The Solution Matters

Enhanced CABG is in Your Hands

DuraGraft
The World's 1st Endothelial Damage Inhibitor

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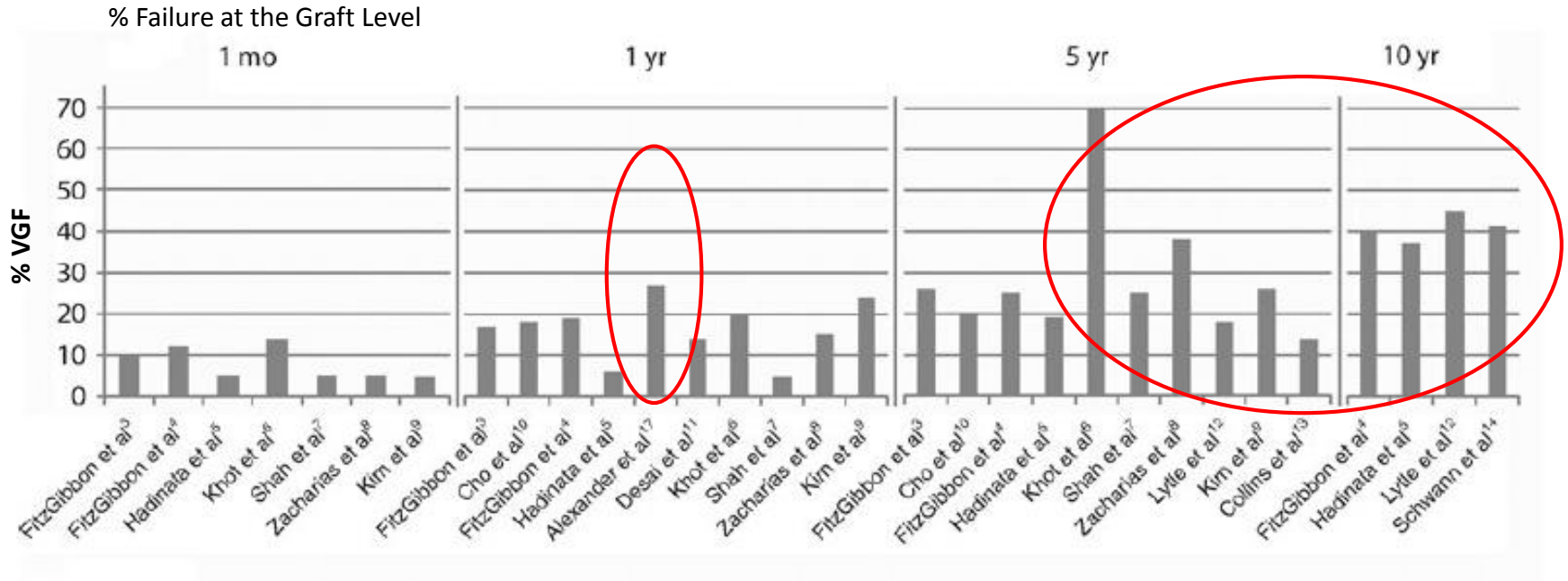
Vein Graft Failure (VGF) Following Bypass Surgery Remains a Significant Unmet Clinical Need Despite Medical Advances

Studies Show Approximately **30%** of Grafts Fail in the First Year and Rates Increase to Over **40%** Between 5-10 Years Following CABG. Resulting in more repeat hospitalization, greater need for surgical and percutaneous revascularization, and escalating costs.*



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*Harskamp RE. et al. Saphenous VGF After CABG Surgery. *Annals of Surgery (2013) Vol. 257: No. 5*

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Vein Graft Disease and Failure…

- A manifestation of Ischemia Reperfusion Injury (IRI)
- A continuous progressive process starting at the time of harvesting and continuing for years thereafter

Ischemia Reperfusion Injury

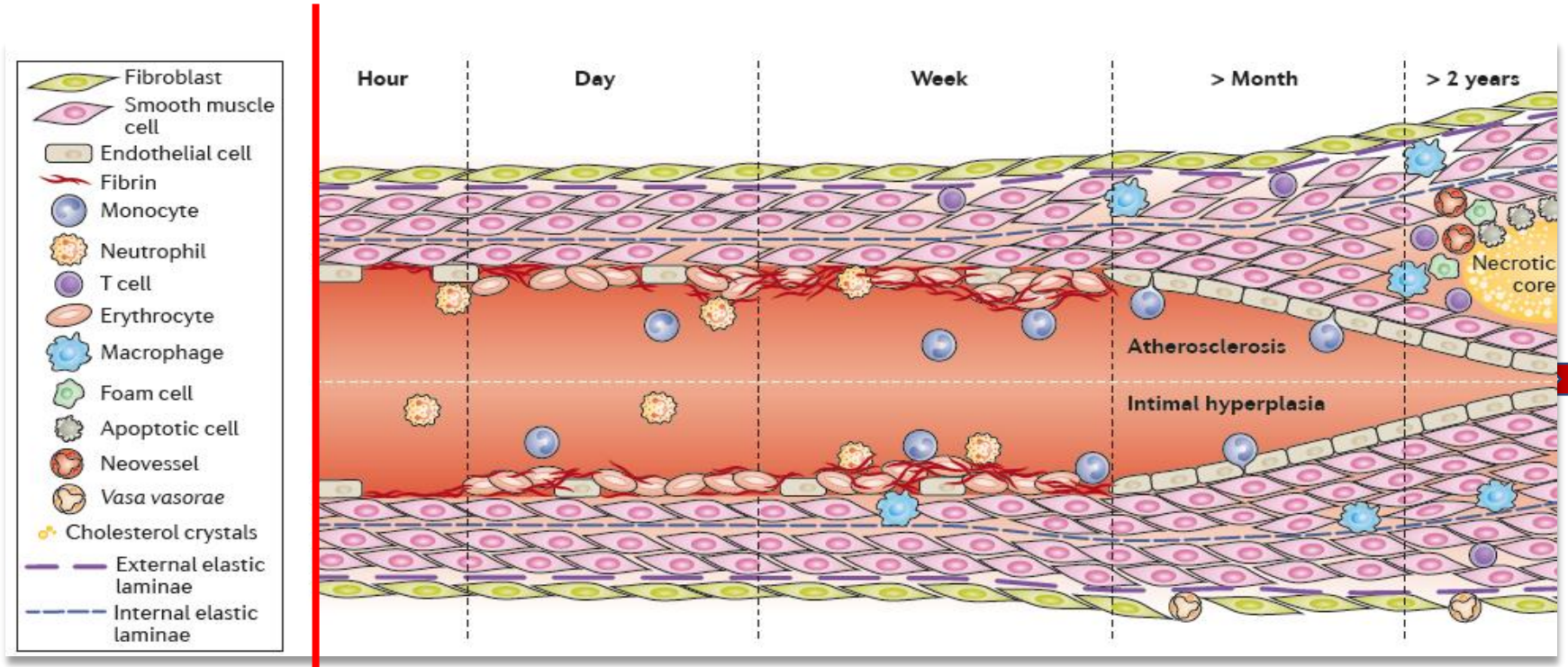
Ischemic Injury- damage that occurs during ischemia

- Characterized by two main forms of damage
  - **Oxidative Damage-** molecular damage to cells, tissues and matrix by free radicals
  - **Metabolic Stress-** loss of tissue components/functions

Reperfusion Injury-severe exacerbation of ischemic injury upon reperfusion

- Immediate Reperfusion Injury (minutes to days)
- Prolonged Reperfusion Injury (weeks to years)
- Reperfusion Injury is mediated in large part by blood cells and cytokines

Ischemia Reperfusion Injury is the Basis of Graft Disease and Failure



Post-CABG Complications and Poor Clinical Outcomes

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Window to Act!

Adapted from De Vries et al. VGF from pathophysiology to clin outcomes *Nat Rev Cardiol* (2016) 13(8):451–70

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Vein Graft Disease (VGD) Affects all Free Vascular Conduits

(SVGs and Free Arterial Grafts)

While patency rates may be different for SVGs and free arterial grafts, free arterial grafts and SVGs develop graft disease and failure.

- SVGs and free arterial grafts are both exposed to ischemic conditions following harvesting
- SVGs and free arterial grafts are equally susceptible to Ischemia reperfusion injury
- Anatomical structure similar for both SVGs and arteries
- Graft disease and failure develop in similar pathophysiological processes
- Progression of disease is similar for both SVGs and free arterial grafts

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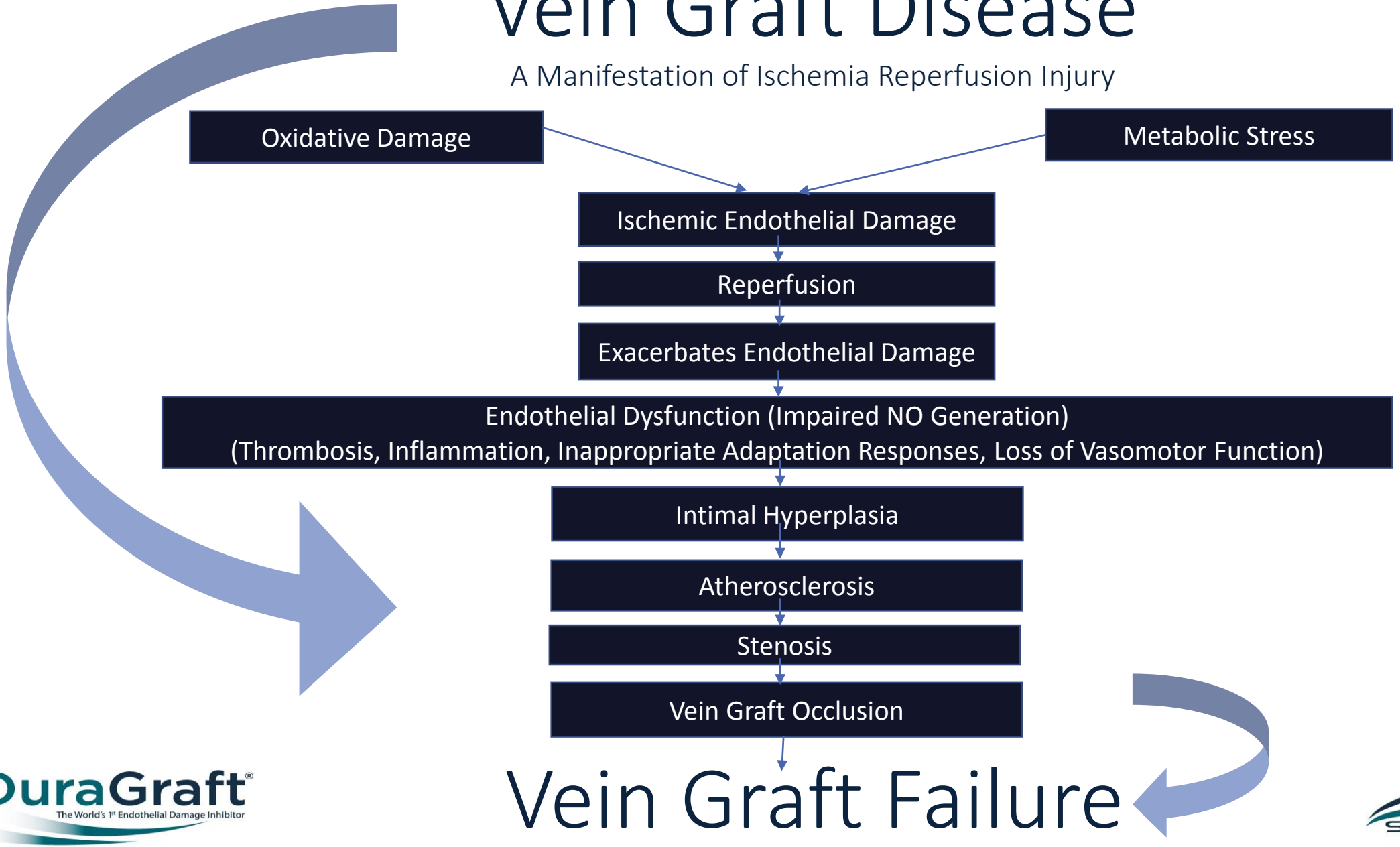
Vein Graft Disease

A Manifestation of Ischemia Reperfusion Injury



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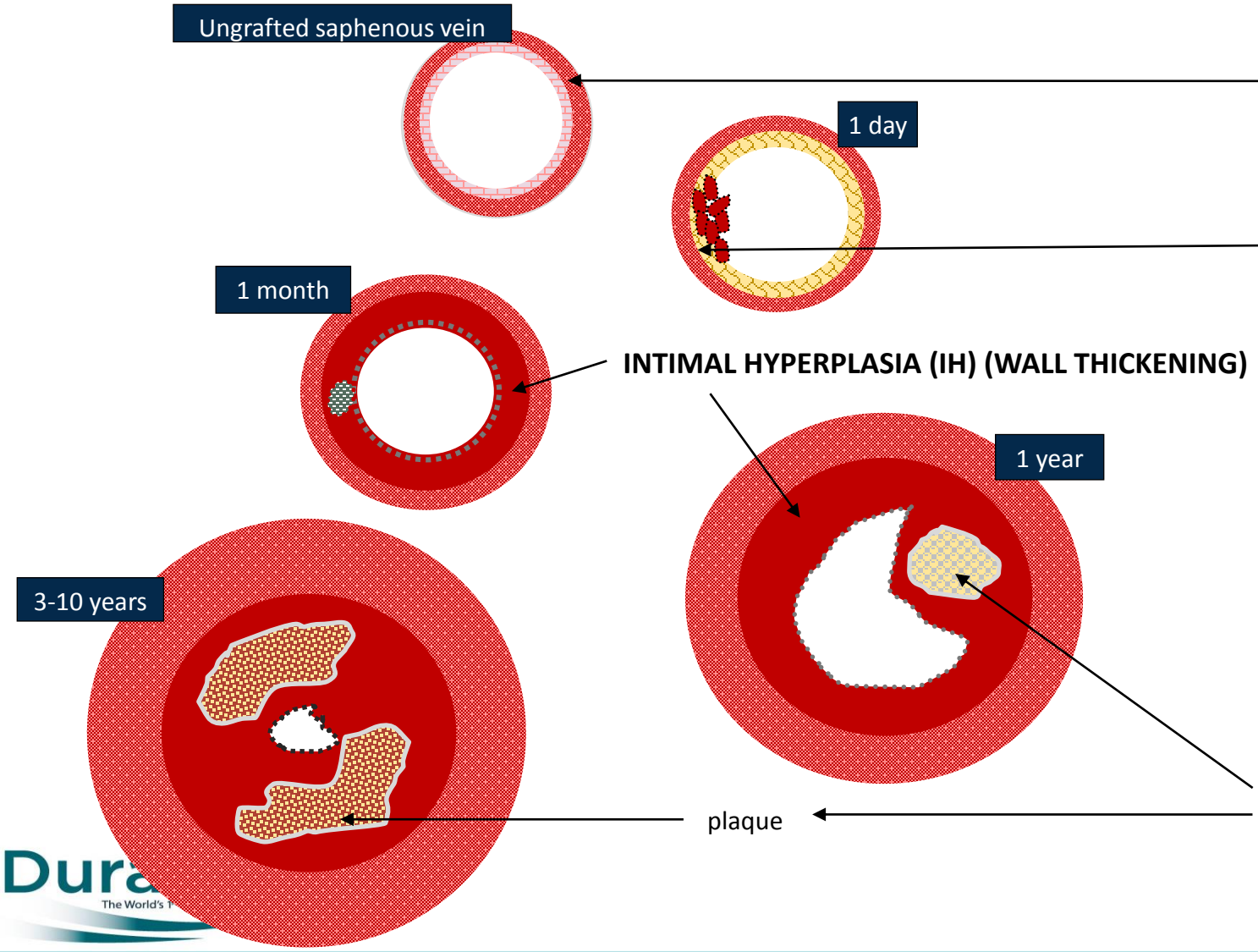
Anatomical Changes Associated with Graft Disease



Importance of Solution

SVGs and Free Arterial Grafts must be Protected against Ischemic Damage to Prevent Graft Disease and Failure

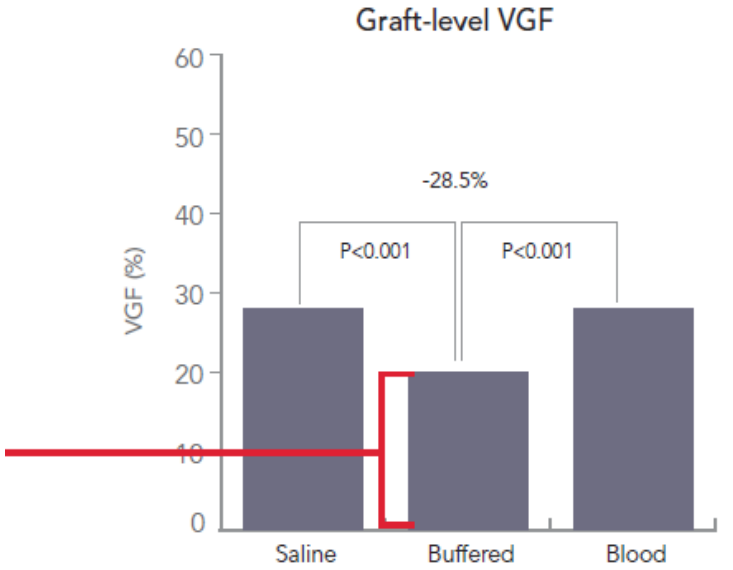
The Solution Does Matter

Learnings from the PREVENT IV Study

Saline and blood-based solutions associated with poorer clinical outcomes and highest 12-month VGF rates.

- Not biocompatible and do not protect against IRI.

Buffered solutions demonstrated significant albeit only incremental reduction in VGF rates but do not protect against IRI.



<u>Focus should be on improving the solution</u>

- **Data supports the importance of the solution and its effect in reducing VGF and the associated negative clinical outcomes.***

*RE Harskamp, JH Alexander, PJ Schulte, CM Brophy, MJ Mack, ED Peterson, JB Williams, CM Gibson, RM Califf, NT Kouchoukos, RA Harrington, TB Ferguson Jr, RD Lopes. JAMA Surg. 2014 Aug;149(8):798-805.

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Graft Preservation Solution Criteria

- **Biocompatible and cytoprotective**
  - Meets ISO 10993 Standards
  - Meets FDA Guidance on Biocompatibility (2016)
    - Cytoprotective
    - Non damaging/ Non irritating/ Non inflammatory
- **Protects against IRI**
  - Prevent oxidative damage
  - Prevent metabolic stress lesions (storage lesions)

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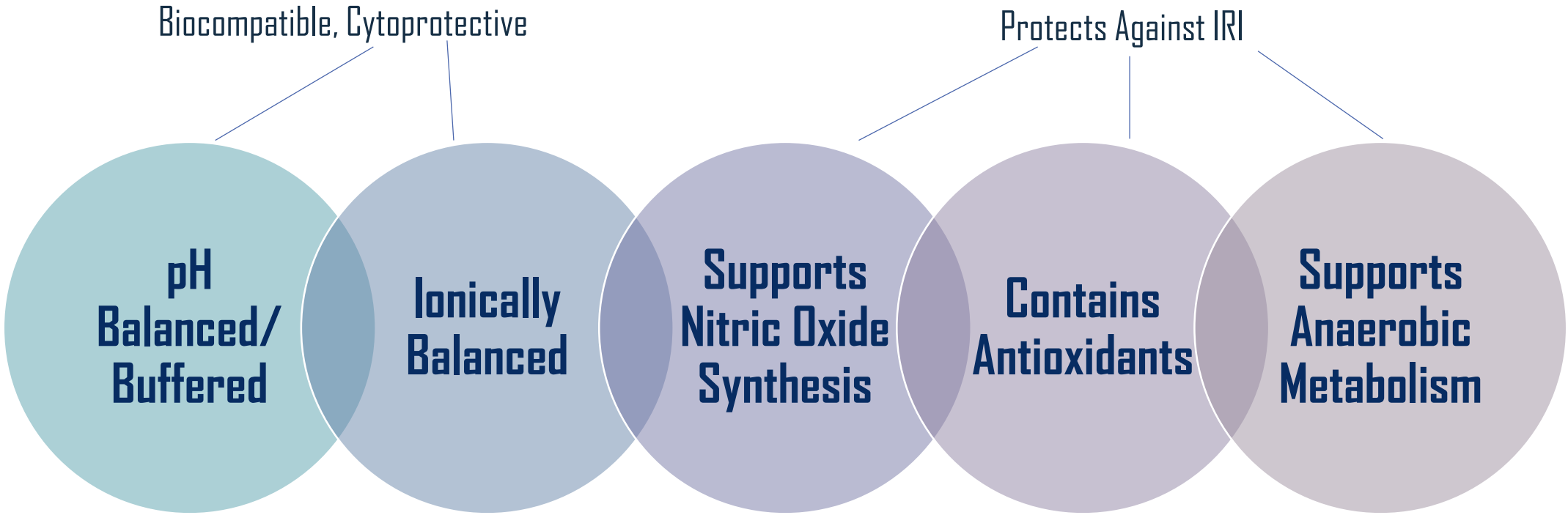
Properties Needed For Appropriate Preservation to Prevent VGD



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The DuraGraft Approach

Biocompatible, Cytoprotective and Protection Against IRI

pH Buffered and prevents pH related Damage

- Maintains a physiological pH to prevent cell damage

Ionically Balanced

- Maintains the normal ionic gradient across cell membranes
- Maintains the aquaporin function avoiding edema

Mitigates Oxidative Damage

- Contains antioxidants
- Neutralizes oxidants that cause chemical alteration of cell /tissue constituents

Supports Anaerobic Metabolism

- Supports metabolism following separation of the graft from blood supply
- Avoids loss of cell structure and functions

Supports Vasomotion Function

- Supports endothelial production of Nitric Oxide

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Antioxidant Activity* of DuraGraft vs. Saline and Buffered Solutions

DuraGraft Protects Against Ischemic Injury

NEGATIVE CONTROL | LACTATED RINGERS | PHY LYTE | NORMAL SALINE | DURAGRAFT

*Antioxidant activity tested in a Thionin oxidant solution

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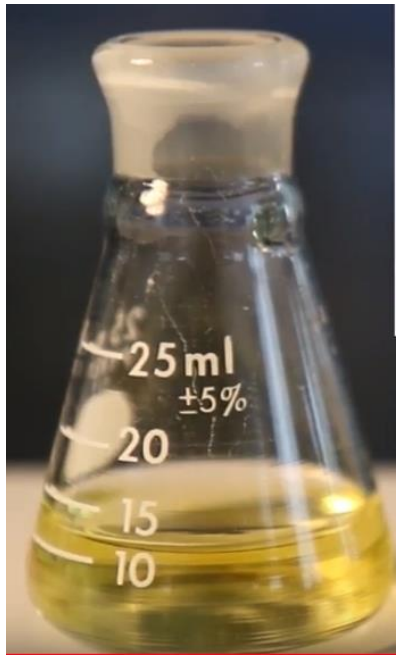
Biocompatible

Bromothymol Blue pH Test

Significant pH-mediated graft damage occurs at both, pH ≤ 6 and pH ≥8



Saline

DuraGraft

Your blood has a normal pH range of **7.35 to 7.45**
DuraGraft closely mimics the natural pH level within the body.

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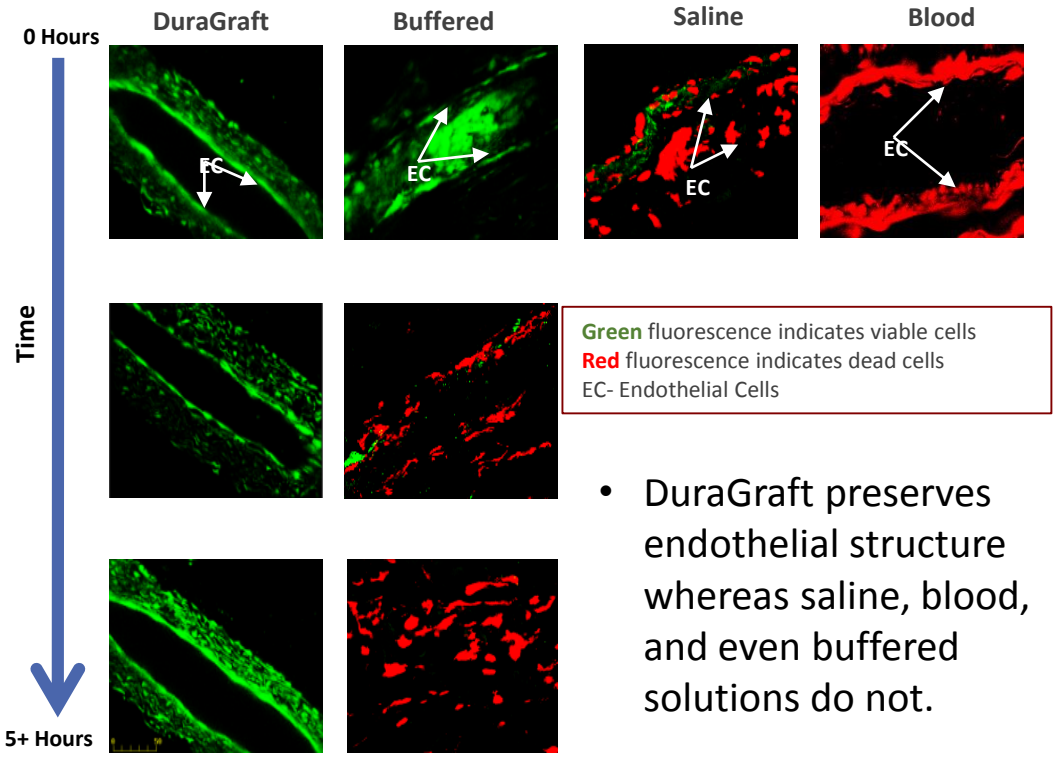
DuraGraft Treatment Preserves Structural Viability and Integrity of Free Vascular Conduits during Ischemia

vs. Blood, Saline and Buffered Solutions.



- DuraGraft preserves endothelial structure whereas saline, blood, and even buffered solutions do not.

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Ann Thorac Surg 2003;75:1145–52; discussion 1152. Printed with permission from Elsevier.

Catherine J. Pachuk, Sophie K. Rushton-Smith & Maximilian Y. Emmert (2019) Intraoperative storage of saphenous vein grafts in coronary artery bypass grafting, Expert Review of Medical Devices, 16:11, 989-997, DOI: 10.1080/17434440.2019.1682996

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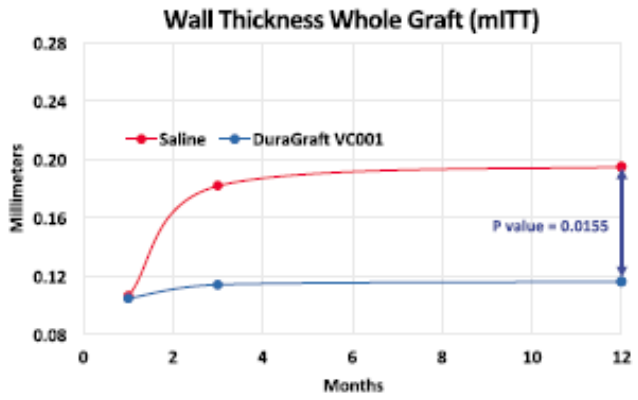
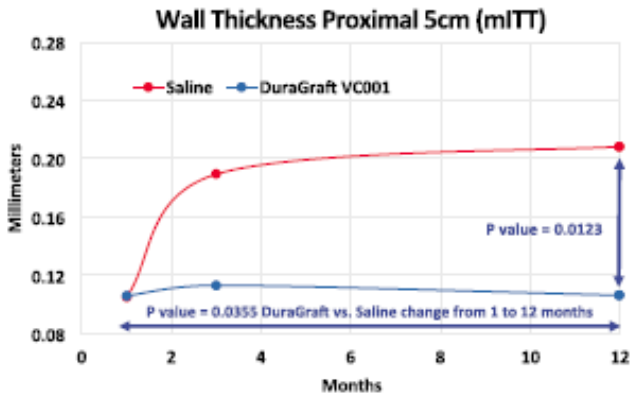
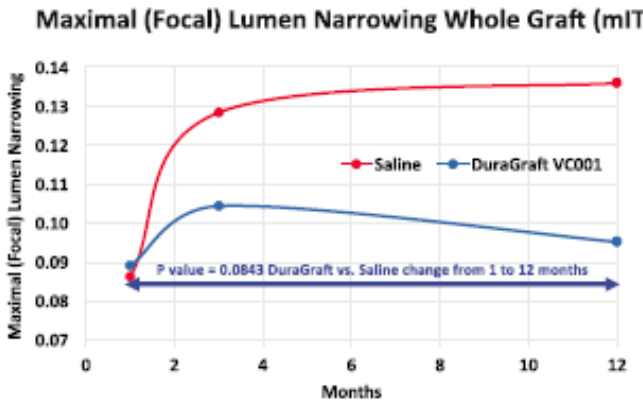
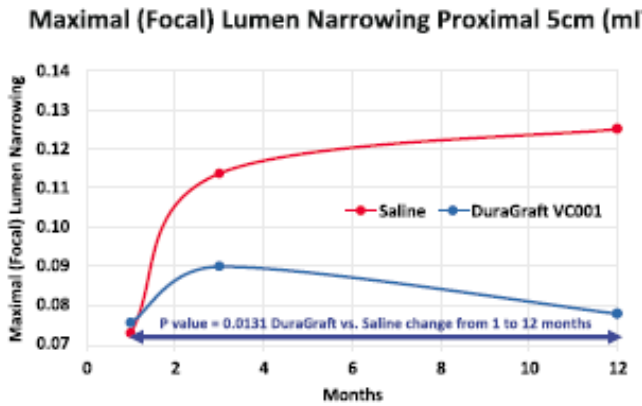
DuraGraft Mitigates the Early Anatomical Markers of VGD

5 North American and 2 European Sites • Double-Blind, Comparative (Within-Person)
DuraGraft Treatment vs Standard of Care • mITT Population • n=97









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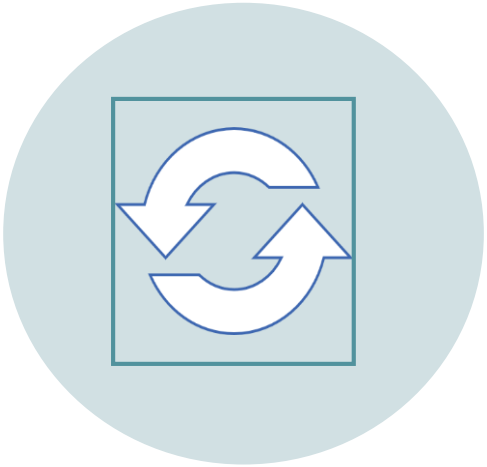
DuraGraft Reduces Clinical Complications Post-CABG

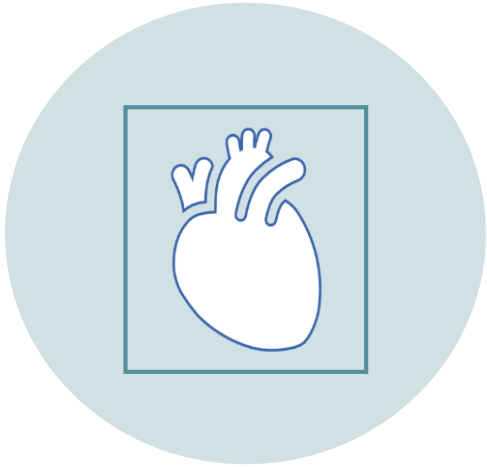
2,436 CABG Patients • DuraGraft Treatment vs Standard of Care

Statistically Significant reductions in long-term clinical events with DuraGraft (up to 15 years)

45% REDUCTION IN MYOCARDIAL INFARCTION



35% REDUCTION IN REPEAT REVASCULARIZATION



19% REDUCTION IN MACE

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Haime et al., Expert Reviews Cardiovascular Therapy 2018; in press

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VASC Study
European Multi-Center Registry

To Assess Outcomes in Patients Undergoing Coronary Artery Bypass Graft Surgery

- 37 Sites
- 2965 Enrolled

ClinicalTrials.gov Identifier: NCT02922088

DuraGraft Outperforms "Standard of Care"

	Standard of Care			
Property	Saline	Blood	Buffered Solutions	DuraGraft
Approved for Indication	✗	✗	✗	✓
Isotonic	✓	✓	✓	✓
pH Balanced	✗	✗	✓	✓
Does Not Actively Cause Harm	✗	✗	✓	✓
Ionically Balanced	✗	✓	✗	✓
Contains Pro-endothelial Components	✗	✗	✗	✓
Prevents Ischemia Reperfusion Injury	✗	✗	✗	✓
Prevents Oxidative Damage	✗	✗	✗	✓
Prevents Metabolic Storage Lesions	✗	✗	✗	✓
Designed to Prevent Inflammation and Pro-Coagulant Responses	✗	✗	✗	✓
Preserves Vascular Endothelium	✗	✗	✗	✓
Designed to Prevent Edema of Graft Tissue	✗	✗	✗	✓

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DuraGraft is a vascular conduit treatment that improves clinical outcomes by reducing the incidence and complications of graft failure by maintaining normal graft function and structure.

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DuraGraft is not yet available in the United States

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Non-buffered, Buffered, and Storage Solutions Used in Clinical Practice Today are not Biocompatible and do not Protect Against IRI

- DuraGraft Alone Meets the Functional Requirements Necessary to Maintain Structural and Functional Integrity of Vascular Endothelium

						Buffered Solutions							
	Properties (Needed to Prevent VGF)	DuraGraft	Circulating Blood	Extracorp. Blood	Saline	Plasmalyte	Normosol	Lactated Ringer's	HTK Custodiol	Univ. of Wisconsin (Viaspan)	Perfadex	HE Solution	TiProtec
biocompatibility	pH Balanced / Buffered	7.3	7.3	8.0	5.5	7.4	7.4	6.5	7.1	7.4	5.5	7.4	7.0
IRI	Ionically Balanced	✓	✓	✓	x	x	x	x	x	x	x	x	x
IRI	Supports Anaerobic Metabolism	✓	✓	x	x	x	x	x	x	x	✓	x	x
IRI	Contains Antioxidants	✓	✓	x	x	x	x	x	x	✓	x	x	± Weak antioxidant properties
IRI	Supports Nitric Oxide Synthesis	✓	✓	x	x	x	x	x	x	x	x	x	x
										*high potassium		*contains a vasodilator and verapamil	*high potassium

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Why Buffered Solutions Are Not Good Enough

- They do NOT protect against IRI.
- They are NOT ionically balanced.
- They are NOT approved or clinically evaluated as a preservation solution.
- They are ONLY pH balanced and don't cause pH-mediated injury.
  - This accounts for some improvement in VGF rates, but rates are still high
- "Buffered Solution" is a generic name that includes many solutions i.e. Plasmalyte and Normosol.

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DuraGraft is the Only Clinically Proven and Approved Preservation Solution that Reduces the Incidence of VGF and the Clinical Complications Associated with VGF Post-CABG.

- Approved for Preservation of Free Vascular Conduits
- Proven to reduce complications associated with VGF post-CABG
- Protects Vein Grafts During the Ischemic Interval

DuraGraft

CURRENTLY USED SALINE AND BLOOD BASED SOLUTIONS

- **X** Not Approved for Vascular Graft Storage
- **X** Saline Actively Causes Tissue Damage
- **X** Saline and Blood-based solutions associated with poorest clinical outcomes and highest VGF rates(1)
- **X** Do Not Protect Against IRI

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1. Harskamp, et al. Vein Graft Preservation Solutions, Patency, and Outcomes after CABG Surgery: Follow-up from the PREVENT IV randomized clinical trial; JAMA Surg. 2014

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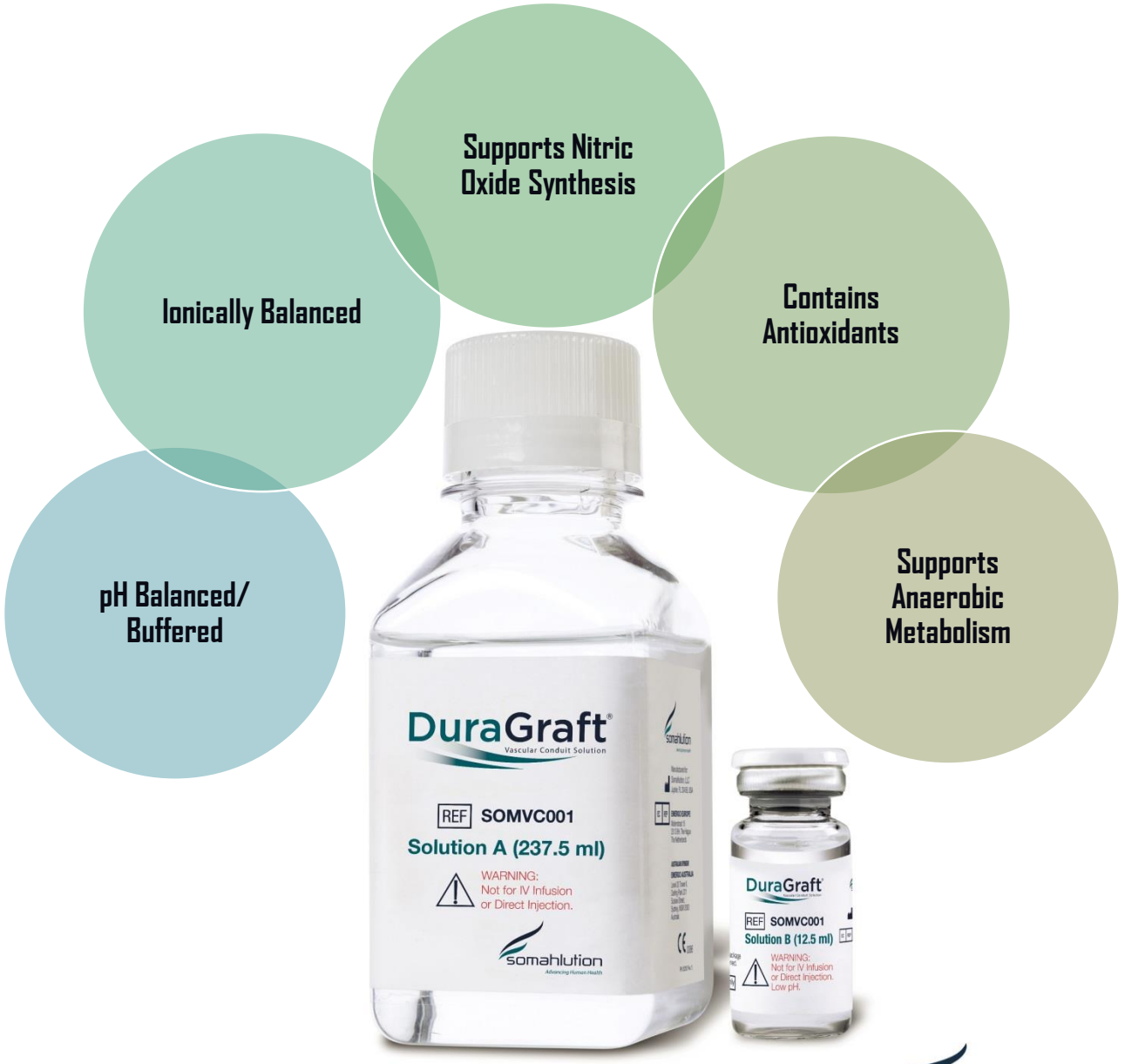
DuraGraft - Reduces Clinical Complications Associated with VGF

Biocompatible, Cytoprotective, Prevents IRI



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DuraGraft is CE Marked.
DuraGraft is not yet available in the United States.

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