Topical application of hyaluronic acid and amino acids in hard-to-heal wounds: a cost-effectiveness analysis

Objective: The aim of this cost-effectiveness analysis was to estimate the monetary cost required to achieve a gain in health benefit. An analytic model to evaluate the cost-effectiveness of a topical medical device comprising a mixture of hyaluronic acid and amino acids (HA+AA medical device) (Vulnamin, Professional Dietetics SpA, Italy) as compared to standard of care (SoC) for hard-to-heal (chronic) wounds is presented.
Method: Retrospective data was analysed from a cohort of patients as well as information from published literature. For each paper, the following information was extracted: number of patients enrolled in each treatment arm and the results of prespecified reviewed outcomes.
Results: A total of six studies involving 378 patients were included in this pooled analysis. Findings showed that treatment with the HA+AA medical device has the potential to lower consumption of resources. With regards to wound healing, in both superficial and deep wounds, treatment benefits of the HA+AA medical device included: rapid wound size reduction; faster healing; reduction of dressing changes; reduced infection risk; and reduced treatment costs. Results showed the HA+AA medical device to be 32% more cost-effective than comparators in the treatment of hard-to-heal wounds (time horizon selected=six months).
Conclusion: The findings of this analysis showed that treatment with the HA+AA medical device is a valid alternative to SoC care because it is cheaper, and its utility and effectiveness are greater. In addition, the results of the analysis showed a direct relationship between the time to complete healing and the increase in costs (increasing the period of time to reach complete healing increases the costs associated with the treatment).
Declaration of interest: FL has received funding from Professional Dietetics SpA, Italy. BA is employed by Professional Dietetics SpA, the manufacturers of Vulnamin.

chronic wound • cost-effectiveness • costs • deep wound • hard-to-heal • hyaluronic acid • Vulnamin • wound • wound care • wound dressing • wound healing

The goal of this cost-effectiveness analysis was to estimate the monetary cost required to achieve a gain in health benefit. Cost-effectiveness analyses estimate the incremental cost required to improve a selected clinical outcome (for example, promoting healing of hard-to-heal (chronic) wounds such as venous, pressure and diabetic foot ulcers (DFU)). Calculating the cost-effectiveness ratio requires estimating the change in cost associated with a given intervention (the numerator of the ratio), as well as the change in health benefit provided by that intervention (the denominator of the ratio). A cost-effectiveness analysis may be used to compare costs associated with selected interventions.[1,2]

The calculated incremental cost-effectiveness ratio may vary considerably depending on the validity of the baseline assumptions. A sensitivity analysis assesses the impact on the cost-effectiveness ratio of varying the baseline assumptions across a range of clinically plausible values.

In this study, an analytical model to evaluate the cost-effectiveness of Vulnamin compared to standard of care (SoC) for hard-to-heal wounds is presented. Retrospective data from a cohort of patients as well as information from published literature was used. Vulnamin (Professional Dietetics SpA, Italy) and referred to in this paper as the 'HA+AA medical device' (Class IIb, regulation 93/42/CEE MDD) is a topical medical preparation comprising a mixture of amino acids and hyaluronic acid. It is approved as an adjuvant wound treatment as it has been shown to help regenerate tissue and re-epithelialise cutaneous lesions.[3–8]

Epidemiology

Hard-to-heal wounds are a major health challenge—estimation of their true impact is difficult since the international consensus about when a wound should be considered hard-to-heal has not yet been reached.[1,2,9] The most common types of hard-to-heal wounds are pressure ulcers (PUs), diabetic foot ulcers (DFUs) and leg

Giorgio Reggiardo,[1] Biostatistics Unit Head; **Barbara Aghina**,[2] Medical Director*; **Francesco Landi**,[3,4] Director
***Corresponding author email:** b.aghina@profdiet.it
1 Department of Biostatistics, Consortium for Biological and Pharmacological Evaluations (CVBF), Pavia, Italy. **2** Professional Dietetics SpA, Milan, Italy.
3 Department of Orthopedic and Rheumatological Aging Sciences, 'Agostino Gemelli' University Polyclinic Foundation IRCCS, 00168 Rome, Italy. **4** Director of the Complex Internal and Geriatric Medicine Unit, 'Agostino Gemelli' University Polyclinic Foundation IRCCS, 00168 Rome, Italy.

ulcers of vascular aetiology. Their prevalence is expected to rise with the ageing of populations and the concurrent increase in predisposing diseases, such as diabetes, hypertension and obesity.[9] In a systematic review of the literature, hard-to-heal wounds of various aetiologies showed a pooled prevalence of 2.21 per 1000 population; among them, hard-to-heal leg ulcers were by far the most frequent type, with an estimated prevalence of 1.51 per 1000 population.[9]

Methods

All studies were intended to be included in this cost-effectiveness analysis; however, only papers in which efficacy endpoint data for the HA+AA medical device were available have been included; some studies were excluded for methodological and statistical reasons. For each paper, the following information was extracted: number of patients enrolled in each treatment arm and the results of prespecified reviewed outcomes. Disagreements on whether a paper should be included were resolved by collegial discussion.

Using a decision-analytical model, we defined a structure to include all relevant quantitative data and which allowed for the insertion of evidence from a specific clinical study's outcomes as well as from the included literature to generalise the results.

The first step was to define all relevant clinical outcomes: lesions healed (Yes/No); reduction in wound area (%); time to achieve complete healing closure (days). The cycle length of treatment was one week and the time horizon for duration of treatment was 70 days.

All costs associated with health states and transition costs in the Markov model used in the analysis were measured in euros (at 2022 values). These costs are from the perspective of the Italian healthcare system.

Definitions

Intervention: studies where patients received the HA+AA medical device as an experimental medical device (all doses were considered).
Comparator: studies where the control group received other treatments.
Outcomes: efficacy data for the following endpoints:
- Reduction in wound area (primary endpoint)
- Percentage of complete healing closure
- Time to achieve complete healing closure.

Not all studies reported data on all of the efficacy endpoints; the details of which studies contributed to a specific analysis are noted in that section. No risk of bias assessment has been performed.

Results

A total of six studies involving 378 patients were included in this pooled analysis. The following endpoints were considered to define the efficacy of the HA+AA medical device:
- Reduction in wound area (primary endpoint)
- Percentage of lesions healed (including time to achieve healing).

Reduction in wound area

In this pooled analysis of efficacy, we adopted the 'percentage of wound area reduction (PAR)' as the primary efficacy endpoint.

Papers excluded (with reason) from the analysis:
- Cassino R. Amino acids and wound bed: a possible interaction for both local and general intervention in the repair of chronic skin lesions. 2005 (no available data).[8]

Papers included in the analysis:
- Cassino R. Feed wounds and patients: effectiveness of amino acids in the treatment of leg ulcers. 2018.[3]
  Design: a randomised study evaluating the comparison between wound area reduction in 60 patients affected by 'leg ulcers in stand-by'[3] for at least two months, divided into three different treatment groups:
  - Group 1: alginate dressing
  - Group 2: amino acids/hyaluronate cream (the HA+AA medical device) under alginate dressing
  - Group 3: as per Group 2 with additional oral amino acid supplementation (8g/day).

  Observation period: 56 days.

- Cassino R, Ippolito AM. Aminoacidic gel versus hydrogel: which is the quicker debrider? 2013.[4]
  Design: a randomised study evaluating debridement time and wound area reduction in 40 patients with hard-to-heal necrotic skin wounds of different aetiologies (21 patients with pressure wounds; nine patients with DFU; seven patients with inflammatory wounds; three patients with vascular wounds) divided into two groups of 20 patients each:
  - Group 1: hydrogel without alginate. The group was composed of nine males and 11 females, with an average age of 82.6 years;
  - Group 2: aminoacidic gel. The group was composed of eight males and 12 females, with an average age of 85.5 years.

  Observation period: until full debridement (average debridement time of 12 days).

- Maggio G, Armenio A, Ruccia F et al. A new protocol for the treatment of the chronic venous ulcers of the lower limb. 2011.[5]
  Design: a non-randomised study evaluating debridement time and wound area reduction in 52 patients with hard-to-heal venous ulcers. The study comprised two groups of 26 patients each:
  - Treatment group: the HA+AA medical device plus Calcium (Ca)-alginate. The group was composed of 14 males and 12 females, with an average age of 58.6 years
  - Control group: Ca-alginate alone. The group was composed of 15 males and 11 females, with an average age of 57.9 years.

  Observation period: 70 days.

- Cassino R and Ricci E. Effectiveness of topical application of amino acids to chronic wounds: a prospective observational study. 2010.[6]
  Design: a non-randomised, multicentre, observational study in 160 patients (66 males, 94 females, with an age of <65 years in 20 patients; 66–74 years for 48 patients; and >75 years for 92 patients) with non-infected cutaneous hard-to-heal wounds.
  Observation period: follow-up at baseline, and after 14 days and 42 days of treatment.

- Abbruzzese L, Rizzo L, Fanelli G et al. Effectiveness and safety of a novel gel dressing in the management of neuropathic leg ulcers in diabetic patients: a prospective double-blind randomised trial. 2009.[7]
  Design: a prospective, double-blind, randomised study evaluating the healing rate of wounds as the primary endpoint. Secondary endpoints were: healing time; reduction in ulcer area and ulceration score in four weeks (28 days); number of infective complications; and overall satisfaction. The study was conducted with 30 patients affected by neuropathic leg ulcers randomised into two groups of 15 patients each:
  - Group A: the HA+AA medical device gel
  - Group B: inert gel vehicle.

  Observation period: three months (or until the lesion had healed).

Linear regression approach

Analysis of the findings of these studies showed that treatment with the HA+AA medical device induced a more rapid and progressive reduction in ulcer areas versus with comparators (Fig 1, Tables 1–4). To evaluate the differences between treatment groups in the pooled cohort we took a linear regression approach, the objective being to provide an analysis of wound area reduction versus time for treatment groups.

Linear regression attempts to model the relationship between two variables by fitting a linear equation to observed data; one variable is considered to be an explanatory variable (time), and the other to be a dependent variable (in this case, percentage wound area reduction).

- HA+AA medical device wound area reduction slope: –1.11 (p-value=0.003)
- Comparator wound area reduction slope: –0.39 (p-value=0.006).

Analysis of covariance (ANCOVA) was used to compare two regression lines by testing the effect of a categorical factor on a dependent variable (y-variable: percentage wound area reduction from baseline to day 70) while controlling for the effect of a continuous covariable (x-variable: time). The regression lines were compared by studying the interaction of the treatment effect (the HA+AA medical device versus comparator) and the independent variable. If the interaction is significantly different from zero it means that the effect of the continuous covariate on the response depends on the level of the categorical factor. In other words, the regression lines have different slopes.

The slope is interpreted as the change of percentage wound area reduction for a one unit increase in time (days). The results of this analysis showed that the HA+AA medical device could significantly accelerate the wound healing process compared to other treatments (Fig 2).

Percentage of wounds healed

Wound management implies healing in the shortest possible time, with minimal pain, discomfort and scarring for the patient, and which leads to wound closure with a flexible and fine scar with high tensile strength. Several factors could impede tissue repair and regeneration, such as hypoxia, infection, and the presence of debris and necrotic tissue.

It is generally accepted that a high availability of amino acids is necessary in wound repair.[3,10,11] Hyaluronic acid is also involved in wound healing.[3,12–14]

Papers excluded (with reason) from this analysis:

- Cassino R. Feed wounds and patients: effectiveness of aminoacids in the treatment of leg ulcers. 2018 (no available data)[3]
- Cassino R, Ippolito AM. Aminoacidic gel versus hydrogel: which is the quicker debrider? 2013 (study results are not shown for a single patient's treatment but on the total cohort).[4]

Papers included in this analysis (for studies already listed, design/observation period are noted in previous section) (Table 5):

- Maggio G, Armenio A, Ruccia F et al. A new protocol for the treatment of the chronic venous ulcers of the lower limb. 2011.[5]
- Cassino R and Ricci E. Effectiveness of topical application of amino acids to chronic wounds: a prospective observational study. 2010.[6]
- Abbruzzese L, Rizzo L, Fanelli G et al. Effectiveness and safety of a novel gel dressing in the management of neuropathic leg ulcers in diabetic patients: a prospective double-blind randomised trial. 2009.[7]
- Cassino R and Ricci E. Amino acids and wound bed: a possible interaction for a topic and general treatment in the chronic skin lesions repair'. 2005.[8]
  Design: an observational study evaluating the effectiveness of the HA+AA medical device, wear time, comfort and adverse reactions in 36 globally recruited (35 treated) patients affected by hard-to-heal skin lesions of different aetiologies.
  Observation period: not specified.

The regression model showed that the complete healing time (100% of wound healed) was significantly faster in patients treated with the HA+AA medical device when compared with the control group (p<0.001) (Fig 3).

Health benefit

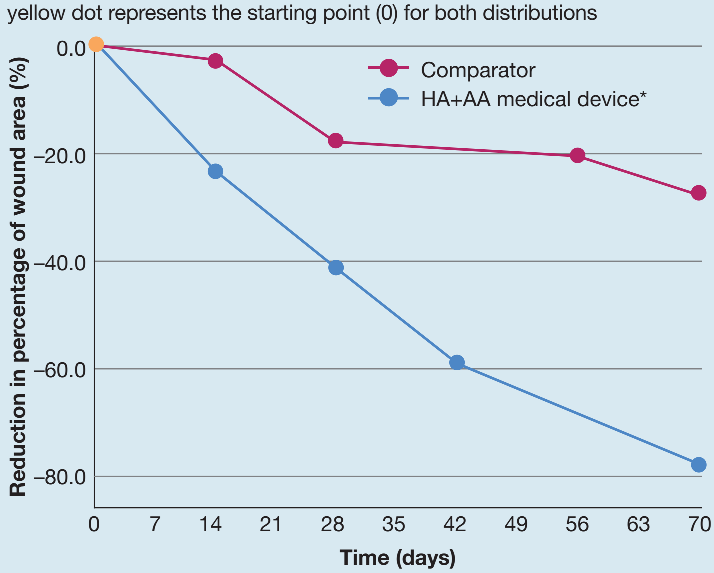
The combined analysis of the two efficacy endpoints (reduction in wound area, percentage of wounds healed)

Table 1. Wound area reduction from baseline to day 70

Study	Treatment	Sample size, n	Change from baseline in wound area (%)					
			Baseline	Day 14	Day 28	Day 42	Day 56	Day 70
Cassino, 2018[4]	Alginate dressing	20	—	—	−10	—	−18	—
	Alginate dressing Amino acids/hyaluronate	20	—	—	−14	—	−23	—
	Alginate dressing Amino acids/hyaluronate Amino acidic oral	20	—	—	−24	—	−38	—
Cassino et al., 2013[5]	Hydrogel	20	—	−3	—	—	—	—
	Hydrogel + HA+AA medical device*	20	—	−13	—	—	—	—
			Change in wound area, cm^2 Mean±SD/(reduction in percentage)					
Maggio et al., 2011[6]	Ca-alginate	26	15.14±4.7	—	—	—	—	10.96±3.8 (−27.7)
	Ca-alginate + HA+AA medical device*	26	13.95±4.5	—	—	—	—	3.04±0.8 (−78.2)
Cassino et al., 2010[7]	HA+AA medical device*	160	11.2±12.1	7.4±8.7 (−33.9)	—	4.6±6.3 (−58.9)	—	—
Abbruzzese et al., 2009[8]	Inert gel vehicle	15	27.3±10.4	—	20.9±12.6	—	—	—
	HA+AA medical device*	15	25.9±8.8	—		—	—	—

*Vulnamin (Professional Dietetics SpA, Italy); AA—amino acids; Ca—calcium; HA—hyaluronic acid; SD—standard deviation

Fig 1. Percentage of wound area reduction from baseline to 70 days. The yellow dot represents the starting point (0) for both distributions



*Vulnamin (Professional Dietetics SpA, Italy)

Table 2. Linear regression analysis: HA+AA medical device* versus comparator

Model summary				
Model	R	R^2	Adjusted R^2	SEM
HA+AA medical device*, n=241	0.983	0.965	0.954	6.5205
Comparator, n=101	0.971	0.943	0.924	3.2339

*Vulnamin (Professional Dietetics SpA, Italy); SEM—standard error of the mean

showed that the healing time can be estimated as (Table 6):

- Comparator: 165 days (95% confidence interval (CI): 149–181 days)
- HA+AA medical device: 97 days (95% CI: 84–110 days).

Costs

The time horizon selected was six months, mainly because this was the standard of care (SoC) healing period of time obtained in this pooled efficacy analysis, but which is also a common time horizon in hard-to-heal wound healing. Most patients were treated on an outpatient basis, although some were occasionally admitted to receive specialist in-hospital treatment.

All costs associated with health states and transition costs in the Markov model are presented in Table 3. For the cost of dressings, a small number of estimations have been made on the average price of a simple and a complex dressing.

Assessing the average duration of the wounds was difficult due to the wide range of healing times that existed in the data. Nevertheless, mean healing time of each treatment group was calculated as shown in Table 6.

The direct medical cost per patient was calculated by multiplying the health resources consumed (measured in units) by its unit cost.

The cost/medication (Table 7) is calculated as follows:

- Comparator (SoC) = cleaning procedure + medication + dressing + nurse time: €9.62
- HA+AA medical device= cleaning procedure + medication + dressing + nurse time + HA+AA medical device: €11.23

Cost-effectiveness ratio

The present analysis evaluates the cost-effectiveness of the HA+AA medical device treatment compared with SoC management of patients with hard-to-heal wounds.

The average number of test-product applications per week varied from 2.2 (for superficial wounds) to 2.9 (deep wounds), with no statistically significant difference regarding depth.

The total cost/week (range shown for superficial–deep wounds) was:

- Comparator = €21.16–27.90
- HA+AA medical device = €24.71–32.57.

Total cost for a time horizon healing period of six months (range shown for superficial–deep wounds):

- Comparator = €498.8–657.6
- HA+AA medical device = €342.4–451.3.

Initially, the HA+AA medical device treatment was more costly but at each treatment cycle (weekly) the cumulative costs became lower than for SoC treatment, and from week 16 the comparator became the most expensive treatment option (Table 8, Figs 4, 5). The HA+AA medical device treatment has the potential to lower consumption of resources.

Superficial wounds

The HA+AA medical device treatment benefits, as shown by the analysis of the findings of the included studies, were: rapid wound size reduction; faster healing; reduction of dressing changes; reduced infection risk; and reduced treatment costs. Results showed the HA+AA medical device to be 32% more cost-effective (€346) than the comparator (€508) in the treatment of hard-to-heal wounds (time horizon selected = six months).

Deep wounds

The HA+AA medical device treatment benefits were the same as those for superficial wounds. Results showed the HA+AA medical device to be 32% more cost-effective (€456), than the comparator (€670) in the treatment of hard-to-heal wounds (time horizon selected=six months).

With regards to effectiveness of the HA+AA medical device, the less time needed to achieve complete healing and, consequently, the longer the wound-free period, appeared to be dependent on the wound size (the larger the wound, the longer the time needed to heal) and on the location of the wound (longer healing times were found for wounds in lower limbs).

The statistically significant findings of this analysis showed that time to complete healing showed a direct relationship with costs and an inverse relationship with wound-free period (i.e., the less time needed to achieve complete healing, the longer the wound-free period).

Timepoint analysis: 70 days

Using a linear regression approach, it was possible to obtain an estimate of the percentage of wound area

Table 3. Analysis of variance: HA+AA medical device* versus comparator

	Sum of squares	df	Mean square	F	Sig.
HA+AA medical device*					
Regression	3562.213	1	3562.213	83.785	0.003
Residual	127.549	3	42.516	—	—
Total	3689.762	4	—	—	—
Comparator					
Regression	517.005	1	517.005	49.435	0.006
Residual	31.375	3	10.458	—	—
Total	548.380	4	—	—	—

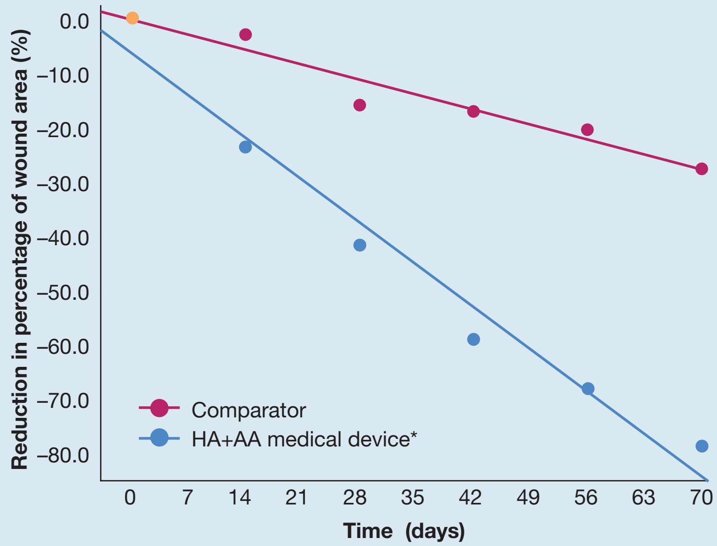
*Vulnamin (Professional Dietetics SpA, Italy); Sig.—statistical signficance

Table 4. Coefficients: HA+AA medical device* versus comparator

Coefficients					
	Unstandardised coefficients		Standardised coefficients	T	Sig.
	B	Std. error	Beta		
HA+AA medical device*					
(Constant)	–6.259	4.734	—	–1.322	0.278
Time	–1.108	0.121	–0.983	–9.153	0.003
Comparator					
(Constant)	–0.242	2.365	—	–0.102	0.925
Time	–0.392	0.056	–0.971	–7.031	0.006

*Vulnamin (Professional Dietetics SpA, Italy); Sig.—statistical signficance; Std. error—standard error

Fig 2. Linear regression analysis: percentage of wound area reduction (PAR) from Baseline to 70 days. The yellow dot represents the starting point (0) for both distributions



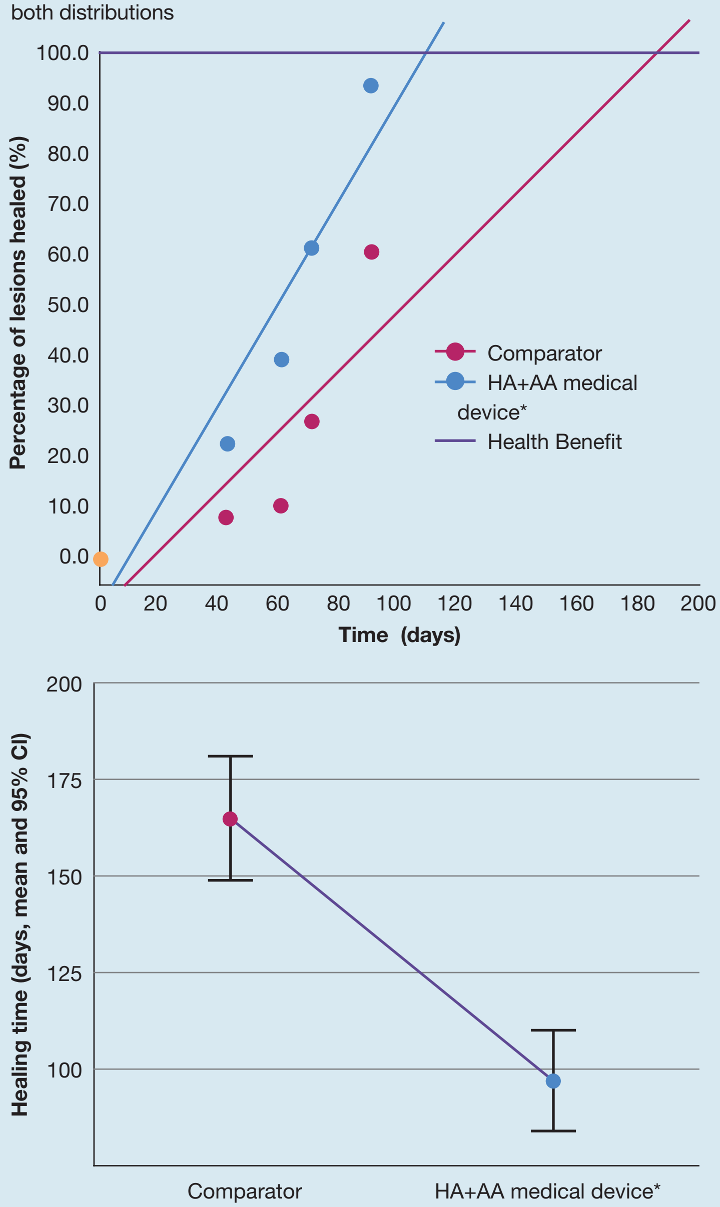
*Vulnamin (Professional Dietetics SpA, Italy)

Table 5. Percentage of lesions healed (complete healing course)

Study	Treatment	Sample size, n	Percentage of lesions healed (time to, days)
Maggio et al., 2011[6]	Ca-alginate	26	27 (70)
	Ca-alginate + HA+AA medical device*	26	61 (70)
Cassino et al., 2010 [7]	HA+AA medical device*	160	22.5 (42)
Abbruzzese et al., 2009[8]	Inert gel vehicle	15	60 (90)
	HA+AA medical device*	15	93 (90)
Cassino and Ricci, 2005[9]	HA+AA medical device*	36	38.9 (60)

*Vulnamin (Professional Dietetics SpA, Italy); Ca—calcium

Fig 3. Percentage of lesions healed (%) over time (days) by treatment group. CI—confidence interval. The yellow dot represents the starting point (0) for both distributions



*Vulnamin (Professional Dietetics SpA, Italy)

Table 6. Healing time (100% wound area reduction) by treatment group

Healing time	100% wound area reduction (95% confidence interval)	
	Comparator	Vulnamin
Days	**165** (149–181)	**97** (84–110)

reduction in the two groups:

- Comparator: –27.7% (95% CI: –33.4––22.1)
- Vulnamin: –83.7% (95% CI: –95.1––72.4).

The costs (€) for the reduction of one point in percentage were:

- Comparator: superficial wounds €7.64; deep wounds €10.07
- HA+AA medical device: superficial wounds €2.95; deep wounds €3.89.

Healing time analysis (100% of wound area reduction)

The linear regression model results showed that the healing time could be estimated as shown in Table 6.

Discussion

The present analysis investigated the cost-effectiveness of the topical application of an HA+AA medical device (marketed as Vulnamin) in the treatment of hard-to-heal wounds. These wounds are a significant healthcare burden, often associated with prolonged healing times, increased risk of infection, and substantial costs.[1,2] Finding effective and cost-efficient wound management strategies is essential for optimising patient outcomes and reducing the economic impact on healthcare systems.

The findings of the analysis presented demonstrated that the topical application of the HA+AA medical device resulted in improved healing outcomes for patients with hard-to-heal wounds, leading to a reduction in overall treatment costs. The positive cost-effectiveness of the HA+AA medical device can be attributed to several factors observed in the studies considered in the analysis.

The reduced healing time associated with the HA+AA medical device is particularly significant in hard-to-heal wound management. These wounds are widely recognised as slow to heal and often require prolonged and costly interventions. By facilitating a faster tissue regeneration and healing process, use of the HA+AA medical device could lead to fewer follow-up visits, decreased use of wound dressings, and a reduced need for other expensive wound care products. Furthermore, the potential for preventing wound complications with the HA+AA medical device may also contribute to its cost-effectiveness. Hard-to-heal wounds (i.e., PUs, DFUs, venous leg ulcers, arterial ulcers, neuropathic ulcers, surgical wounds with delayed healing, traumatic wounds) are prone to infection, which can further prolong healing times and escalate treatment costs. By facilitating faster healing, the HA+AA medical device may decrease the associated complications, leading to further cost savings and improved patient outcomes.

The positive effect of the HA+AA medical device is correlated with the potential effects of topical application of hyaluronic acid and amino acids. The topical application of dressings containing hyaluronic acid and amino acids has shown great promise in improving cutaneous wound healing.[3–8]

Hyaluronic acid is a naturally occurring polysaccharide found in the extracellular matrix of connective tissues, and plays a crucial role in tissue repair and regeneration.[12] When applied topically to wounds, hyaluronic acid creates a moist environment that promotes cell migration, proliferation and tissue granulation.[13,14]

A key benefit of hyaluronic acid is its ability to retain water, which helps keep the wound hydrated. Hyaluronic acid helps prevent further tissue damage and supports the formation of healthy granulation tissue.[12–14] Moreover, hyaluronic acid has been found to contribute to collagen synthesis, an essential component of wound healing. By promoting the deposition and organisation of collagen fibres, it helps strengthen the newly formed tissue, leading to improved wound closure and reduced scar formation.[12] Clinical studies have demonstrated the efficacy of hyaluronic acid dressings in various types of wounds, including hard-to-heal ulcers, surgical incisions and burns. These dressings have been associated with faster wound healing, reduced pain, and improved overall wound appearance.[13,14] Finally, the synergistic effects of these components of hyaluronic acid and amino acids contribute to enhanced wound healing rates, reducing the overall duration of treatment and consequently the overall associated costs.[6–8]

Amino acids are the building blocks of proteins, and they play a crucial role in various physiological processes, including tissue repair and regeneration.[10] Studies have demonstrated that the application of dressings with hyaluronic acid and amino acids combined can support the wound healing process.[6–8,11]

Amino acids provide essential nutrients, all of which are vital for proper wound closure and tissue regeneration.[10] A significant advantage of using amino acid-based dressings is their ability to support the formation of new tissue. The topical application of hyaluronic acid and amino acids can lead to better cosmetic outcomes and improved functional recovery.[10,11]

Limitations

This evaluation related to analysis based only on clinical trials without assessing the cost-effectiveness in real practice settings. Furthermore, there are a number of well-known limitations to the modelling of cost-effectiveness; these are intrinsic to modelling itself, and they centre on the need for combining various clinical data sources into a single economic model.

Conclusion

In conclusion, the present analysis (including observational and randomised controlled data for a total of 378 patients) provides evidence supporting the

Table 7. Data used in the model: costs

Parameter	Value, €	Minutes to prepare dressing (complete procedure)/medication	Total cost/medication, €
Nurse/minute	0.30	20	6.00
Cleaning and dressing (material)	—	—	3.62
Cleaning and dressing (material) + HA+AA medical device*	—	—	5.23

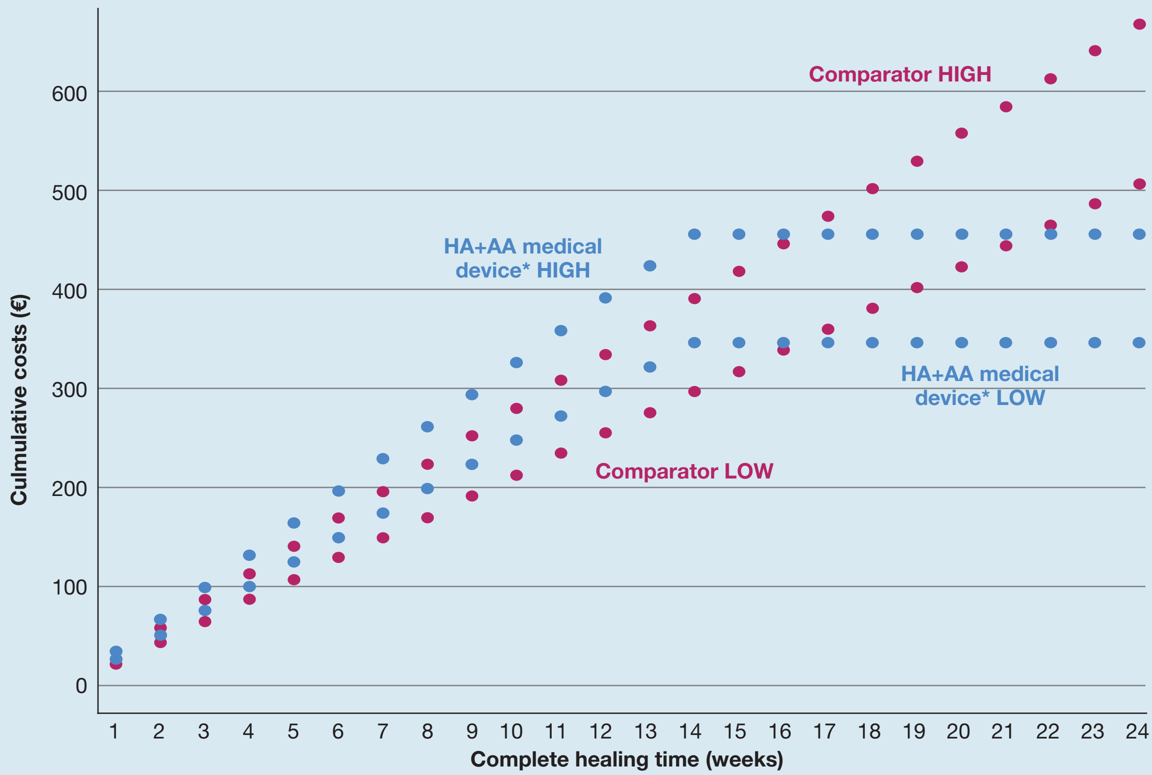
*Vulnamin (Professional Dietetics SpA, Italy)

Table 8. Cumulative costs for complete healing time (weeks)

Complete healing time, week	Cumulative costs (€)			
	Comparator		HA+AA medical device*	
	Superficial wounds	Deep wounds	Superficial wounds	Deep wounds
1	21.2	27.9	24.7	32.6
2	42.3	55.8	49.4	65.1
3	63.5	83.7	74.1	97.7
4	84.6	111.6	98.8	130.3
5	105.8	139.5	123.6	162.9
6	127.0	167.4	148.3	195.4
7	148.1	195.3	173.0	228.0
8	169.3	223.2	197.7	260.6
9	190.4	251.1	222.4	293.1
10	211.6	279.0	247.1	325.7
11	232.8	306.9	271.8	358.3
12	253.9	334.8	296.5	390.8
13	275.1	362.7	321.2	423.4
14	296.2	390.6	345.9	456.0
15	317.4	418.5	345.9	456.0
16	338.6	446.4	345.9	456.0
17	359.7	474.3	345.9	456.0
18	380.9	502.2	345.9	456.0
19	402.0	530.1	345.9	456.0
20	423.2	558.0	345.9	456.0
21	444.4	585.9	345.9	456.0
22	465.5	613.8	345.9	456.0
23	486.7	641.7	345.9	456.0
24	507.8	669.6	345.9	456.0

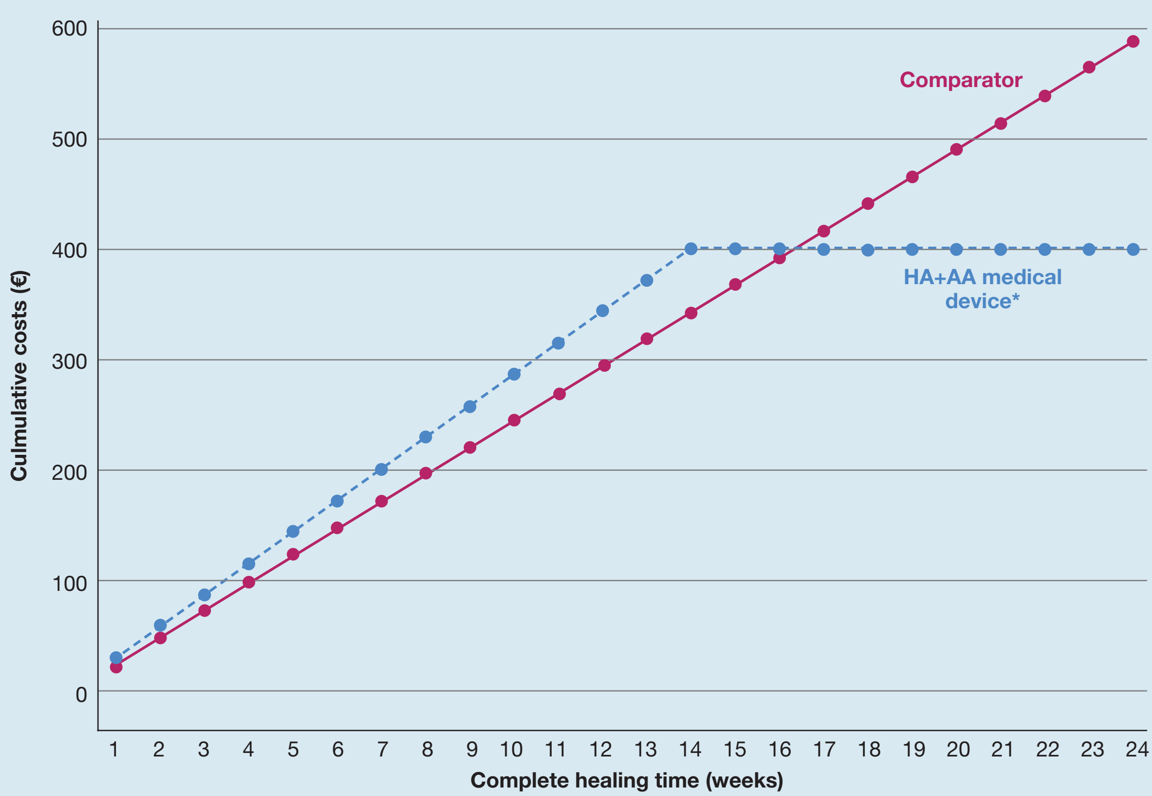
*Vulnamin (Professional Dietetics SpA, Italy); HA+AA—from week 15 (shaded cells), the cumulative cost does not increase as healing has been achieved

Fig 4. Cumulative costs for complete healing time (weeks)



*Vulnamin (Professional Dietetics SpA, Italy)

Fig 5. Cumulative costs (mean) for complete healing time (weeks)



*Vulnamin (Professional Dietetics SpA, Italy) positive cost-effectiveness of the HA+AA medical device in the treatment of hard-to-heal wounds. The topical application of hyaluronic acid and amino acids offers a promising treatment approach that not only improves healing outcomes (lesions healed, reduction in wound area, time to achieve complete closure) but also reduces the overall economic burden associated with hard-to-heal wound (superficial and deep wounds) management. However, further research, including larger and longer randomised controlled trials and cost-effectiveness analyses in different healthcare settings, is warranted to strengthen the evidence base, and confirm the potential benefits of the HA+AA medical device in the broader context of wound care. Finally, healthcare providers and policymakers should consider incorporating this innovative treatment option into clinical practice to optimise outcomes for patients with hard-to-heal wounds while minimising healthcare costs. **JWC**

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Reflective questions

- To what extent do you plan to use the results of this benefit-cost analysis in your clinical practice?
- What are the greatest advantages of using this cost-effectiveness analysis in your clinical practice?
- To what extent can this cost-benefit analysis of the hyaluronic acid and amino acids-based formula impact the patient’s quality of life?