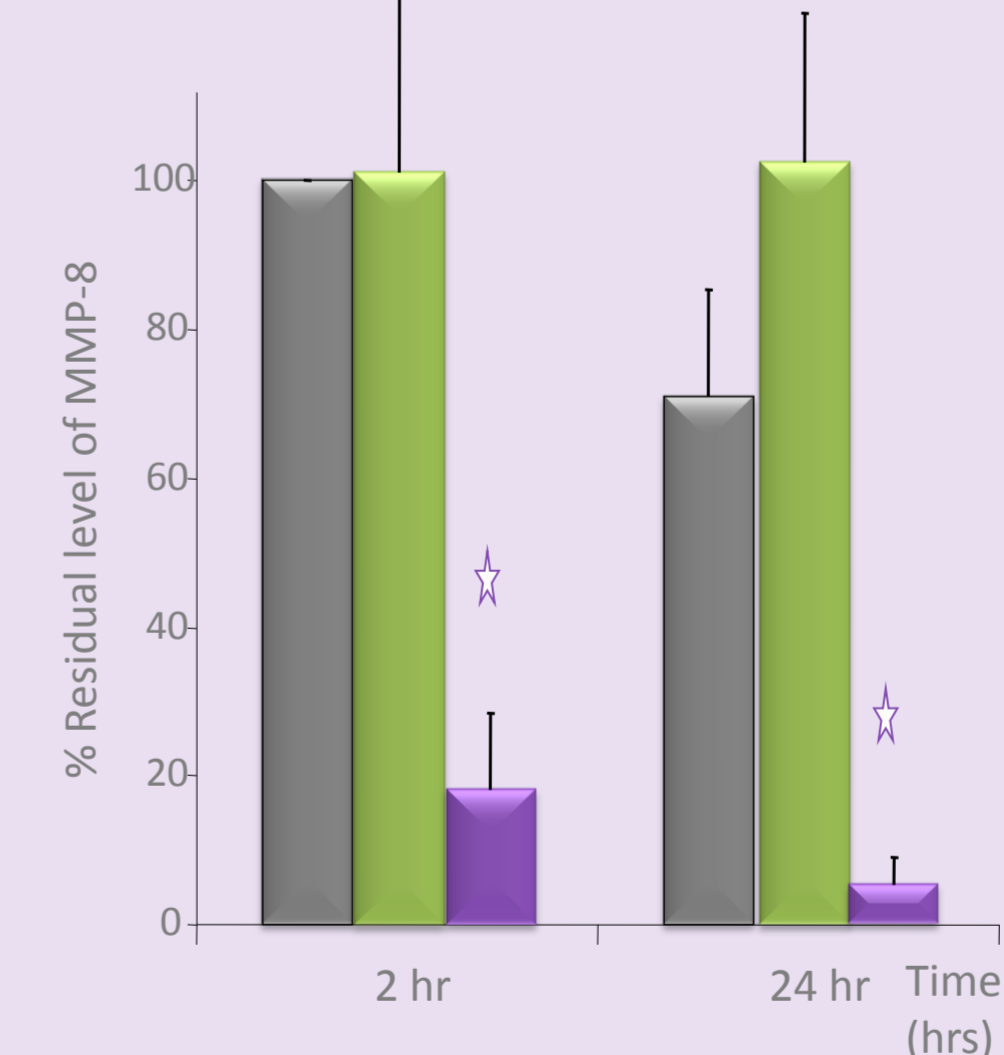


Level 3 Evidence - Collagen/ORC Reduces Protease Levels – Elastase, MMP-8, MMP-2, MMP-9

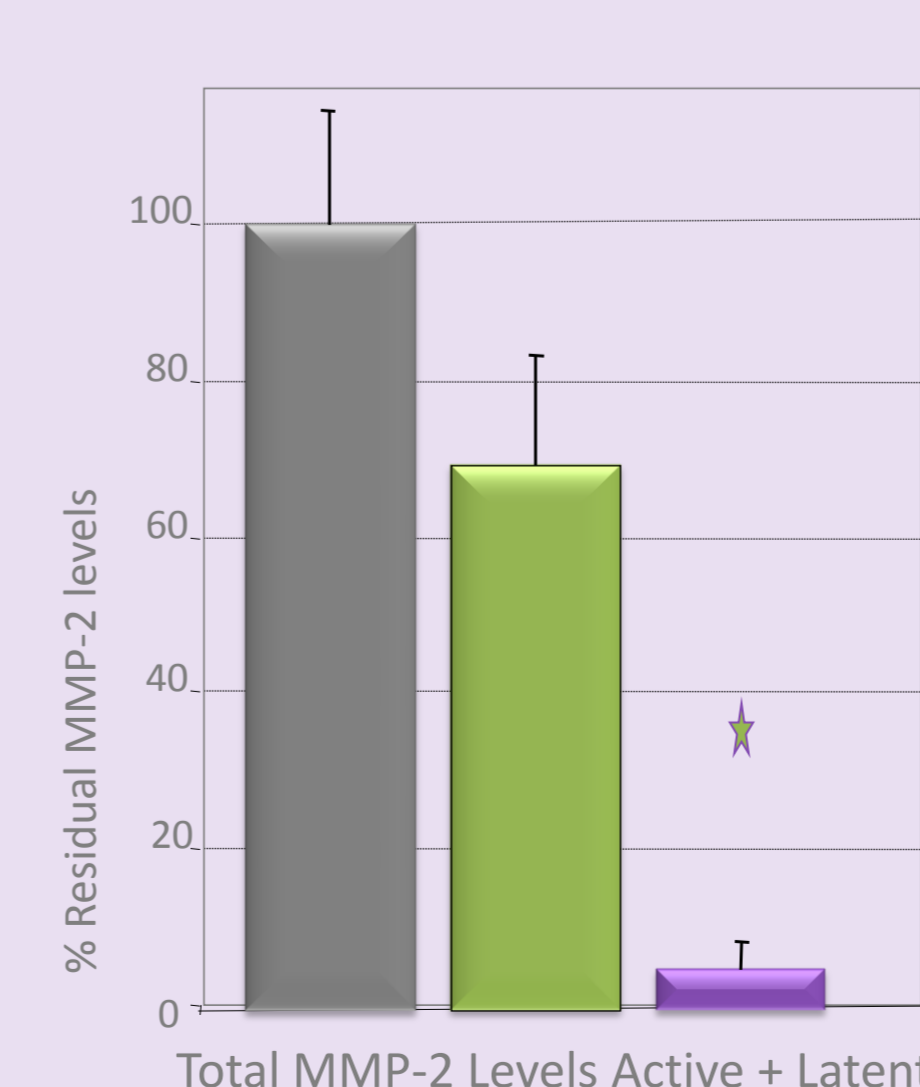
Effect on Elastase Activity



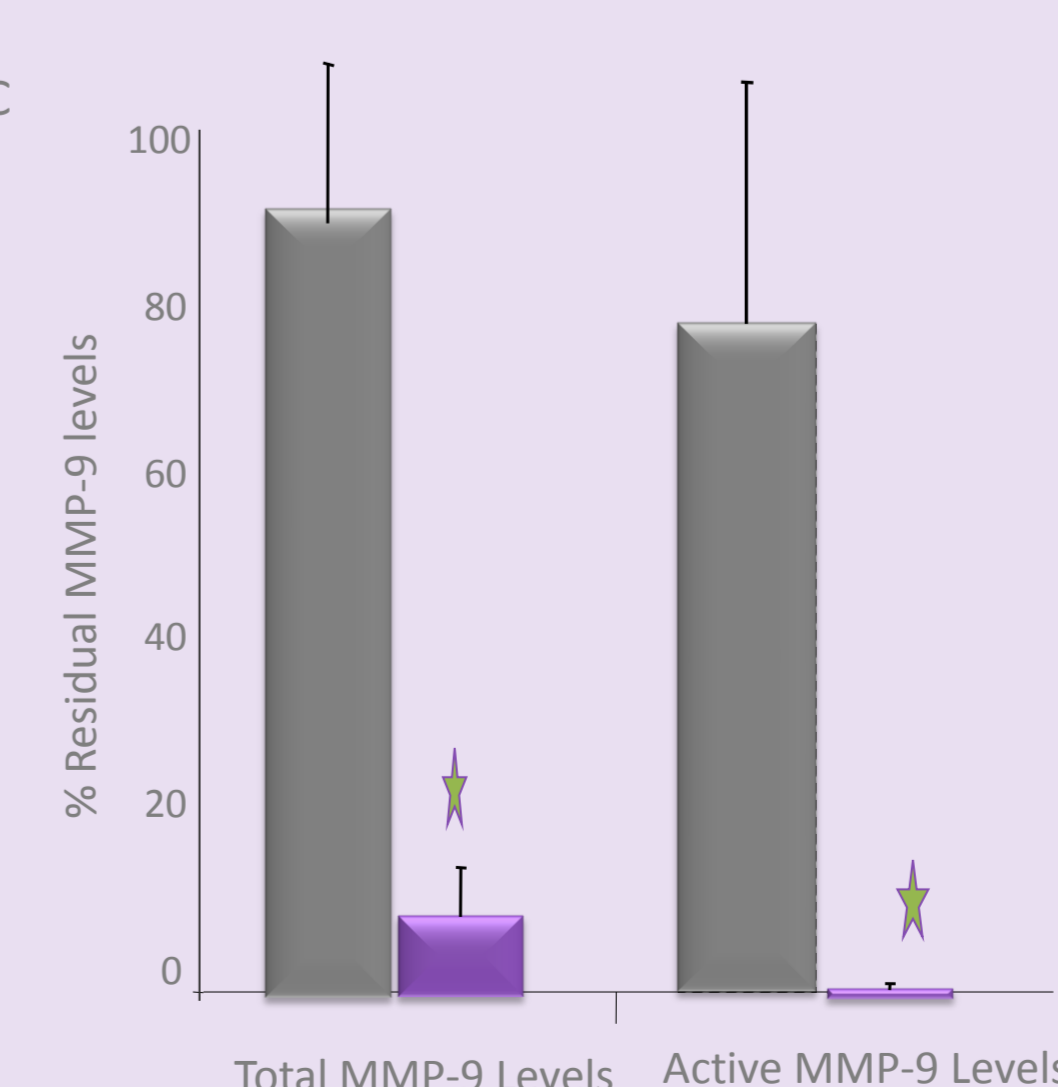
Effect on MMP-8



Effect on MMP-2 After 24hrs



Effect on MMP-9 After 24hrs



CONCLUSIONS

All types and levels of evidence are important as they increase our understanding of product function and efficacy

Multiple types and levels of evidence have been published in support of the efficacy and function of collagen/ORC therapies in the treatment of chronic wounds; publications which are lacking for other collagen dressings on the market

7 RCT studies in 599 patients, represented as Level 1 evidence show increased efficacy of Collagen/ORC over control dressings.

Other clinical research studies also demonstrate that Collagen/ORC inactivates inflammatory proteases which have been shown to be in excess in chronic wounds

PROMOGRAN® and PROMOGRAN PRISMA® are the only dressings which incorporate both collagen and ORC

* This product is a trademark of its owner

