Interventional Cardiovascular Medicine: Past, Now, and Future Perspectives

Martin B. Leon, MD

Columbia University Medical Center Cardiovascular Research Foundation New York City



TCTAP 2014

19th April 22-25, 2014 COEX, Seoul, Korea www.summit-tctap.com





Disclosure Statement of Financial Interest TCTAP2014: Seoul, Korea; April 22-25, 2014 Martin B. Leon, MD

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation / Financial Relationship

- Grant / Research Support
- Consulting Fees / Honoraria
- Shareholder / Equity

Company

- Abbott, Boston Scientific, Edwards Lifescience, Medtronic
- Angioscore, Meril Lifescience, Micell,
- Apica, Angiometrix, Backbeat, Caliber, Cappella, Claret, Coherex, Elixir, GDS, Medinol, Mitralign, Valve Medical







Interventional Perspectives

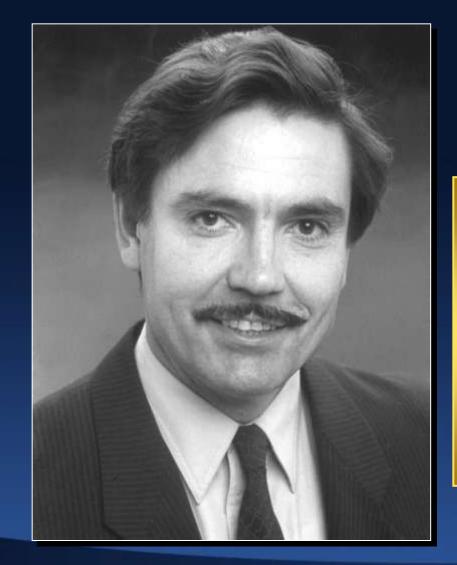
TCT at 25 Years







The Father of PTCA!



Andreas Gruentzig 1939 - 1985

His dream was the catheter-based percutaneous treatment of vascular disease in alert, awake patients!







The TCT Career Achievement Award





Andreas Gruentzig







GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE AND HOSPITAL Washington, D.C.

Department of Cardiology

presents

TRANSCATHETER CARDIOVASCULAR THERAPEUTICS

New Device Development in Coronary Artery Disease, Peripheral Vascular Disease; and Valvular Heart Disease

> Course Directors: Kenneth M. Kent, M.D. Martin B. Leon, M.D.

November 10 - 12, 1988 Omni Shoreham Hotel Washington, D.C.

The 1st TCT - 1988

PURPOSE

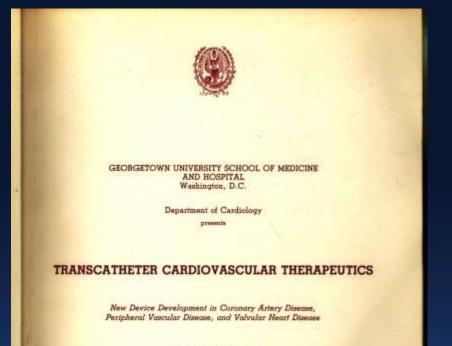
- Explore a new era of interventional device therapies - innovation!
- Re-introduce the live case demonstration format
 - education
 - education

- Apply rigorous methods to evaluate devices and clinical outcomes - evidence-based
 - Create an international network of multi-disciplinary scientists - *GLOBAL!*





The 1st TCT - 1988



Course Directors: Kenneth M. Kent, M.D. Martin B. Leon, M.D.

November 10 - 12, 1988 Omni Shoreham Hotel Washington, D.C.

Meeting Details

• FACULTY: 25

- PARTICIPANTS: 225
- LECTURES: 32
- LIVE CASES: 5 (+ 3 taped)
- INDUSTRY EXHIBITORS: 23
- VENUE: Omni Shoreham Hotel; Washington, DC







TCT 2013: In Partnership with ACC San Francisco, CA; Oct 27 – Nov 1, 2013









TCT 2013 Meeting Milestones

- 11,500 attendees from >90 countries (52% US, 48% non-US)
 - 1,220 Full-time Faculty
- 34 Late Breaking Trials, First Reports and Featured Clinical Research
 - 851 peer-reviewed Abstracts presented (from 1750 submitted)
- 300 peer-reviewed Challenging Cases presented (from 626 submitted)
 - ~100 HD live case transmissions from 20 sites





TCT Perspectives: 1988 - 2013

Phase 1: 1988 - 1993

Exploring and Validating the New Device Era

- 'Post-balloon' proliferation of new devices early collaborations with industry/engineers
- Rudimentary clinical research initiatives (the "age of empiricism")
- Reinforcement of the live case format as a vital educational vehicle

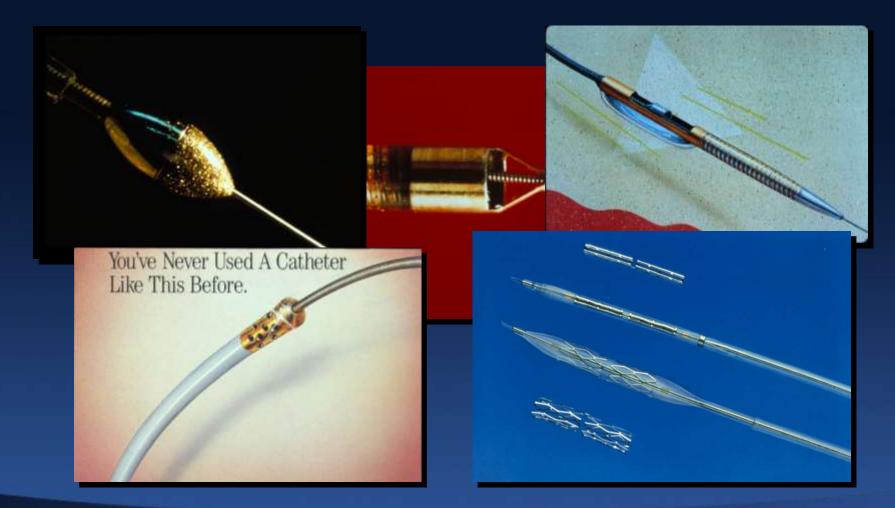


Partnership with the Acc einventing the Future very Year

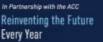


CARDIOVASCULAR RESEARCH FOUNDATION At the heart of innovation

TCT Perspectives: 1988 - 2013 Early Innovation









The Palmaz-Schatz Stent









Early Days of Coronary Stents



First Palmaz-Schatz Stent in Human December 31st, 1987

tct²⁵



TCT Perspectives: 1988 - 2013

Phase 2: 1993 - 1998

TCT Goes Global!

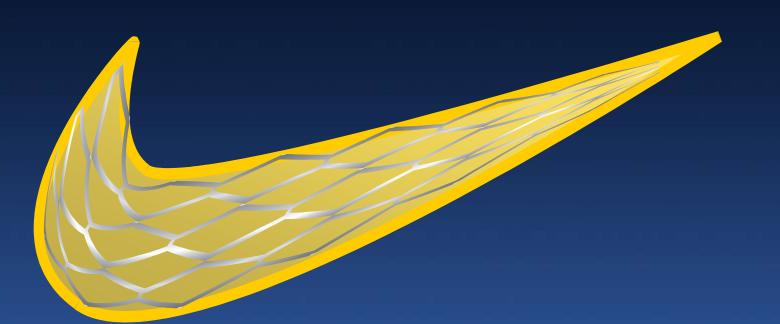
- Stents "reign supreme" dramatic growth of interventional cardiology
- Early RCTs evolution to strict evidence-based medicine principles for clinical research
- Shift from U.S. to EU device availability, early clinical experiences, live cases





Intervention 1998

Just Stent It!









TCT Perspectives: 1988 - 2013

Phase 3: 1998 - 2008

The Birth of a Subspecialty

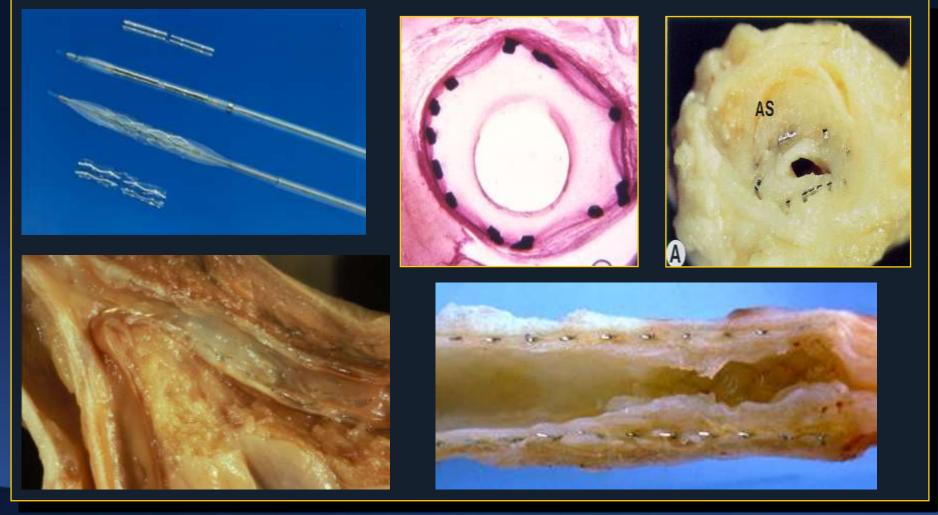
- DES dominate Restenosis "cured" but "dark side" (late ST) emerges - a rosy prophesy can stumble
- EBM "goes wild" and subspecialty recognition
- Expansion to extra-coronary targets (endo-vascular, early structural and imaging)
- Shift from U.S. / EU to Asia-Pacific and beyond

5 In Partnership with the ACC Reinventing the Futur Every Year



CARDIOVASCULAR RESEARCH FOUNDATION At the heart of innovation

Bare Metal Stents.... the good, the bad, and the ugly!

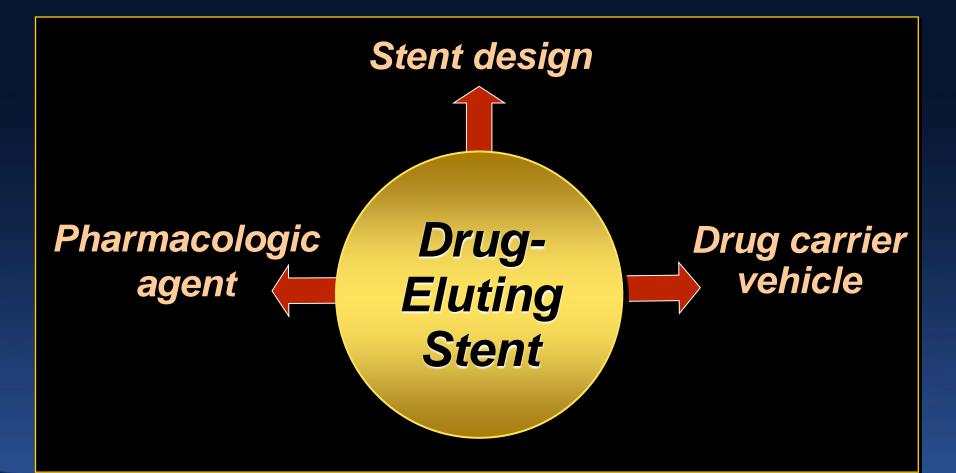








Drug-Eluting Stents Advanced Biotechnology Platform









First-In-Man study with CYPHER Sao Paulo, FU completed









DES - A Transforming Technology

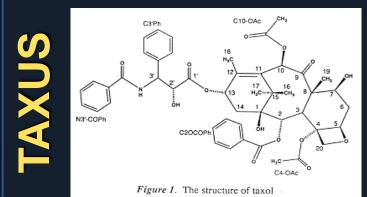




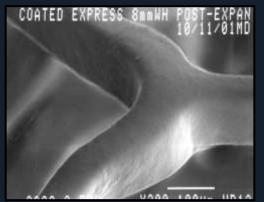




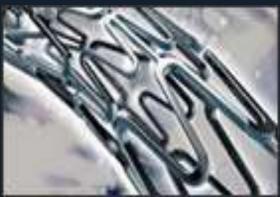
First Generation DES



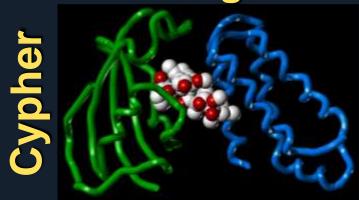
Paclitaxel
Drug



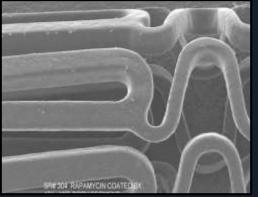
Polyolefin derivative Polymer



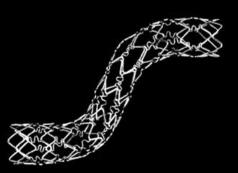
Express² Stent



Sirolimus



PEVA + PBMA blend



BX Velocity

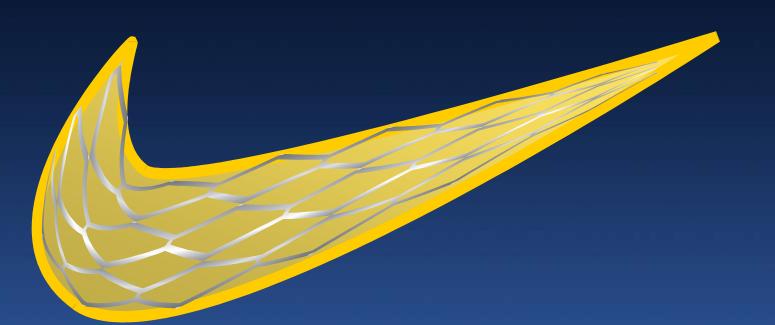






Intervention 2006

Just DEStent It!









The ESC Firestorm (August '06)



Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drugeluting stents (DES) may increase death, Qwave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) halied the data as one of the most important presentations to come out of this year's meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown," said Yusuf. "I've a feeling the data we're seeing today is only the tip of the loeberg. We need to encourage more pother access to the data."



obtain this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

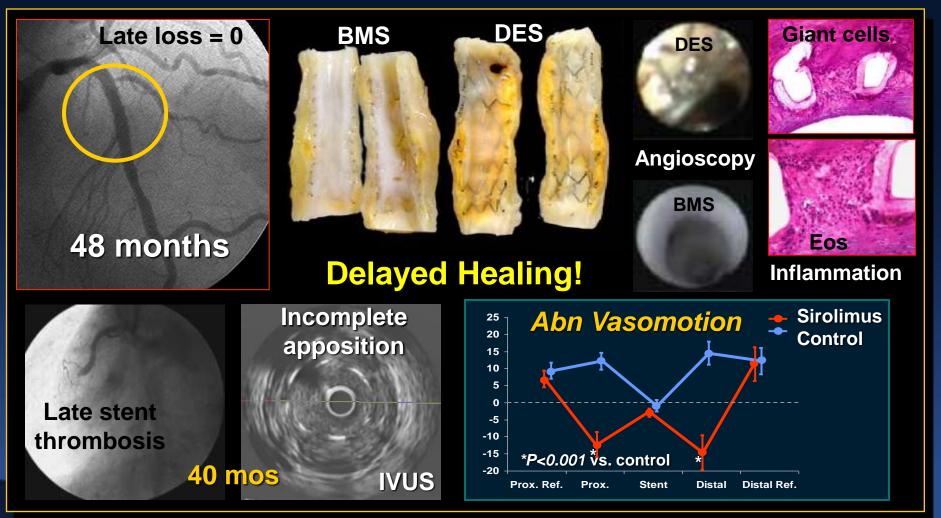
"There's no beneficial influence on mortality -PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It's not re-stengels that wills but the







DES....the good, the bad, and the ugly!





DES Clinical Trials Evidence-Based Medicine

Over 2,500 peer review manuscripts on DES clinical use have been published between 2002 and 2012!



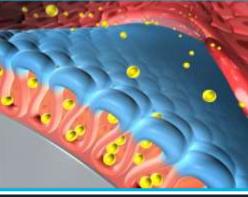


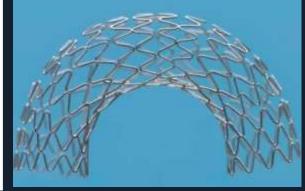


Second Generation DES

Resolute



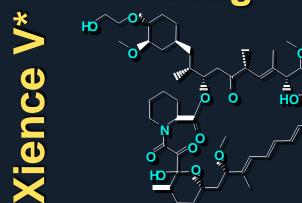


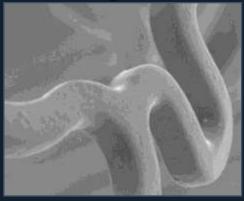


Zotarolimus Drug

Everolimus

BioLinx copolymer Polymer Driver Stent





VDF + HFP copolymer



Vision



***AKA Promus**





Intervention 2001



TCT Perspectives: 1988 - 2013

Phase 4: 2008 - 2013

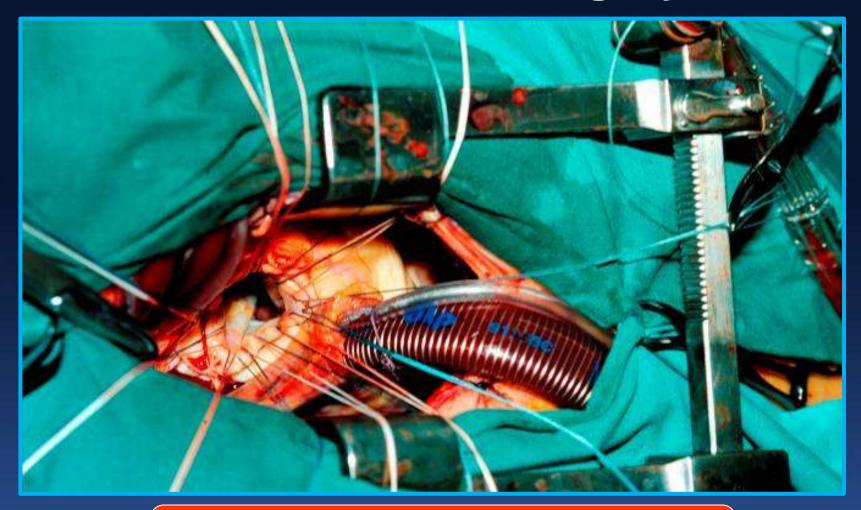
Evolution to Extravascular and Mainstream Therapies

- Ascent of the structural revolution (case study = TAVR); rise of multi-disciplinary heart teams
- EBM is now a global affair and broadly accepted
- Shift to mainstream therapies e.g. VHD, HBP, AF
- International networks solidified for innovation, clinical research, and education

25 In Partnership with the Reinventing the Every Year



Conventional Surgery



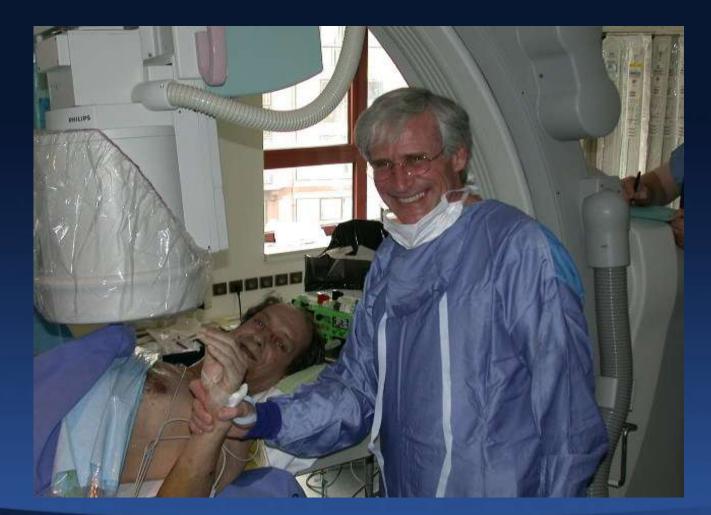
Is there a better way?







Dr. Alain Cribier First-in-Man PIONEER



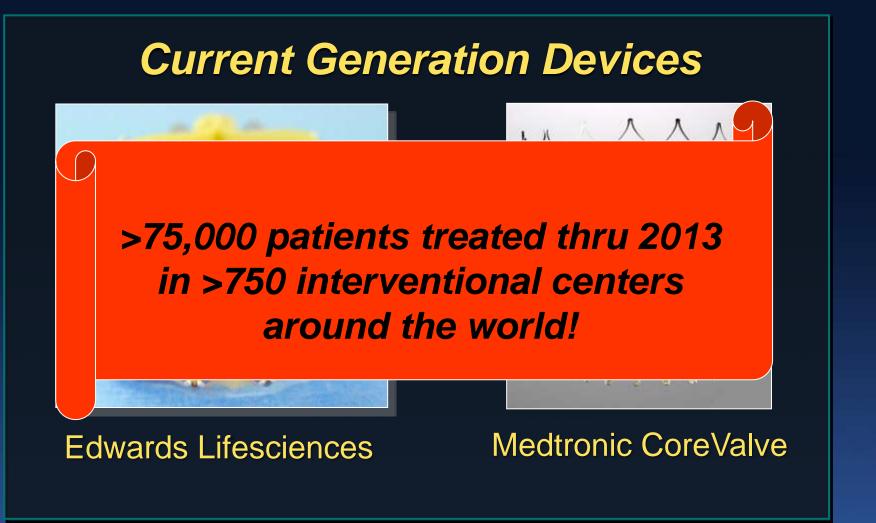


April 16, 2002





TAVR Arrives









PARTNER Manuscripts in NEJM (October, 2010 – May, 2012)



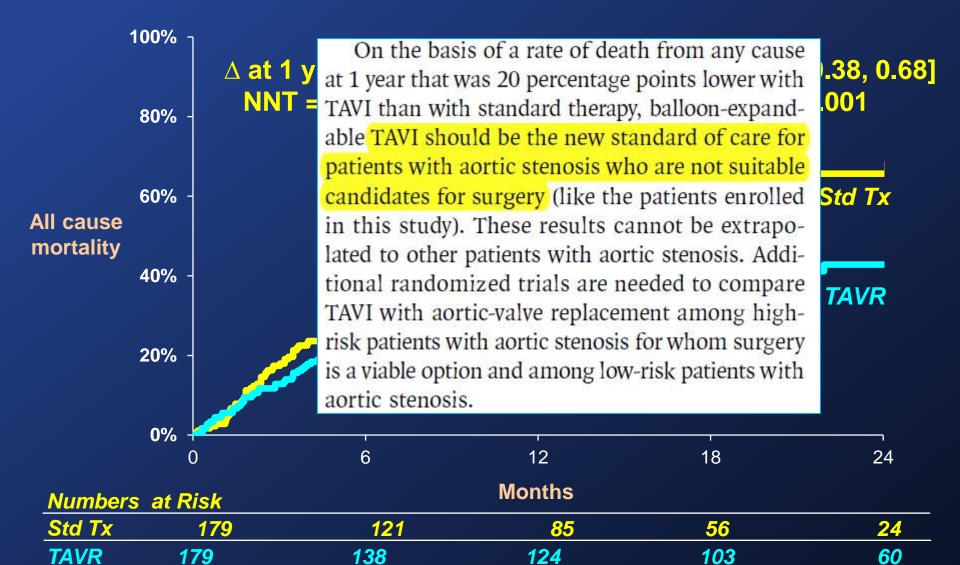
for the PARTNER Trial Investigators*



William N. Anderson, Ph.D., Stuart Pocock, Ph.D., Craig R. Smith, M.D., and Martin B. Leon, M.D., for the PARTNER Trial Investigators*

Primary Endpoint: All Cause Mortality





CoreValve High-Risk U.S. Pivotal Trial (presented at ACC 2014)

ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis

 David H. Adams, M.D., Jeffrey J. Popma, M.D., Michael J. Reardon, M.D., Steven J. Yakubov, M.D., Joseph S. Coselli, M.D., G. Michael Deeb, M.D., Thomas G. Gleason, M.D., Maurice Buchbinder, M.D., James Hermiller, Jr., M.D., Neal S. Kleiman, M.D., Stan Chetcuti, M.D., John Heiser, M.D., William Merhi, D.O., George Zorn, M.D., Peter Tadros, M.D., Newell Robinson, M.D., George Petrossian, M.D., G. Chad Hughes, M.D., J. Kevin Harrison, M.D., John Conte, M.D., Brijeshwar Maini, M.D., Mubashir Mumtaz, M.D., Sharla Chenoweth, M.S., and Jae K. Oh, M.D., for the U.S. CoreValve Clinical Investigators*

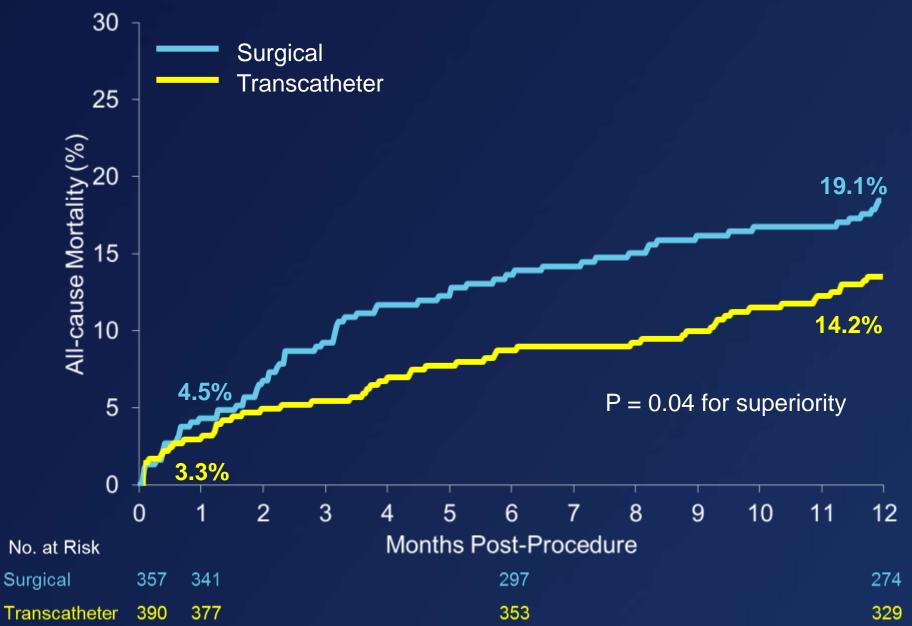
Adams DH, Popma JJ, Reardon MJ, et al. Published in N Engl J Med on March 29, 2014 at NEJM.org



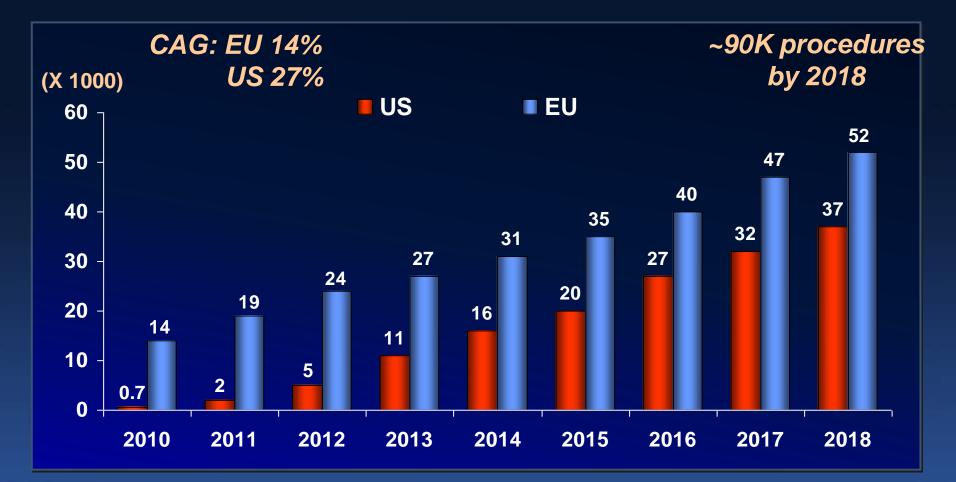




CoreValve US Clinical Trials Primary Endpoint: 1 Year All-cause Mortality ACC 2014



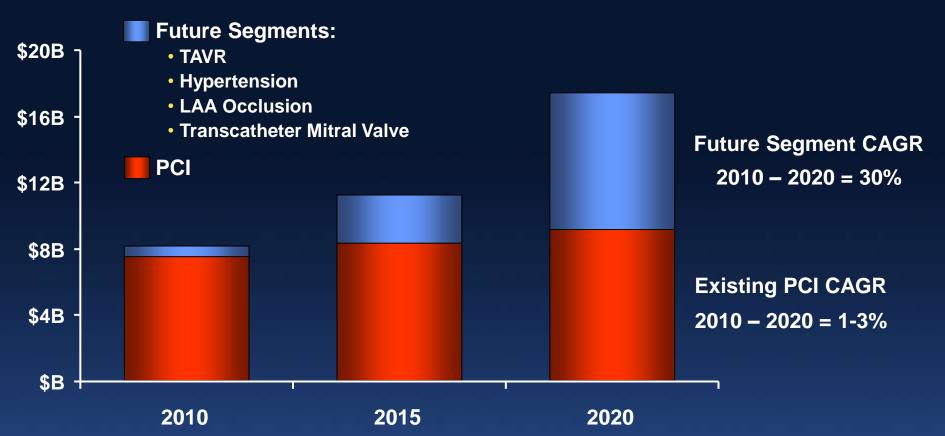
TAVR ProceduresGrowth from 2010 - 2018



Multiple Industry Sources - 2013



WW Cardiology Market Trends



- New market segments may exceed PCI market size by 2020
- Emergence of future segments relies on technology and clinical data
- OUS markets will lead and exceed the size of US markets

Source: Industry, May 2011





TCT Perspectives: 1988 - 2013 Evolution to Mainstream Therapies

- The less-invasive (non-surgical) use of catheterbased therapies to remotely treat distant disease targets has transformed medicine.
 - Neuro-radiology and neuro-surgery
 - Minimally invasive endoscopic surgery
 - Gastroenterology
 - Orthopedics
 - Oncology
 - Pulmonology (and ENT)
 - Urology and gynecology







TCT Perspectives: 1988 - 2013 *Evolution to Mainstream Therapies*

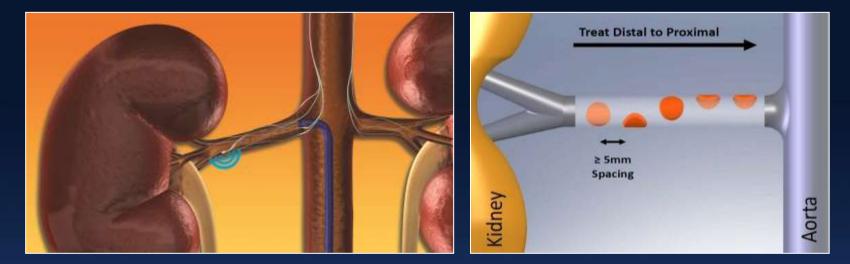
- The less-invasive (non-surgical) use of catheterbased therapies to remotely treat distant disease targets has transformed medicine.
- A major current effort is to redirect intra-vascular interventional therapies to address "mainstream" cardiovascular and non-cardiovascular disease (e.g. new HTN, AF, and CHF therapies).







Renal Denervation for Refractory Hypertension



- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
 - Automated
 - Low-power
 - Built-in safety algorithms









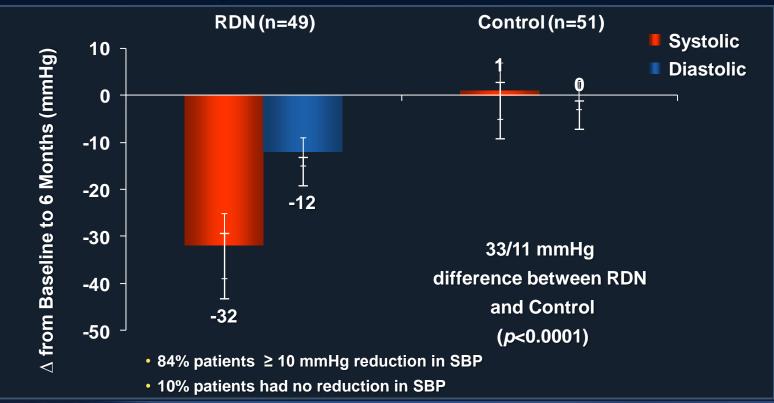
THE LANCET

Renal sympathetic denervation in patients with treatmentresistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Symplicity HTN-2: RDN vs. Control

Symplicity HTN-2 Investigators*

Primary Endpoint: 6-Month Office BP



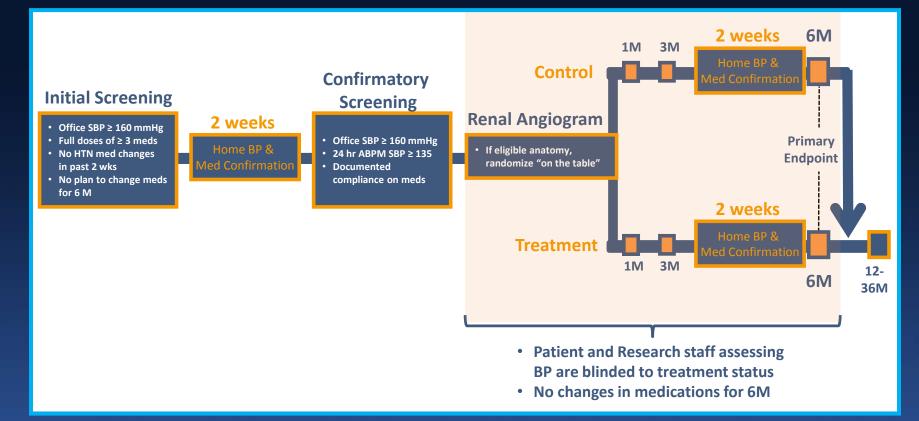
Lancet. 2010;376:1903-190





Symplicity HTN-3 Study Design

- Uncontrolled (refractory) HTN (535 patients)
- 2:1 randomization TREND vs. sham control

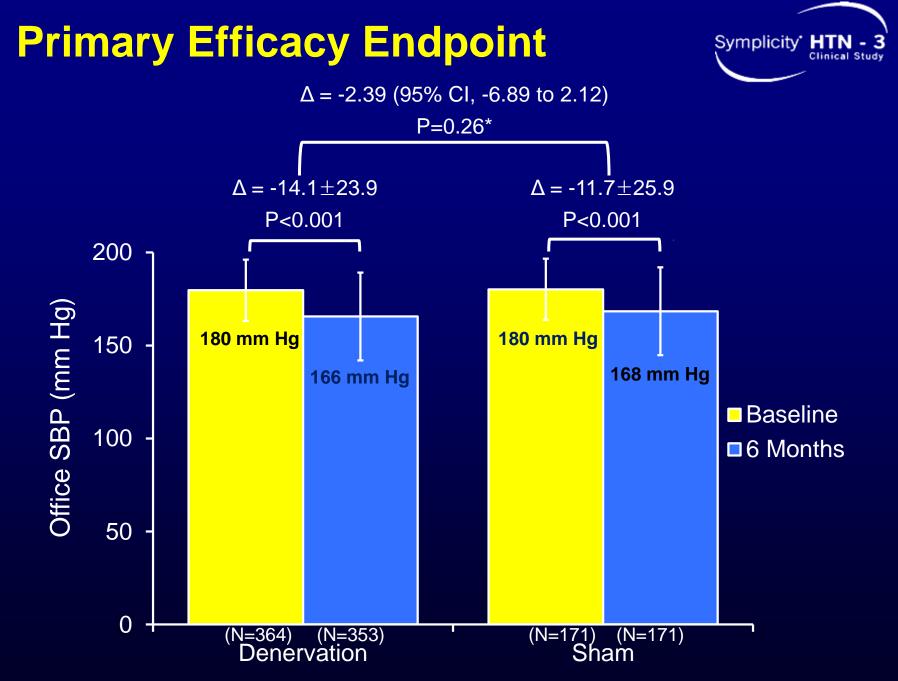


1^{ry} effectiveness endpoint: \triangle SBP at 6 months









*P value for superiority with a 5 mm Hg margin; bars denote standard deviations

Bhatt DL, Kandzari DE, O'Neill WW, et al...Bakris GL. N Engl J Med 2014

Renal Denervation for Refractory Hypertension

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

CONCLUSIONS

This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPLICITY HTN-3 ClinicalTrials.gov number, NCT01418261.)

Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPLICITY HTN-3 Investigators*

What Next ???







TCT Perspectives: 1988 - 2013 Evolution to Mainstream Therapies

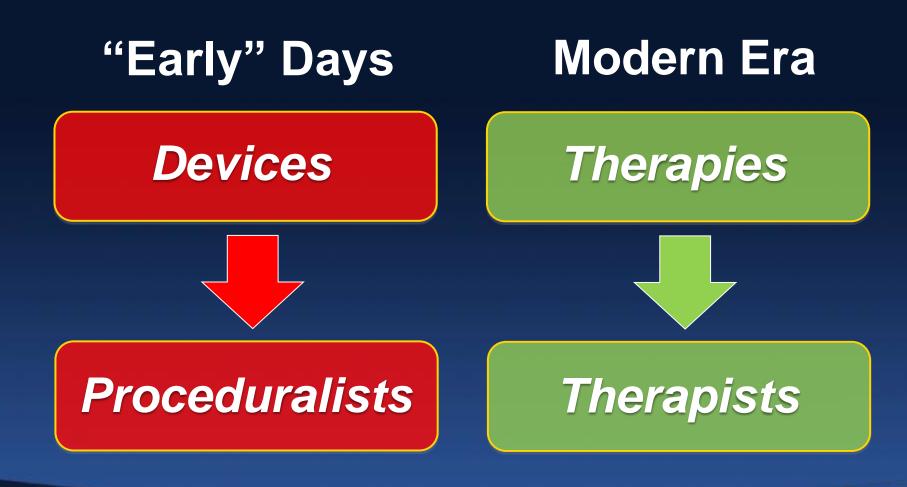
- The less-invasive (non-surgical) use of catheterbased therapies to remotely treat distant disease targets has transformed medicine.
- A major current effort is to redirect intra-vascular interventional therapies to address "mainstream" cardiovascular and non-cardiovascular disease (e.g. new HTN, AF, and CHF therapies).
- This requires that the interventionalist become an integrated member of a multi-disciplinary team AND learn new cognitive skills; the transformation from isolated proceduralist to engaged therapist!







TCT Perspectives: 1988 – 2013 **Important Evolution**









Future Directions







What lies ahead?









The Next Big Breakthrough? New CHF Therapies...

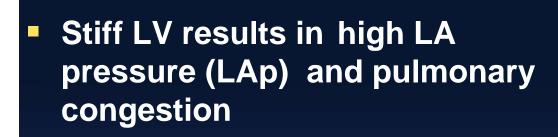
- Sensors to monitor therapy
- LV remodeling devices
- Contractility modulation
- Micro-VADs (interventional)
- Inter-atrial shunt implants
- Stem cell therapies







Inter-Atrial Shunt Device (IASD) (DC Devices)



Transcatheter implant to create permanent interatrial shunt

- - Shunt allows blood to move from the higher pressure LA to the lower pressure more compliant right heart which reduced LAp without affecting cardiac output







LA

Important Iterative Changes Vascular Therapies

- Bioabsorbable stents
- Drug-coated balloons
- Advanced balloon technologies
- Vascular remodeling
- New therapeutic targets







Fully Bioresorbable Stents (Scaffolds)

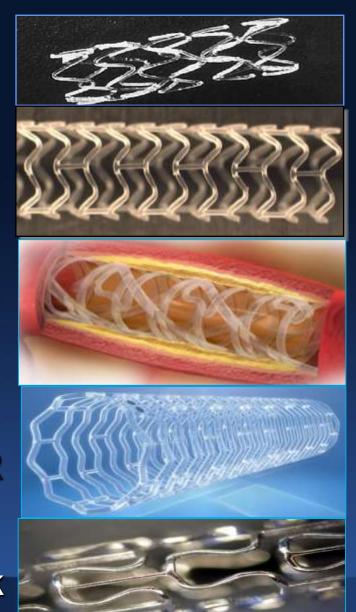
Igaki-Tamai

BVS

REVA

ELIXIR





PLA

PLLA (with everolimus)

lodinated tyrosinepolycarbonate (with sirolimus)

PLLA (with novolimus)

Magnesium (with sirolimus) RESEARCH FOUNDATION

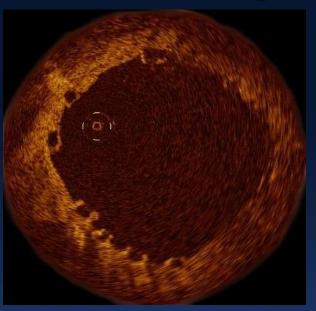


Absorb Trial: OCT Results

Post-stenting

6-month

24-month



Complete strut apposition

Late acquired incomplete stent apposition with tissue bridges between the struts

Corrugated endolumen

Smooth endoluminal lining

Struts largely disappeared although remnant just visible (arrow)



Serruys et al Lancet 2009



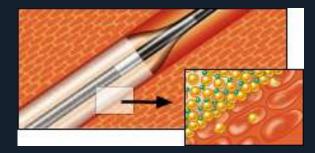


Drug-Eluting Balloons (and beyond)

SeQuent[®] Please Paccocath[®] Technology – B. Braun In.Pact Invatec



DIOR® - EuroCor



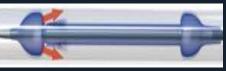
Elutax[®] - Aachen Resonance



Cricket™ Mercator







ClearWay™ Atrium

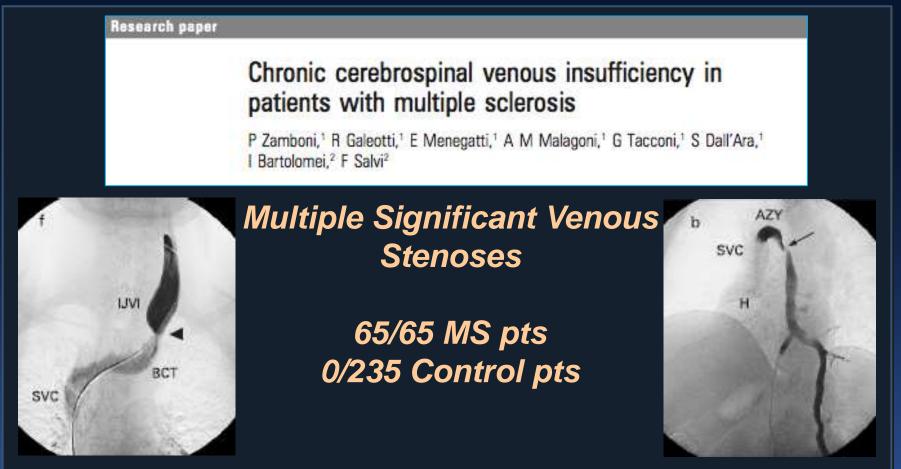








Chronic CerebroSpinal Venous Insufficiency (CCSVI) and Multiple Sclerosis



Jugular veins – 91%

Azygos vein – 86%

ໄລ້ເຫຼີຍົວກູ່ໂອt al. J Neurol Neurosurg Psychiatry 2009;80:392-9

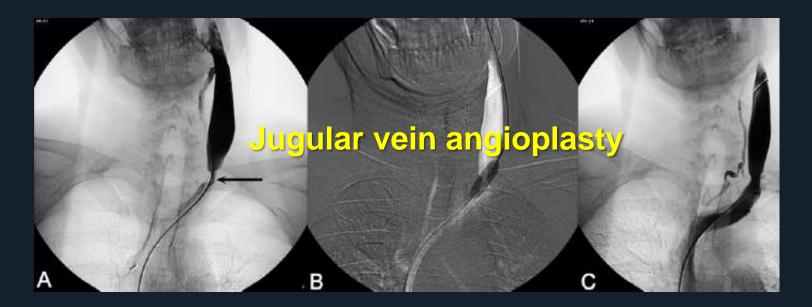




Chronic CerebroSpinal Venous Insufficiency (CCSVI) and Multiple Sclerosis

A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency

Paolo Zamboni, MD,^a Roberto Galeotti, MD,^a Erica Menegatti, RVT,^a Anna Maria Malagoni, MD,^a Sergio Gianesini, MD,^a Ilaria Bartolomei, MD,^b Francesco Mascoli, MD,^a and Fabrizio Salvi, MD,^b *Ferrara and Bologna, Italy*





Zamboni et al. J Vasc Surg 2009;50:1348-58





Chronic CerebroSpinal Venous Insufficiency (CCSVI) and Multiple Sclerosis

A prospective open-label study of endovascular treatment of chronic cerebrospinal venous

Menegatti, RVT," Anna Maria Malagoni, MD,"

Is it REAL?

- LITICACY espen
- 12 month patency
 - IJV 53%
 - Azygos 96%

Zamboni et al. J Vasc Surg 2009;50:1348-58



als



Interventional Perspectives Future Directions...

- Enhanced diagnostics
- Emphasis on prevention (digital healthcare)
- Robotics and tele-manipulation
- Sympathetic / hormonal modulation
- The Structural revolution
- Advanced imaging modalities
- New platform technologies







Non-invasive FFR_{CT} from coronary CT scans

<u>3D Computational Model</u> <u>based on coronary CTA</u>

Physiologic models:

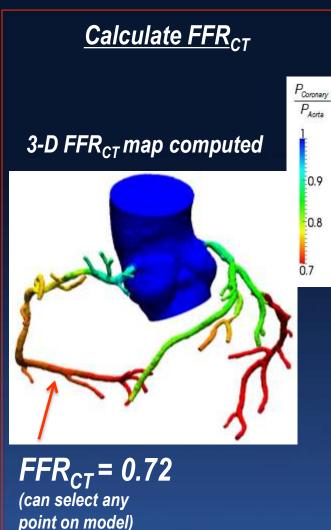
- Myocardial mass
- Morphometry-based boundary conditions
- Effect of adenosine on microcirculation

<u>CFD Blood Flow</u> <u>Solution</u>

Blood flow equations solved on supercomputer

$$\begin{aligned}
\bar{\rho v}_{,t} + \bar{\rho v \cdot \nabla v} &= -\nabla p + \nabla \cdot \underline{\tau} \\
\nabla \cdot \overline{v} &= 0
\end{aligned}$$











Consumer Paths...will be patient paths



- Decrease 30 day rehospitalization for heart failure patients
- Prevent episodes of hypoglycemia for diabetic patients
- Decrease ER visits for childhood asthma exacerbations





No lead, no radiation & less X-ray and contrast for our patients.... 0 00.27

0 17:08

Device Landscape 2014 Percutaneous MV Repair

Edge-to-edge
• Evalve MitraClip*

Chordal shortening and other

- Cardiosolutions Mitra-Spacer*
 - NeoChord
- Valtech VChordal

Coronary sinus annuloplasty

Cardiac Dimensions Carillon*
 Cerclage annuloplasty

MV replacement

- EndoValve
 - CardiAQ
- Valtech Cardiovalve
 - ValveXchange
 - Neovasc
 - ? Medtronic
 - •? Edwards

Direct annuloplasty

- Mitralign Bident*
- GDS Accucinch*
 ReCor (US)*
- Quantum Cor (RF)
- Valtech Cardioband
 - Micardia enCor

*In patients

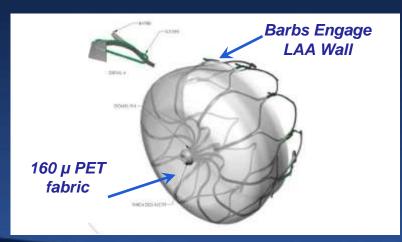
LAA Closure for Stroke Prevention in AF

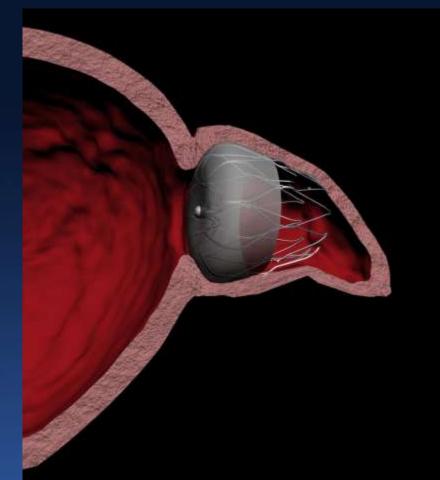
• Difficulties with Warfarin use

- Frequent Monitoring
- Difficulty in Compliance (TTR 48-63%)
- Drug / Diet Interactions
- Bleeding Risk (ICH)
- Risks in Elderly (Falls, Poly-pharmacy)

Autopsy & TEE data implicate LAA

LAA Closure Devices











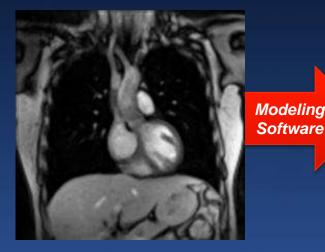


3D Bioprinting: The Unlimited Potential of Automated Tissue Engineering Processes

Biocompatible Matrix

+ Cells

Cell friendly printing conditions



3D-Bioplotter



Patient Scan

Solid Model File

Printed Valve



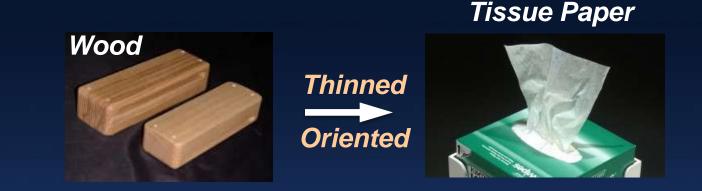
Daniel B. Spoon, MD





Flexible Electronics: From Sensors to Therapy Delivery

Core Technology = Soft biointegrated electronics







tct 25





Final Thoughts







Heritage of Intervention

- We believe that "less invasive" is better (certainly for patients and also for the healthcare system in general; and less-invasive means catheter-based, non-surgical, whenever possible)
- We are technology addicts (esp. new gizmos which can shorten procedures, improve outcomes, and expand treatment indications)
- We are passionate about experimental and clinical research and evidence-based medicine (fundamental to every important therapy change and to the interventional device development process)







Heritage of Intervention

- We rely heavily on adjunctive imaging a visual subspecialty (a growing trend...echo/IVUS, MR/CT, "fusion" imaging, and other new invasive imaging modalities)
- We are passionate about the interface of clinical medicine and the rapid communication of ideas (educational meetings, physician training, new IT developments, patient care initiatives, and marketing opportunities)
- We have a vibrant entrepreneurial spirit, are risk-takers, and rapidly embrace new therapies
- We strongly support and promote global and multidisciplinary collaborations







Heritage of Intervention

 We have a cultural identity ... innovation, strong industry partnerships, impatience leading to evolution and forward motion; we have a need to stimulate change and to continually re-invent ourselves, in pace with advances in bio-medical science and technology!







Interventional Perspectives The FUTURE!

There's never been a better time to be an interventional cardiologist!







Interventional Perspectives The FUTURE!









TCT Perspectives: 1988 - 2013 It's All About the Patients!













