Hemodialysis Access

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Disclosures

**Employment**
- Humacyte, Inc.
  - Clinical Development / Clinical Operations

**Ownership**
- InnAVasc Medical, Inc.
  - Founder, COO
  - IP – Bullet Proof Vascular Graft

**Paid Consultant**
- Merit Medical
  - KOL, speaker, training

**Research Funding**
- Duke Translational Medicine Institute
- NIH/NIDDKD STTR R41
  - Bullet Proof Vascular Graft
Disclosure Information

Financial Disclosure and Conflicts:

Humacyte Clinical Operations: Salary and Stock Options

Disclaimer:

The Humacyte investigational bioengineered vessel is an investigational biologic currently being studied in Poland and the US to evaluate its potential safety and preliminary efficacy when used as a vascular access in patients with End Stage Renal Disease requiring hemodialysis and in patients with Peripheral Arterial Disease.

This investigational product has not been submitted for regulatory approval by the FDA or any other regulatory authority. Both the clinical significance of the data reviewed in this presentation, and any potential future indication(s), warnings, precautions, and adverse reactions are unknown at this time.
In 2013, more than 26 million Americans had CKD

Slow progression (> 3mo) to renal dysfunction

Classified by GFR

- Stage I (> 90 mL/min)
- Stage II (60-89 mL/min)
- Stage III (44-59 mL/min)
- Stage IV (15-29 mL/min)
- Stage V (<15 mL/min) → ESRD
ESRD

- Renal Replacement Therapy (RRT) required to sustain life
- RRT = Renal Tx, HD, PD
- Signs/symptoms
  - Uremia
  - Edema
  - HF
  - Respiratory distress
  - Encephalopathy
ESRD

• In 2013, > 650,000 Americans had ESRD
• ~ 420,000 treated with HD
• Incidence of ESRD increased by 68% since 2000.
• 120,000 new cases per year
• ESRD costs 30.9 billion per year
  – 7.1% of overall Medicare costs
  – ESRD patients comprise < 1% of total Medicare population
Renal Dialysis

**Acute Renal Failure**
- sudden/severe decrease in kidney function.
- Intense dialysis over days/weeks until normal renal function.

**Chronic Renal Failure**
- progressive kidney dysfunction.
- hemodialysis several times a week or for life time until renal transplant

**HEMODIALYSIS**
- blood cycles through machine/filter and returns it to body.

**PERITONEAL DIALYSIS**
- fluid cycled into & out abdomen through peritoneum (filter).
Hemodialysis and Peritoneal Dialysis

Components of Hemodialysis

Vascular Access

• Arteriovenous connection
  – AV fistula
  – AV graft
• Venous catheter
  – Jugular vein
  – Subclavian vein
  – Femoral vein
• Dialyser
• Disposable equip./semi perm. membranes
• Dialysis Machine
  – Process -4 hours/ 3-5 times a week

Components of Peritoneal Dialysis

• Tenckhoff Catheter
• Peritoneum
• Dialysis Machine
• Dialysate Solution

- Continuous Ambulatory Peritoneal Dialysis
  no machine required 4-6 hours/4 times a day
- Continuous Cycling Peritoneal Dialysis
  special machine, overnight
Types of access for hemodialysis

- **Primary/AV Fistula**
- **Secondary/Graft**
- **Venous/Temporary Catheter**
Figure 4.7.a Change in type of vascular access during the first year of dialysis among patients starting ESRD via hemodialysis in 2014 quarterly: (a) type of vascular access in use (cross-sectional), ESRD Medical Evidence form (CMS 2728) and CROWNWeb, 2014-2015

Data Source: Special analyses, USRDS ESRD Database. Data from January 1, 2014 to December 31, 2014: a) Medical Evidence form (CMS 2728) at initiation and CROWNWeb for subsequent time periods. Patients with a maturing AV fistula / AV graft with a catheter in place were classified as having a catheter. Abbreviations: AV, arteriovenous; CMS, Centers for Medicare & Medicaid; ESRD, end-stage renal disease; HD, hemodialysis; PD, peritoneal dialysis.

2016 Annual Data Report, Vol 2, ESRD, Ch 4
Figure 4.7.b Change in type of vascular access during the first year of dialysis among patients starting ESRD via hemodialysis in 2014 quarterly: (b) longitudinal changes in vascular access use and other outcomes, ESRD Medical Evidence form (CMS 2728) and CROWNWeb, 2014-2015

Data Source: Special analyses, USRDS ESRD Database. Data from January 1, 2014 to December 31, 2014: (b) ESRD patients initiating hemodialysis (N =102,367). Patients with a maturing AV fistula / AV graft with a catheter in place were classified as having a catheter. The apparent decrease in arteriovenous fistula and arteriovenous graft use at 1 month is related to missing data due to the different data sources used for incident and prevalent patients. Abbreviations: AV, arteriovenous; CMS, Centers for Medicare & Medicaid; ESRD, end-stage renal disease; HD, hemodialysis; PD, peritoneal dialysis.
Central Venous Catheter

- Used in emergency or urgent need for vascular access
- Vas Cath (non-tunneled) - used for short term
- Permcath (tunneled) – used for longer term dialysis
- ~ 80% of ESRD patients initiate with catheter

**Pros**
- used right away for hemodialysis
- once in place, no needle contact
Venous Catheter

Cons

• Blood stream infection
• Central venous stenosis
  – limiting future access
• Highest morbidity
• Highest mortality
• Multiple interventions
• Venous thrombosis
• Low blood flow rates, longer tx time
• Poorer dialysis adequacy
• Cannot get wet (no swim, showers)
• Placement injuries (neck or chest)
  – pneumothorax, arterial injury, thoracic duct injury, air embolus, inability to pass the catheter, bleeding, nerve injury, and great vessel injury.
Figure 1: Algorithm demonstrating order of basic access site selection from new renal failure patient to end stage access patient.
The Arteriovenous Shunt

- Belding Scribner - early 1960’s
- External high flow shunt
- Teflon

Bronx VA, 1964
Native AV Fistula (AVF)

Completely Autogenous AV Access

• Concept of connecting a vein to artery.
• No synthetic material
• Relatively low risk

Brescia, NEJM, 1966
Native AVF

Preferred access method

- Palpable "thrill" (distinct buzzing), by placing finger over mature fistula.
- Audible “whooshing” (with stethoscope) or *bruit*.
- Fistulas usually in nondominant arm, (3-6 month maturation).
- ~ 65% of all HD access
Examples of AV fistulas:

- Radial branch-cephalic direct access (snuffbox fistula)
- Radiocephalic Autogenous ulnar-cephalic forearm transposition,
- Brachiocephalic (antecub. V. to brachial artery),
- Brachiobasilic V transposition
- Saphenous loop (FA-FV)
- Distal SFA-Saphenous AFV
- SFV transposition
Why are AVFs Preferred??

• CMS Cross Sectional Study
  – AVF is cheapest form of Access ~ $40k
  – AVG ~ 60K
  – CVC ~ 80-100k

• National Kidney Foundation

• KDOQI guidelines

• KDOQI recommends
  – ~65% AVF rate
Native AVF

• **Pros:**
  - Lower infections
  - Higher blood flow rates
    (effective dialysis)
  - Lower incidence of thrombosis
  - More durable
  - Fewer revisions

• **Cons:**
  - High early failure rates
  - Lack of maturation
  - Aneurysm/bulging in wall of vein from long-term use
  - Long Maturation times
Keep Dialysis Simple

• How do you get blood out of a patient to a machine and back three times a week?
  – Life sustaining therapy
• Flow rates > 600 ml/min
• A part of the body that is accessible
• Rule of 6’s
  – 6 mm in diameter
  – 6 cm long
  – 6 mm from the skin
Fistula Biology
Can we influence the path?

Native Vein → Maturing → Mature
Native Vein → Stenosis → Angioplasty
Native Vein → Severe Stenosis → Occluded

?
Fistula Maturation

• DAC Study (Dember) 2008
  – Plavix vs placebo for AVF thrombosis
  – 44% mature at 6 months

• HFM Study 2016
  – ~60% mature by 9 months

• FAVOURED (Irish) 2017
  – Fish oil / ASA for AVF thrombosis/maturation
  – ~50% failure by 12 months
Maturation and Secondary Patency

Functional Patency

Survival Distribution Function Estimate

Time (days) to maturation or functional patency with decay to secondary patency

- 97% at 6 months
- 66% at 12 months
- ~40% at 18 months
- ~25% at 24 months
- ~12% secondary patency

Legend:
- Humacyte MA - AVF
- DAC - AVF 2008
- HFM 2015
- Humacyte V001 & V003 combined
Percutaneous Fistula Creation
The Bridging Dialysis Fistula

- Saphenous vein forearm AVF in 1969
- Flores (Mexico) and May (Australia)
A New Material

- Expanded polytetrafluoroethylene (ePTFE) vascular graft
- Developed in the 70’s for use as a vascular conduit
- Helped to revolutionize AV Access care and availability

AV Grafts (Prosthetic)

AVGs inserted when native vasculature does not permit a fistula.

AVG much like fistulas except prosthetic material joins vessels.

Grafts classified **biological** or **synthetic**.
(Biological limited by availability, expensive, size and quantity)

- Biological grafts include: denatured homologous vein allograft, cryopreserved saphenous vein, bovine heterografts, human umbilical vein and sheep collagen grafts.

- Common synthetic grafts: Dacron, **polytetrafluoroethylene (PTFE)** and polyurethane grafts (self-sealing)

- ~ 15% of all HD access
AV Grafts

Pros

- Shorter maturation time, can be used with weeks of surgery
- Permanent access option if a fistula won’t work
- Upper arm grafts have a high flow rates
Access options for AVG
AV Graft Placement – Any “stickable” place that connects an Artery to a Vein

Figure 16: Various AVG insertion sites and configurations (A) Ax-Ax teardrop (B) Ax-Ax chestwall loop (C) Femoral SFA to CFV (D) Upper arm brachial artery to axillary vein.
US Vascular Access Problems

AV Grafts

– Poor long-term patency
  • Vein neointimal hyperplasia
  • Stenosis
  • Thrombosis
  • Graft infections
  • Graft wall deterioration/abuse

– DAC study indicated loss of patency in 75% of AVGs at one year

Current Work to Improve Grafts

Bleeding/Weeping

Needle Stick Sealing
Grafts

??Early Access??

 Vectra
 Expedial
 Vascutek
 Flixene
 Acuseal
Gore Acuseal

• Cleared for early cannulation
• Reduce catheter time
Current Work to Improve Grafts

Bleeding

Thrombosis

Proliferation

Physiology

Graft Flow Hemodynamics

Outflow Hemodynamics
Axillary/Subclavian Vein Pathology
the Gore Hybrid

• ePTFE vascular prosthesis that has a section reinforced with a nitinol stent is partially constrained to allow for easy insertion and deployment into a vessel

• CARMEDA® BioActive Surface (CBAS® Surface) consisting of a stable covalently bonded, reduced molecular weight heparin of porcine origin.

CARMEDA® and CBAS® are trademarks of Carmeda AB, a wholly owned subsidiary of W. L. Gore & Associates.
Thromboresistant Surface

- Unique Heparin Bonded CBAS® Surface
- Proprietary end-point covalent bonding
- Sustained bioactivity

GORE® Hybrid Vascular Graft with CBAS® Surface

Control ePTFE Graft

*The bioactive luminal surface of a GORE® Hybrid Vascular Graft (top) remains free of thrombus, while the non-bioactive surface of a control graft (bottom) is covered with thrombus. Grafts were compared in a 90 minute acute canine blood contact model.*
Gore Hybrid Dialysis Access Application

- Subclavian/Axillary vein and lateral
- **Peripheral Vein pathology**
- Manage venous outflow
- High axillary dissection
- Graft replacement and salvage
- Access site salvage
Hemodynamics and Intimal Hyperplasia

End-to-side Anastomosis

- Intimal hyperplasia formation corresponds to areas of flow separation, impingement and at the suture line
Computational Fluid Dynamics

Conventional End-to-side Anastomosis

Oscillatory Shear Index (OSI)*

<table>
<thead>
<tr>
<th>OSI (0 – 0.5)</th>
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<tbody>
<tr>
<td>Conventional End-to-Side</td>
</tr>
<tr>
<td>GORE® Hybrid Vascular Graft</td>
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<tr>
<td>0.25</td>
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<td>&lt; 0.001</td>
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Endoluminal Anastomosis with the GORE® Hybrid Vascular Graft

* CFD 600 mL / min, 4.8 mm 30°, t = 0.4s
Stages of Deployment

The nitinol reinforced section should be introduced into the vessel by at least 2.5 cm.
Over the Wire Implantation Technique

6. Tunnel the device carefully toward the arterial anastomosis site while maintaining the secure placement of the nitinol reinforced section.

7. Suture the arterial anastomosis in a standard manner.
Thoracic Venous Pathology

- Axillary/Subclavian
- Costco-clavicular
- SVC/brachiocephalic
Central Venous Obstruction
What to Do??
A Brief Review

- **HeRO™** Hemodialysis Reliable Outflow
- Hybrid vascular access device
- 2 primary components: ePTFE graft with Titanium connector 6mm ID, and radiopaque silicone outflow component with braided nitinol reinforcement 5mm ID
- Common access veins include: Subclavian and Internal Jugular
- End stage access device
- Indicated for catheter dependent patients with central venous stenosis and/or occlusion
Hematoma - Back/Side Wall Injuries
Hematoma

- Poor hemostasis technique at decannulation
- Access posterior and side wall trauma and degradation
  - Inadvertent NEEDLE injury (more common)
  - Repetitive NEEDLE injury
Back/Side Wall Injuries

- These injuries occur as a result of the front wall collapsing down on the back wall during needle puncture.
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Bleeding

- Bleeding diathesis
- Downstream stenosis
  - Anastomotic or Central
- Access posterior and side wall injury and degradation
  - Secondary to repetitive NEEDLE injury
Pseudoaneurysm - Graft Degradation
Pseudoaneurysm

- Access posterior and side wall trauma and degradation
  - Repetitive NEEDLE injury (more common)
  - Inadvertent NEEDLE injury
- Worsened by downstream stenosis
Stenosis

- Neointimal hyperplasia of the outflow vein
- Intragraft stenosis
  - Secondary to repetitive NEEDLE cannulation
  - Tissue ingrowth through puncture sites and ePTFE flaps
    - Irregular, foreign luminal surface
    - Leads to platelet aggregation and sclerosis
  - Difficult to Access graft (sclerotic, irregular lumen)
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Infection

- Blood Stream infection
  - Access seeded by TDC
  - Access seeded by other local infection (e.g. osteo, UTI)
- Local Access infection
  - NEEDLE Inoculation (without fluid collection i.e. hematoma or seroma)
  - Infected Hematoma (caused by NEEDLE injury)
  - Infected pseudoaneurysm (caused by NEEDLE injury)
  - Skin ulcer/erosion/access exposure (NEEDLE injury)
Thrombosis

- Neointimal hyperplasia of the outflow vein
- Chronic hypotension
- Hypercoagulable syndrome
- Overly aggressive compression at decannulation
- Intragraft stenosis
  - Secondary to repetitive NEEDLE cannulation
  - Sclerotic, Irregular Lumen
- Hematoma
  - Impingement on access secondary to NEEDLE injury
- Pseudoaneurysm
  - Due to NEEDLE injury and causes turbulence and mural thrombus
The Innovation

Novelty

- ERROR PROOF
- IMMEDIATE USE
- SELF SEALING
- CANNOT MISS
Current Standard of Hemodialysis Access Care

1. **Patient required to initiate Hemodialysis**
2. **Tunneled PermCath inserted**
3. **Patient receives Hemodialysis**
4. **AV Access surgery for AVF or AVG**
   - 1-2 months post catheter
5. **Discharge home and referral for AV access surgery**
6. **AV access ready to use**
   - Avg. 3 months later

**Catheter for 3-6 months!!**
A Change in Paradigm to Hemodialysis Access Care

1. Patient required to initiate HD
2. Temporary VasCath Inserted
3. Patient receives HD
4. Bullet Proof implanted
5. VasCath removed and patient D/C’d to home WITHOUT catheter
6. Hemodialysis same day or next day via Bullet Proof

No More Catheters!!
Potential Benefits

- Provide immediate access
- Promote reliable access for nurses, techs, and patients
- Promote home hemodialysis
- Prevent graft degradation
- Prevent back or side wall injuries
- Reduce cost – Hospital / Home Hemodialysis
Duke Doctors Create First

BIOENGINEERED BLOOD VESSELS
Polymer scaffold is designed to guide tissue shape...

...and designed to degrade
Automated Decell Process

- Automated Decell Process
  - PLC controller for onboard pumps, valves, liquid sensors
  - All buffer bags stored on station before start of decell
Quantitative assessments confirm adequate removal of cellular components:

- MHC-I from the plasma membrane
- β–Actin from the cytoplasm
- Double Stranded DNA from the nucleus

First use of a **decellularized, bioengineered blood vessel**
Animal Explant at 6 months
6 Month Explant (Animal Model)

- No Cells Pre-Implant
- Smooth muscle Alpha Actin
- CD 31 (endothelial)
18 Months post implant

Image Courtesy of Duke University
Needle cannulation sites re-populate with blood-derived monocytic CD68+ cells, may contribute to smooth muscle.
Bioengineered human acellular vessels for dialysis access in patients with end-stage renal disease: two phase 2 single-arm trials

Jeffrey H Lawson, Marc H Glickman, Marek Ilzecki, Tomasz Jakimowicz, Andrzej Jaroszynski, Eric K Peden, Alison J Pilgrim, Heather I Prichard, Małgorzata Guziewicz, Stanislaw Przywara, Jacek Szmidt, Jakub Turek, Wojciech Witkiewicz, Norbert Zapotoczny, Tomasz Zubilewicz, Laura E Niklason

Summary

Background For patients with end-stage renal disease who are not candidates for fistula, dialysis access grafts are the best option for chronic haemodialysis. However, polytetrafluoroethylene arteriovenous grafts are prone to thrombosis, infection, and intimal hyperplasia at the venous anastomosis. We developed and tested a bioengineered human acellular vessel as a potential solution to these limitations in dialysis access.
Initial Clinical Outcomes of First-in-Man Human Implants (6 months)

No indication of immune response

- No change in PRA Class I Reactivity [N=6]

- 0% reactivity to PRA Class 2 in pre- & post-implant measurements [N=6]

Lawson et al., American Heart Association Meeting, Dallas TX, 2013
Kaplan-Meier Curves for HAV Patencies (V001 and V003)
Summary

• AV Access is complicated
• Expensive
• AVF are best........when they work
• 50% AVFs fail
• Multiple AVG options
• Catheters are worst
• Haven't come very far in 50 years
• New products and devices on the horizon