



**We walk the walk...
so your patients can too.**

Unique home care therapy that addresses health disparities, drives compliance, and delivers proven, sustained healing – directly reducing healthcare costs.

A trusted partner of public payers.

AOTI has treated over 20,000 members with non-healing wounds across NY Medicaid and the Veteran's Administration nationwide.



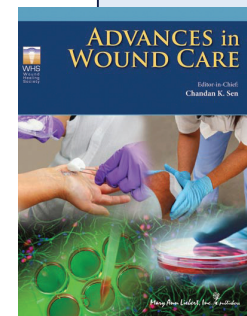
DIFFERENCE:

TWO2 therapy is different from other topical oxygen delivery systems because it uses a higher cyclical-pressure approach that combines non-contact compression and humidification.

These multiple modalities provide higher oxygen diffusion gradients to the wound and surrounding skin, while reducing edema.

Proven to deliver sustained wound healing
Supported by the highest level scientific studies, designed with integrity.

REAL-WORLD EVIDENCE STUDY



88% REDUCTION in Hospitalizations

71% REDUCTION in Amputations

#1 Ranked Journal in Wound Care

RANDOMIZED CONTROLLED TRIAL

6X MORE LIKELY TO HEAL in 12 weeks

6X LOWER RECURRENCE rate at 12 months



Study Received Perfect Cochrane Score for Quality of Research

Proven to significantly reduce hospitalizations, amputations and ulcer recurrence over 12 months thereby directly reducing healthcare costs.

REFERENCES:

- **Reduced Hospitalizations and Amputations in Patients with Diabetic Foot Ulcers Treated with Cyclical Pressurized Topical Wound Oxygen Therapy: Real-World Outcomes;** Jessica Izhakoff Yellin, Julia A. Gaebler, Frank F. Zhou, Timothy Niecko, Olivia Novins, Amelia Ockert, Darcy Krzynowek, Matthew G. Garoufalis, Aliza M. Lee, and Robert G. Frykberg; *Advances in Wound Care* 2022; <http://doi.org/10.1089/wound.2021.0118>
- **A Multinational, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy of Cyclical Topical Wound Oxygen (TWO2) Therapy in the Treatment of Chronic Diabetic Foot Ulcers;** Robert G. Frykberg, Peter J. Franks, et al. *The TWO2 Study; Diabetes Care* 2020;43:616-624 | <https://doi.org/10.2337/dc19-0476>.

RANDOMIZED CONTROLLED TRIAL, DOUBLE-BLIND, SHAM CONTROLLED



A Multinational Multicenter, Randomized, Double-Blinded Placebo-Controlled Trial to Evaluate the Efficacy of Cyclical Topical Wound Oxygen Therapy (TWO2) in the Treatment of Chronic Diabetic Foot Ulcers: The TWO2 Study

Robert G. Frykberg, Peter J. Franks, Michael Edmonds, Jonathan N Brantley, Luc Te 'ot, Thomas Wild, Matthew G. Garoufalos, Aliza M. Lee, Janette A. Thompson, Gérard Reach, Diabetes Care Publish Ahead of Print, published online October 16, 2019 Karim Lachgar, Cyaandi R. Dove, Dirk Grotemeyer, and Sophie C. Renton, on behalf of the TWO2 Study Group*

Study Received Perfect Cochrane Score for Quality of Research

Level 1A evidence published in the high impact factor journal, **Diabetes Care**, demonstrating the efficacy of cyclical pressure Topical Wound Oxygen (TWO2) therapy in healing and reducing recurrence of Diabetic Foot Ulcers (DFU).

RESEARCH DESIGN:

- A Group Sequential Design was utilized for the study with three predetermined analyses and hard stopping rules at 73, 146 and 220 on completing a 12-week treatment phase (resulting in a more rigorous $p < 0.022$ at each analysis point).
- An independent data monitoring board was utilized to make decisions on safety, efficacy, and to review the outcomes at each predetermined analysis point per the protocol.
- All data analysis was conducted under the more stringent Intention-to-treat approach.

Patients meeting eligibility criteria were enrolled into a 2-week run-in with study defined optimal standard-of-care (SOC). Only hard-to-heal ulcers were randomized into the active phase of the study. 25% of run-in patients were excluded prior to randomization due to achieving 30% wound area reduction on SOC alone.

OUTCOMES:

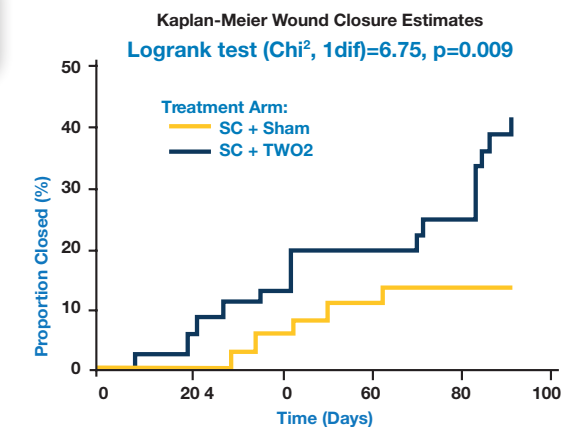
"...RCT demonstrates that, at both 12 weeks and 12 months, adjunctive cyclical pressurized TWO2 therapy was superior in healing chronic DFUs compared with optimal SOC alone."

An independent 2021 published systematic review with meta-analysis of seven topical oxygen studies awarded this TWO2 therapy RCT with a perfect Cochrane Score for quality of research and avoidance of bias.

6X MORE LIKELY TO HEAL in 12 weeks

Primary Outcome: Healed Ulcers at 12 Weeks

After adjusting for UTC ulcer severity, produced an odds ratio (OR) of **6.00** (97.8% CI 1.44,24.93), **P=0.004**

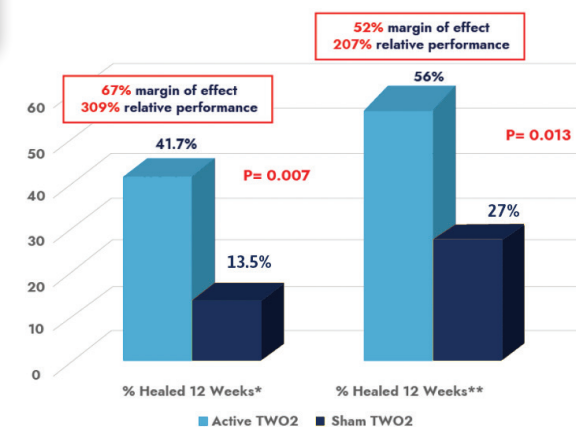


6X LOWER RECURRENCE rate at 12 months

Durable Healing Shown: 12 Months Post Enrollment

56% of active arm ulcers were **Closed** compared to 27% of the sham arm ulcers (**p=0.013**)

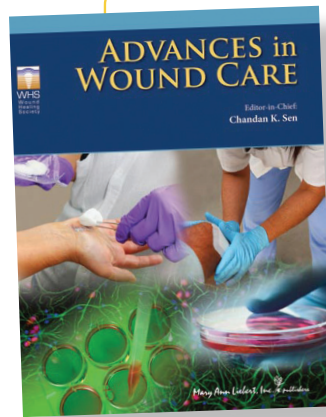
6.7% of healed active arm ulcers **recurred** compared to **40%** in the sham arm



REFERENCES:

- A Multinational, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy of Cyclical Topical Wound Oxygen (TWO2) Therapy in the Treatment of Chronic Diabetic Foot Ulcers; Robert G. Frykberg, Peter J. Franks, et al. The TWO2 Study; *Diabetes Care* 2020;43:616-624 | <https://doi.org/10.2337/dc19-0476>.
- Topical Oxygen Therapy for Diabetes-Related Foot Ulcers: A Systematic Review and Meta-Analysis. Thanigaimani S, Singh T, Golledge J. *Diabet Med*. 2021 Aug;38(8):e14585. doi: 10.1111/dme.14585. Epub 2021 Apr 29. PMID: 33871095.

REAL-WORLD EVIDENCE



Reduced Hospitalizations and Amputations in Patients with Diabetic Foot Ulcers Treated with Cyclical Pressurized Topical Wound Oxygen Therapy: Real-World Outcomes

Jessica Izhakoff Yellin, Julia A. Gaebler, Frank F. Zhou, Timothy Niecko, Olivia Novins, Amelia Ockert, Darcy Krzynowek, Matthew G. Garoufalis, Aliza M. Lee, and Robert G. Frykberg

#1 Ranked Journal in Wound Care

Substantial Real-World Evidence study validating long-term healing outcomes demonstrated in Level 1A RCT.

RESEARCH DESIGN:

- Large, multi-site retrospective cohort study of highly co-morbid patients treated within the Veterans Affairs system with full-thickness DFUs that had failed to heal with SOC.
- The patients were treated adjunctively with TWO2 therapy (TWO2 arm) or only other available modalities (NO TWO2 arm). All patients had outcome records for at least one year. Initial findings in the unmatched cohorts were substantiated by a propensity scored matched cohort that included all major (19) covariates.

UNMATCHED Cohorts 202

91 received TWO2 therapy, 111 did NOT receive TWO2.

MATCHED Cohorts 140

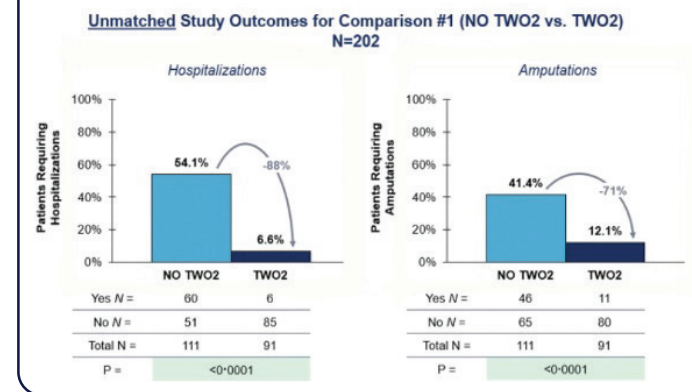
70 received TWO2 therapy, 70 did NOT receive TWO2.

BOTH cohorts received Standard of Care (SOC) and may have received adjunct therapies including negative pressure wound therapy (NPWT), skin substitutes (SS), and/or growth factors (GF).

OUTCOMES:

“Demonstrated that treating non-healing DFU patients with TWO2 leads to highly statistically significant reductions in hospitalizations and amputations in the real-world setting”

OUTCOMES: Unmatched Cohort at 360 Days



88% REDUCTION in Hospitalizations

71% REDUCTION in Amputations

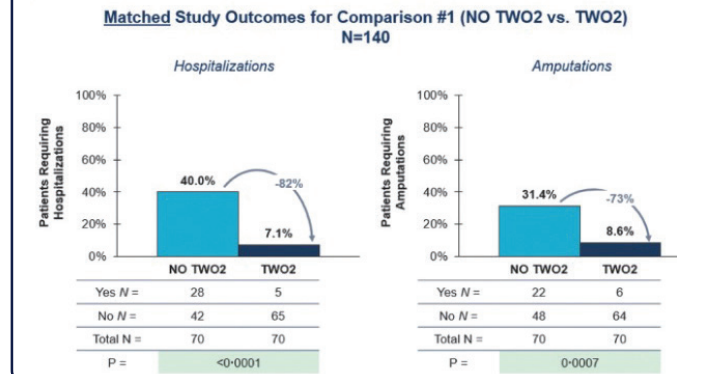
- Unmatched cohort representing the real world heterogenic mix of patients treated for DFU

82% REDUCTION in Hospitalizations

73% REDUCTION in Amputations

- Matched cohort of DFU patients with balanced covariates demonstrates similar outcomes to unmatched cohort

OUTCOMES: Matched Cohort at 360 Days

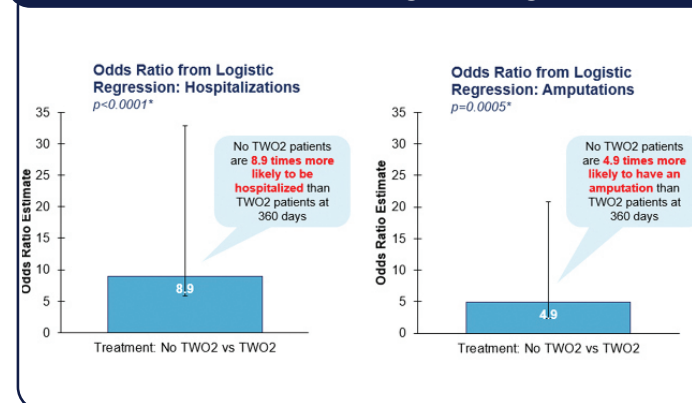


9X HIGHER RISK of Hospitalization

5X HIGHER RISK of Amputation

- The logistic regression of matched cohorts demonstrate the odds of hospitalization and amputation when **not** treated with TWO2

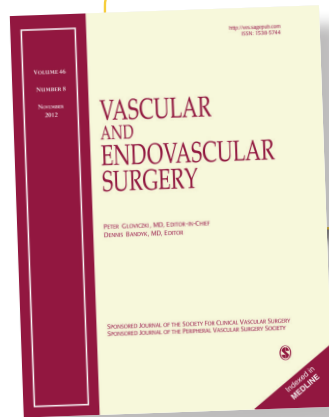
ODDS RATIO from Logistic Regression



REFERENCES:

- Reduced Hospitalizations and Amputations in Patients with Diabetic Foot Ulcers Treated with Cyclical Pressurized Topical Wound Oxygen Therapy: Real-World Outcomes; Jessica Izhakoff Yellin, Julia A. Gaebler, Frank F. Zhou, Timothy Niecko, Olivia Novins, Amelia Ockert, Darcy Krzynowek, Matthew G. Garoufalis, Aliza M. Lee, and Robert G. Frykberg; *Advances in Wound Care* 2022; <http://doi.org/10.1089/wound.2021.0118>

PROSPECTIVE CONTROLLED TRIAL IN VENOUS LEG ULCERS



Technical and Clinical Outcome of Topical Wound Oxygen in Comparison to Conventional Compression Dressings in the Management of Refractory Nonhealing Venous Ulcers

Wael A. Tawfick, MRCSI, and Sherif Sultan, MD, FRCS, EBQS-VASC, FACS

Refractory non-healing venous ulcers of minimum 2 years duration.

RESEARCH DESIGN:

- A university hospital vascular surgery department study of 132 patients with refractory venous leg ulcers with a mean of eight years duration, and a mean ulcer size of 19 cm² were assigned to receive TWO2 therapy or SOC (conventional compression dressings, CCD).
- Primary endpoint was complete healing at 12 weeks.
- Secondary endpoints included ulcer recurrence at 36 months, reduction in pain, reduction in infection, and healing trajectories.

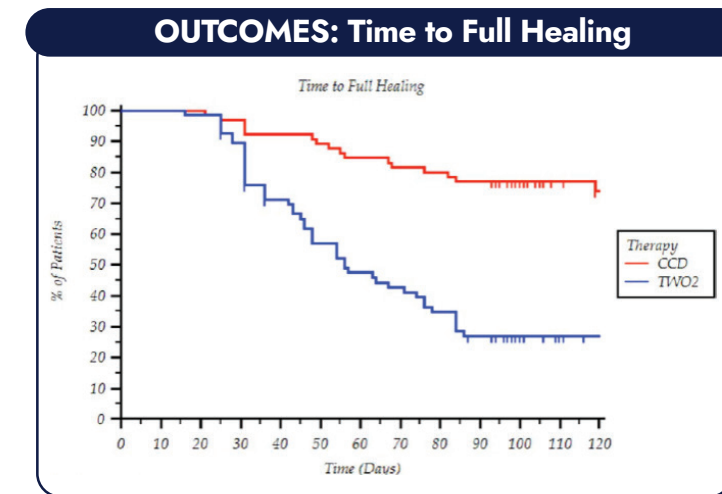


OUTCOMES:

"... TWO2 slashed the time needed for recalcitrant venous ulcer healing and is successful in pain alleviation, MRSA elimination, and management."

SUPERIOR HEALING RATE at 12 weeks **76%** | vs. SOC **46%**

SHORTER HEALING TIME **57 DAYS** | vs. SOC **107 DAYS**

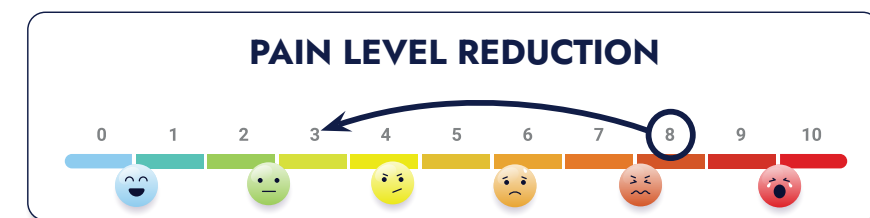


- "... TWO2 radically degrades recurrence rates, thus providing an improved quality of life."

LOWER RECURRENCE RATE at 36 months **6%** | vs. SOC **47%**
3/51 | 14/30

SIGNIFICANT MRSA ELIMINATION after 5 weeks **46%** | vs. SOC **0%**
11/24 | 0/19 CCD

- **Reported pain levels were reduced from 8 to 3** on the pain numerical rating scale in patients treated with TWO2 therapy within 13 days.



REFERENCES:

• Technical and Clinical Outcome of Topical Wound Oxygen in Comparison to Conventional Compression Dressings in the Management of Refractory Nonhealing Venous Ulcers. Wael A. Tawfick, MRCSI, and Sherif Sultan, MD, FRCS, EBQS-VASC, FACS, 2. *Vascular and Endovascular Surgery*, 2012.

THE ONLY MULTI-MODALITY OXYGEN THERAPY: CREATES A POWERFUL HEALING COMBINATION



BENEFITS OF SUPPLEMENTAL OXYGEN

TWO2 provides the highest penetration of oxygen into the wounded tissue. The immediate availability of oxygen at a partial pressure of approximately 800 mmHg provides the greatest diffusion gradient into the tissue and supercharges cellular activity.

TWO2 propels stalled non-healing wounds that lack adequate oxygen, which prevents essential enzymatic production responsible for immune response to fight infection, cellular metabolism, and collagen production, into a robust healing pathway.



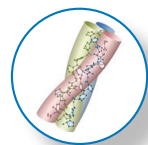
TWO2 amplifies local immune response to fight infection

Upregulation of leucocyte function potentiates both neutrophil effectiveness and any concurrent antibiotic therapy being utilized to treat infected wounds. As bacterial metabolism accelerates, senescent bacteria become more susceptible to these defensive mechanisms. The increased oxygen levels also have a direct bactericidal effect on any anaerobic bacteria present.



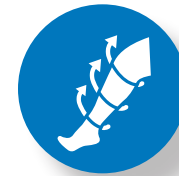
TWO2 stimulates the proliferation of angiogenesis

An increase in the production of vascular endothelial growth factors (VEGF) results in prolific new blood vessel growth. Additionally, there is a synergistic effect of oxygen on the reactive oxygen species (ROS) needed for transforming growth factor beta (TGF β) and platelet derived growth factor (PGF).



TWO2 promotes stronger collagen synthesis

Promotes the synthesis of superior quality triple-helix collagen for improved tensile strength, while healing the wound with ideal histology that results in little to no scarring, healthy desquamation, reducing the risk of callus formation, resulting in lower recurrence.



BENEFITS OF CYCLICAL COMPRESSION

The non-contact cyclical compression provided is between 10 mb and 50 mb pressure that is equivalent to a level 3 conventional compression dressing (CCD). This helps to reduce both edema and the hydrostatic pressure in the lower leg that is a frequent component of lower extremity peripheral vascular disease. The higher positive pressure more effectively delivers oxygen deep into the wound bed, thereby encouraging granulation from the base. The cyclical nature of the pressure delivery eliminates concerns when treating ischemic wounds.



HUMIDIFICATION

A medical nebulizer delivers particulate humidity to the chamber to create an ideal moist wound healing environment.

**TWO2 therapy is easily applied by the patient at home
5 days per week for 90 minutes duration with gas
permeable dressings left in place.**

DRIVING COMPLIANCE



A Game Changer for Patients and Clinicians:

- ✓ An easy-to-use, non-invasive therapy that patients can self-administer in the **convenience of their own home**.
- ✓ **No need to remove gas permeable dressing.**
The cyclically-pressured oxygen diffuses through CCD, UNNA Boot and TCC.
- ✓ Our **dedicated Wound Care Team** is there to handle everything: ordering, delivery, patient training and monitoring.
- ✓ **Regular communication with the patient** encourages therapy compliance and keeping their scheduled follow-up appointments.
- ✓ Our **ongoing patient engagement** helps overcome transportation issues, language barriers, and health literacy.

AOTI's AOTI's patient engagement at home approach and evidence-based outcomes offers payers a path to addressing health disparities and reducing spending for one of the highest cost populations in healthcare.



We welcome a conversation on how we can work together to resolve non-healing wounds in your patients.

Visit www.AOTInc.net for more information.

AOTI, Inc. The global leader in topical oxygen wound healing solutions.

A FDA QSR, ISO 13485 and ACHC accredited company, demonstrating our commitment to quality in all that we do.



Health
Canada



**Advanced Oxygen
Therapy Inc.**

3512 Seagate Way, Suite 100
Oceanside, CA 92056, USA
P: 1-760-431-4700 • F: 1-760-683-3063