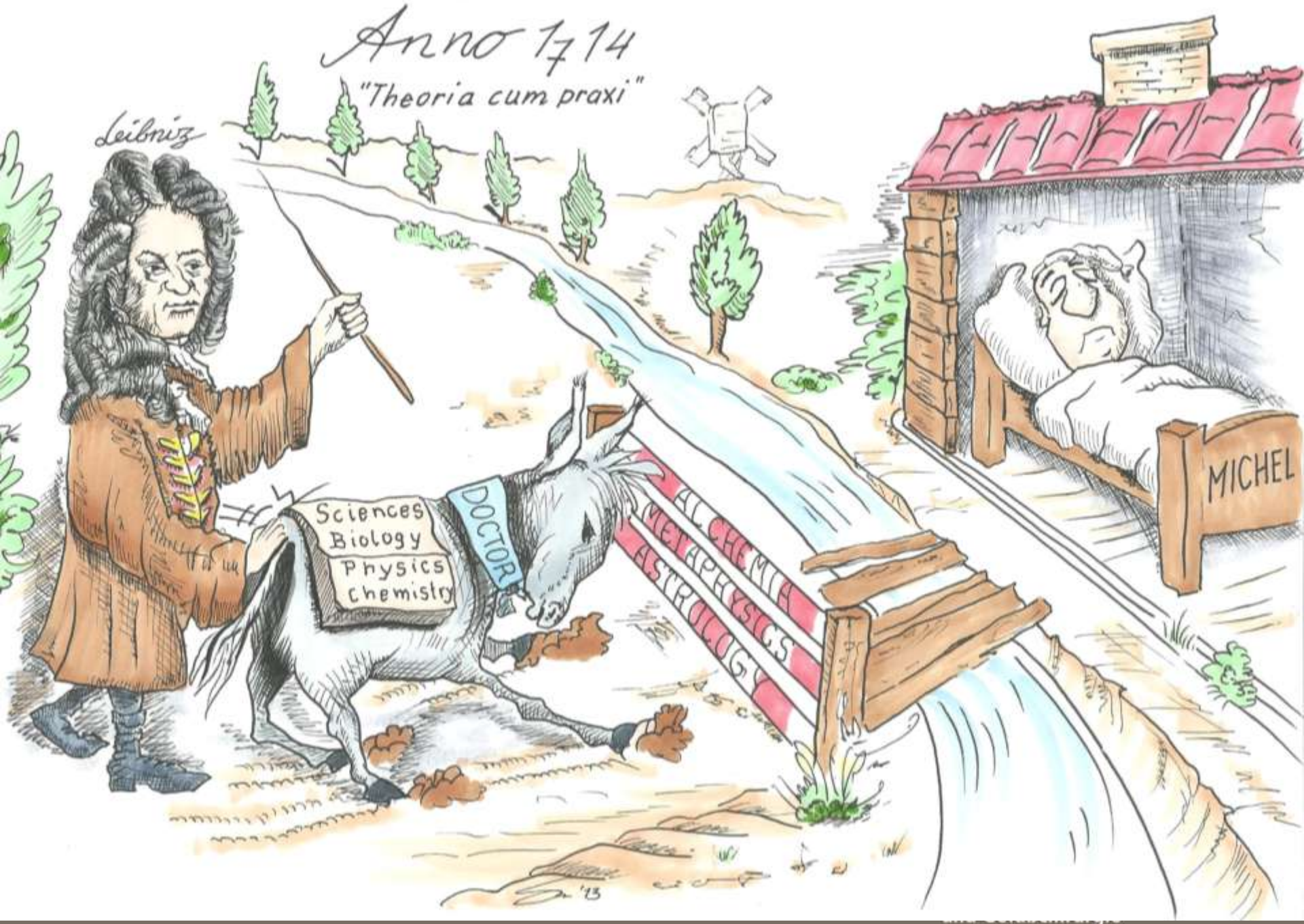
MHH

Herz-, Thorax-, Transplantations- und Gefäßchirurgie

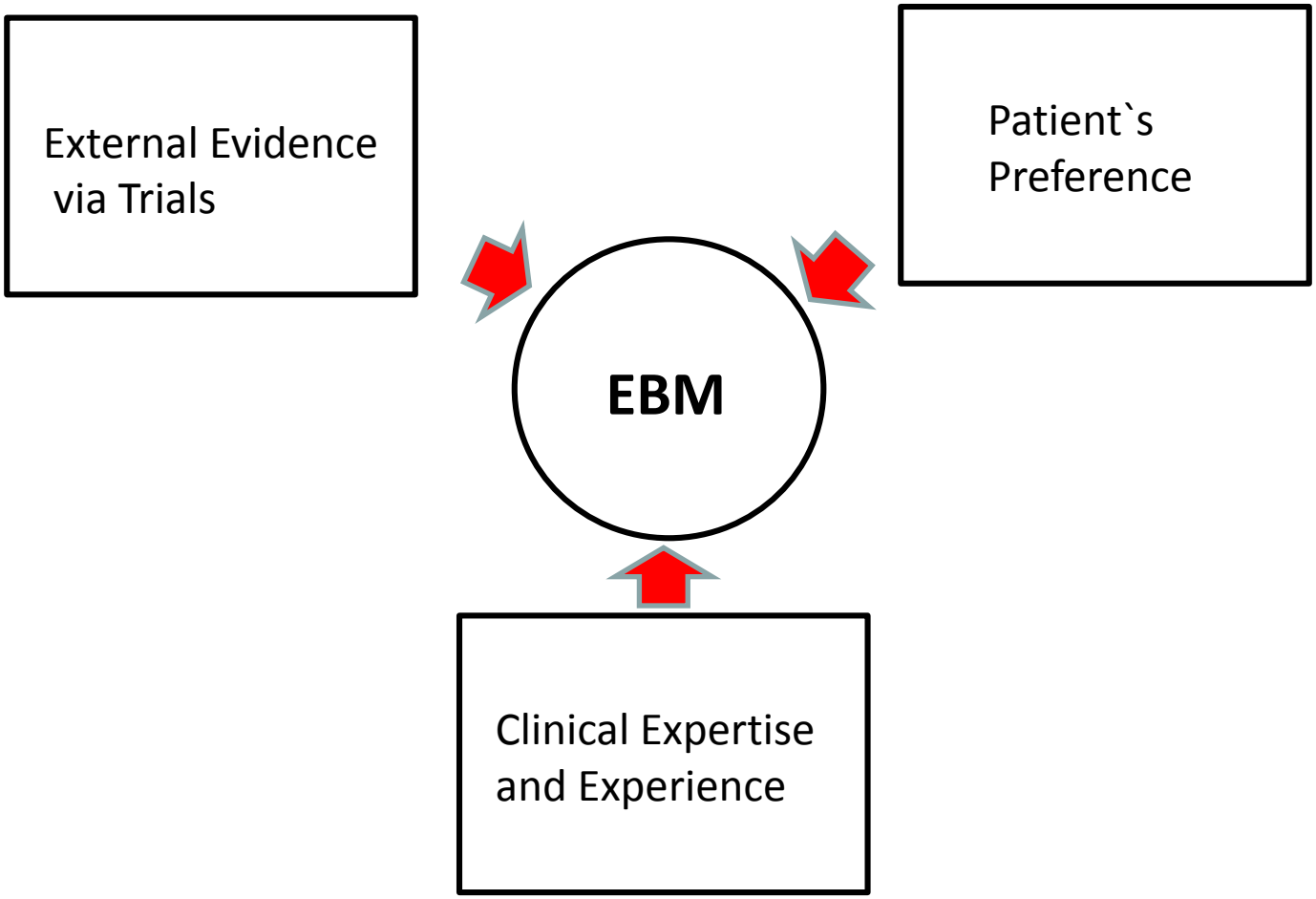
Der Weg von der Forschung zur Patientenversorgung

Prof. Dr. Dr. h. c. Axel Haverich

MIT SICHERHEIT.


Anno 1714
"Theoria cum praxi"
Leibniz
Sciences
Biology
Physics
Chemistry
DOCTOR
ALCHEMIA
METAPHYSICS
ASTROLOGY
MICHEL

- Evidenz
- RCTs
- Registries
- Tierversuche
- Chirurgie
- Pharmazie vs Implantate vs ATMP



Evidenz Basierte Medizin nach der Originalpublikation von Sackett 1996

Sackett`s Schema der EBM

- wird heute grundsätzlich auf die kontrollierte Studie reduziert, die externe Evidenz. Klinische Erfahrung und Beurteilung werden ebenso ignoriert wie die Präferenz betroffener Kranker.

- In der Geschichte der Chirurgie hingegen hat ein Fallbericht zur erfolgreichen Operation eines Patienten mit einer bis dato nicht zu heilenden Erkrankung genügend Evidenz geschaffen, um von anderen Chirurgen übernommen zu werden (Organtransplantatation, Bypasschirurgie).

- Auch die Präsentation kleiner Serien von erstmals durchgeführten Eingriffen bei Erkrankungen, in denen das konventionelle Vorgehen ein hohes operatives Risiko oder eine eingeschränkte Langzeitprognose mit sich brachten, führten zu einer raschen Verbreitung des Verfahrens

Evidence-based Medicine

„ If you find that a study was not randomized, we`d suggest that you stop reading and go to the next article“

Sackett DL. Richardson WS. Rosenberg W. Haynes RB.
Evidence-based medicine: how to practice and teach EBM. New York: Churchill Livingstone; 1997

„ The popular belief that only randomized, controlled trials produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and the education of health care professionals.“

Concato J. Shah N. Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2002;342:1887-92

Evidence-based Medicine

- levels of evidence -

Level A	Mindestens 2 prosp. rand. Studien
Level B	Eine prosp. rand. Studie, Meta-analyse
Level C	Experten-Consensus basierend auf klinischen Studien oder klin. Erfahrung

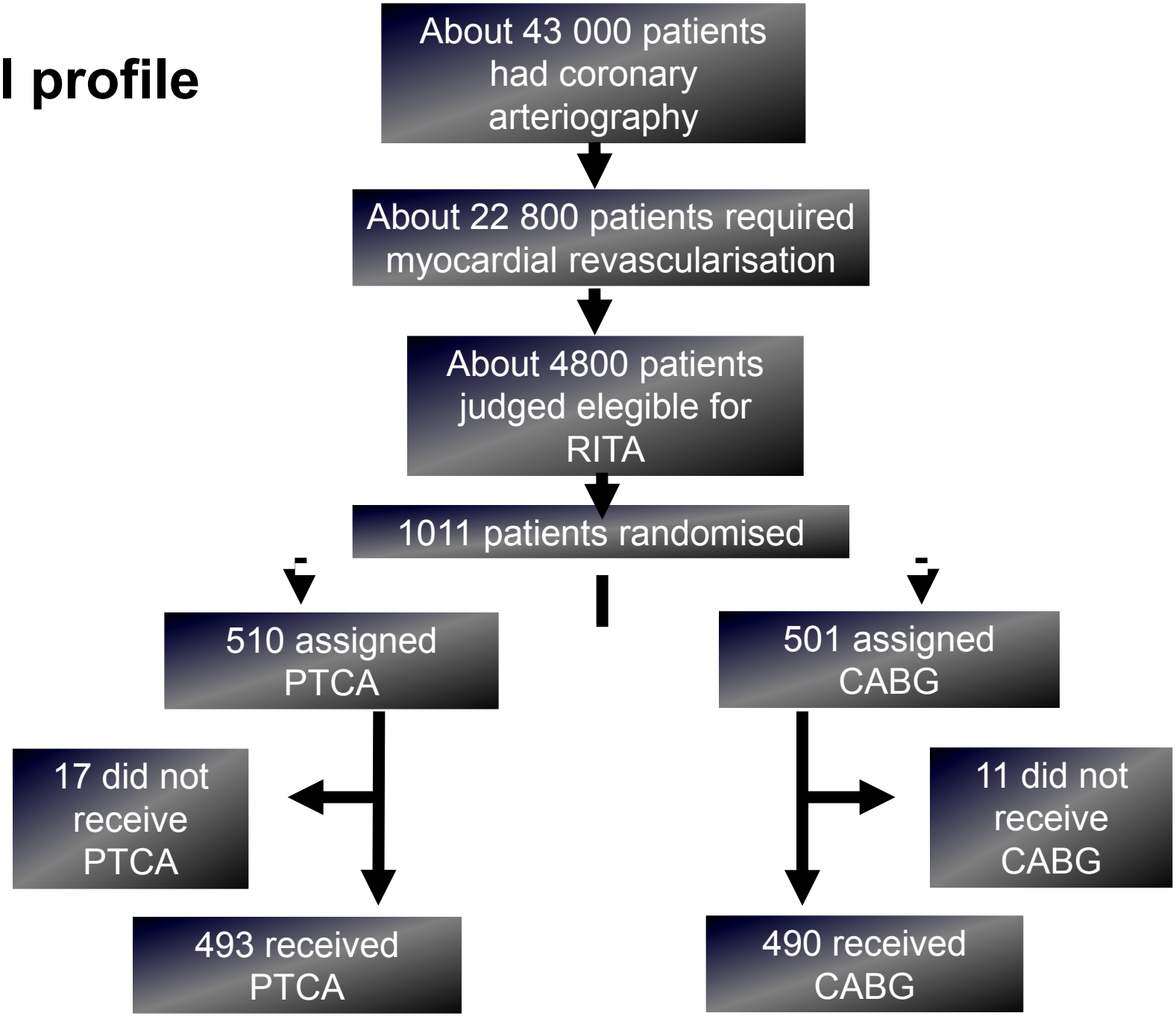
COMPARISON OF CORONARY-ARTERY BYPASS SURGERY AND STENTING FOR THE TREATMENT OF MULTIVESSEL DISEASE

PATRICK W. SERRUYS, M.D., FELIX UNGER, M.D., J. EDUARDO SOUSA, M.D., ADIB JATENE, M.D., HANS J.R.M. BONNIER, M.D., JACQUES P.A.M. SCHÖNBERGER, M.D., NIGEL BULLER, M.D., ROBERT BONSER, M.D., MARCEL J.B. VAN DEN BRAND, M.D., LEX A. VAN HERWERDEN, M.D., MARIE-ANGÈLE M. MOREL, B.SC., AND BEN A. VAN HOUT, PH.D., FOR THE ARTERIAL REVASCULARIZATION THERAPIES STUDY GROUP*

Serruys et al, N Engl J Med, Vol. 344, No. 15 – April 2001

Methods A total of 1205 patients were randomly assigned to undergo stent implantation or bypass surgery when a cardiac surgeon and an interventional cardiologist agreed that the same extent of revascularization could be achieved by either technique. The primary clinical end point was freedom from major adverse cardiac and cerebrovascular events at one year. The costs of hospital resources used were also determined.

Trial profile



Henderson et al., The Lancet Vol. 352 October 1998

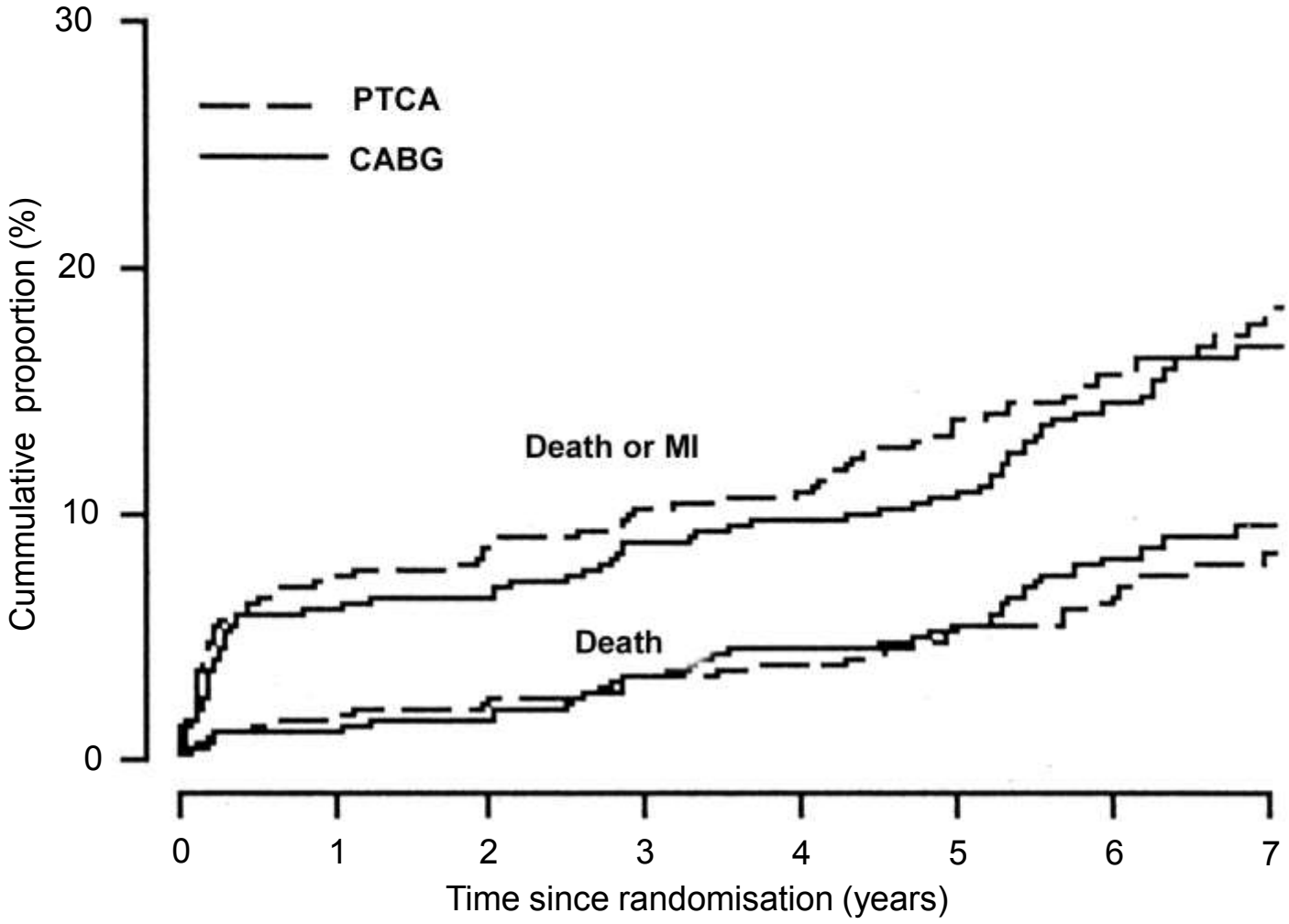


Figure 2: **Cumulative risk of death and death or non-fatal myocardial infarction by treatment group**

Henderson et al., The Lancet Vol. 352 October 1998

Conclusions As measured one year after the procedure, coronary stenting for multivessel disease is less expensive than bypass surgery and offers the same degree of protection against death, stroke, and myocardial infarction. However, stenting is associated with a greater need for repeated revascularization. (N Engl J Med 2001;344:1117-24.)

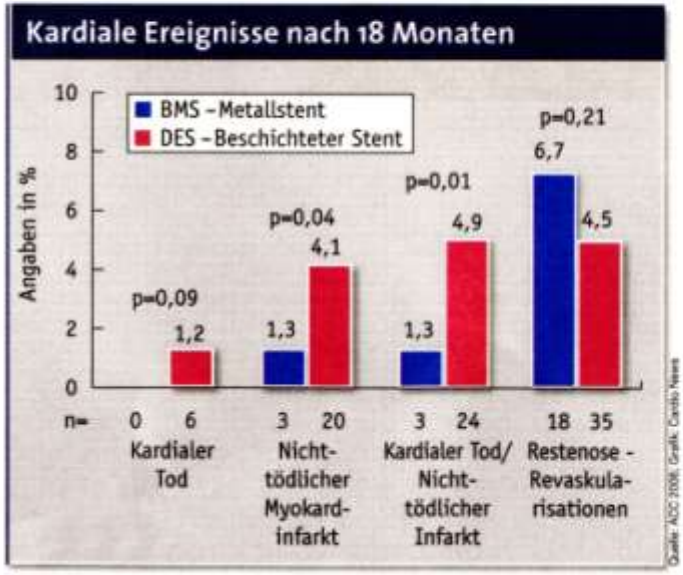
Copyright © 2001 Massachusetts Medical Society.

Serruys et al, N Engl J Med, Vol. 344, No. 15 – April 2001

Stentthrombosen bleiben ein Problem der beschichteten Gefäßstützen

Kommt eine Renaissance der reinen Metallstents?

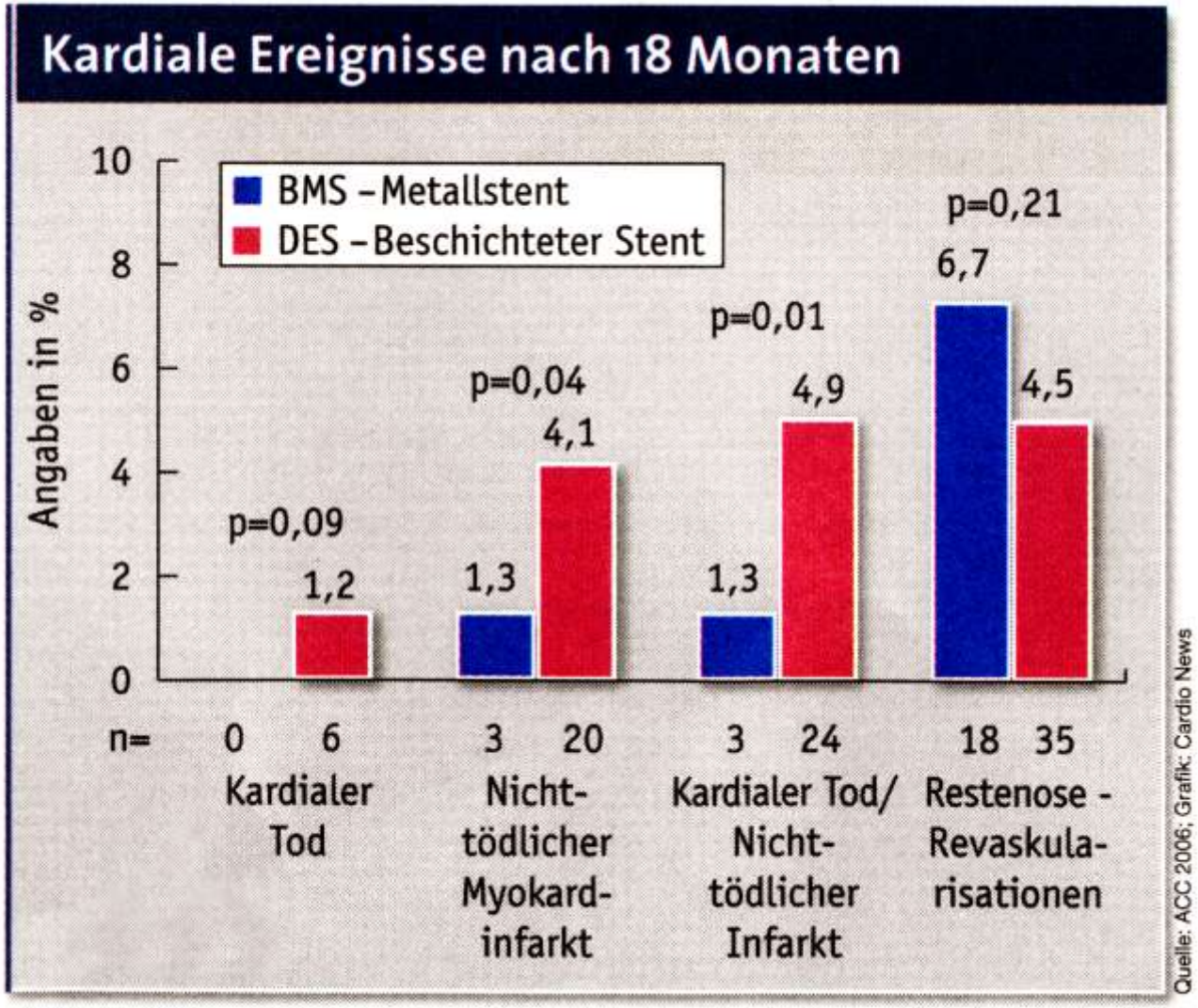
Die späte Stentthrombose nach Implantation eines beschichteten Stents scheint in der klinischen Praxis nach wie vor ein Problem zu sein. Stentthrombosen können noch bis zu einem Jahr und mehr nach einer Intervention mit Implantation von beschichteten Stents vorkommen. Das hat eine Schweizer Studie ergeben, die beim ACC für einigen Gesprächsstoff gesorgt hat. In den Vereinigten Staaten erhalten derzeit nur noch etwa zehn Prozent der Patienten einen unbeschichteten Metallstent. Die DES, Drug-eluting Stents, haben gemäß den Daten der BASKET-LATE-Studie von Professor Matthias Pfisterer aus Basel/Schweiz späte Nachteile gezeigt. Wie Pfisterer in Atlanta berichtet hat, kam es in dieser von niemandem gesponsorten Nachuntersuchung von 746 Patienten zwar zu weniger Restenosen in der Gruppe mit den beschichteten Stents (6,7 vs. 4,5). Andererseits wurden kardiale Ereignisse in der Folge einer Stentthrombose aber verstärkt in der DES-Gruppe registriert. So lag die Zahl der nicht-tödlichen Herzinfarkte bei 4,1 unter den beschichteten Stents im Vergeich zu 1,3 Prozent bei den Metall-Stents.



Späte Nachteile zeigten sich für die beschichteten Stents.

Auch war die Zahl der Todesfälle nach zwölf Monaten und nach Absetzen der Clopidogrel-Behandlung in der Gruppe mit den beschichteten Stents statistisch signifikant erhöht – immer im Vergleich zu der Gruppe mit den reinen Metallstents.

Umgekehrt verhielt es sich mit der Restenoserate. Hier gab es einen statistisch signifikanten Vorteil zugunsten der beschichteten Stents. Nach Pfisterer Daten werden durch einen DES bei 100 Patienten während sechs Monaten fünf Revaskularisierungen verhindert – aber es kommt auch zu 3,3 späten Todesfällen. *RK*



Späte Nachteile zeigten sich für die beschichteten Stents.

European Heart Journal (2014) 35, 2821–2830
doi:10.1093/eurheartj/ehu213

Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial

Stuart J. Head[1†], Piroze M. Davierwala[2†], Patrick W. Serruys[1], Simon R. Redwood[3], Antonio Colombo[4], Michael J. Mack[5], Marie-Claude Morice[6], David R. Holmes Jr[7], Ted E. Feldman[8], Elisabeth Ståhle[9], Paul Underwood[10], Keith D. Dawkins[10], A. Pieter Kappetein[1], and Friedrich W. Mohr[2*]

($n = 1095$). The rate of major adverse cardiac and cerebrovascular events (MACCE) was significantly higher in patients with PCI compared with CABG (37.5 vs. 24.2%, respectively; $P < 0.001$). Percutaneous coronary intervention as opposed to CABG resulted in significantly higher rates of the composite of death/stroke/myocardial infarction (MI) (22.0 vs. 14.0%, respectively; $P < 0.001$), all-cause death (14.6 vs. 9.2%, respectively; $P = 0.006$), MI (9.2 vs. 4.0%, respectively; $P = 0.001$), and repeat revascularization (25.4 vs. 12.6%, respectively; $P < 0.001$); however, stroke was similar

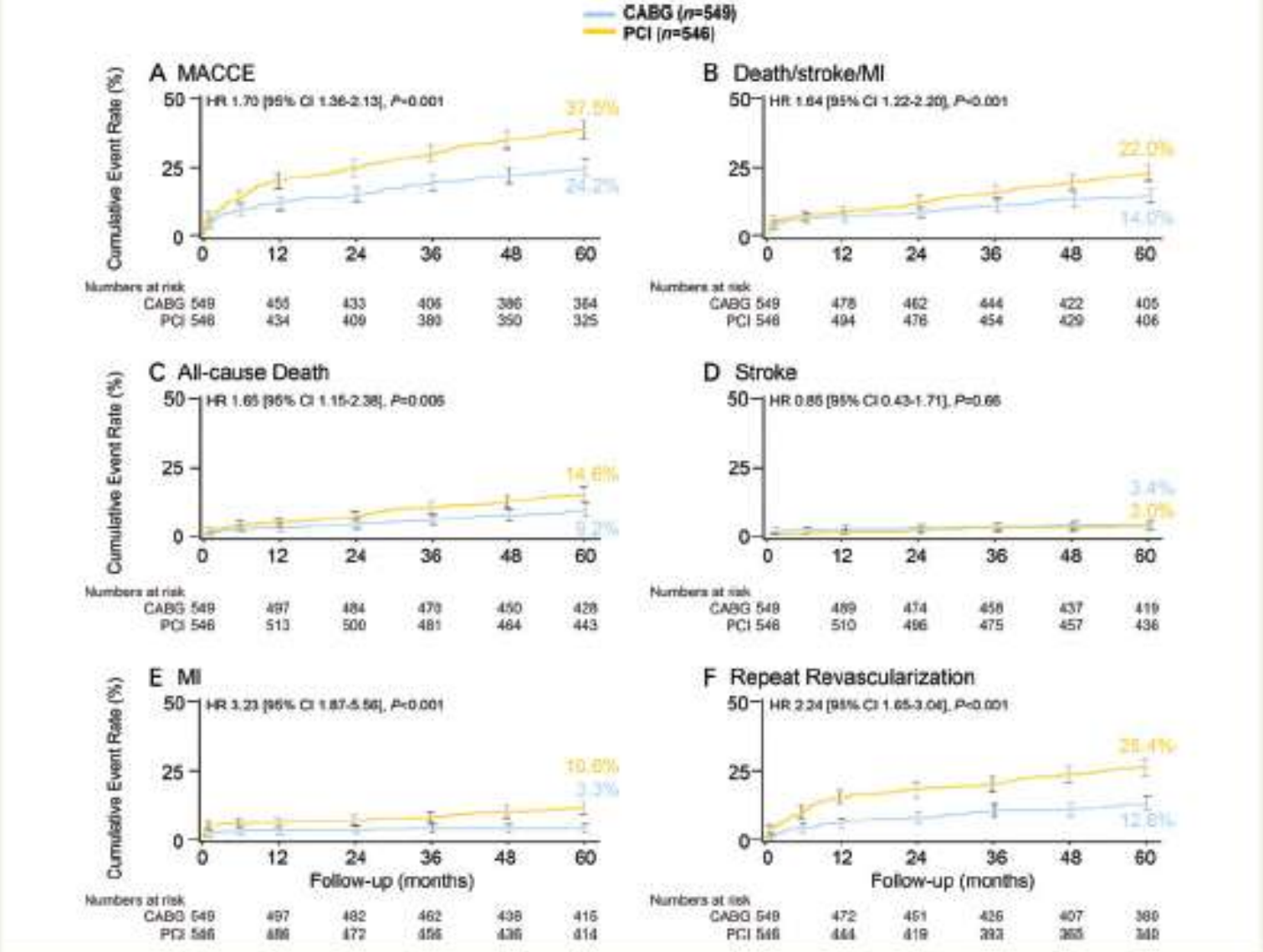


Figure 1 Five-year estimates of adverse events. Kaplan–Meier curves for (*A*) MACCE, (*B*) all-cause death/stroke/MI, (*C*) all-cause death, (*D*) stroke, (*E*) MI, and (*F*) repeat revascularization. Bars represent ±1.5 standard error. *P*-values from log-rank test. CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.

Evidence-based Medicine

- Studie Tierärztliche Hochschule Hannover -

HYPOTHESE:

Rinder und Pferde können gleich hoch springen

Evidence-based Medicine

- Studie Tierärztliche Hochschule -

Study Design

40 Tiere prospektiv randomisiert getestet
(doppel-blind)
Alter: 0-3 Tage

Ergebnis:

Kälber sprangen 12,6%+/- 3,1% höher als Fohlen
(p< 0.0001)

Conclusion:

Rinder springen höher als Pferde

Sperrfrist 01.14.04

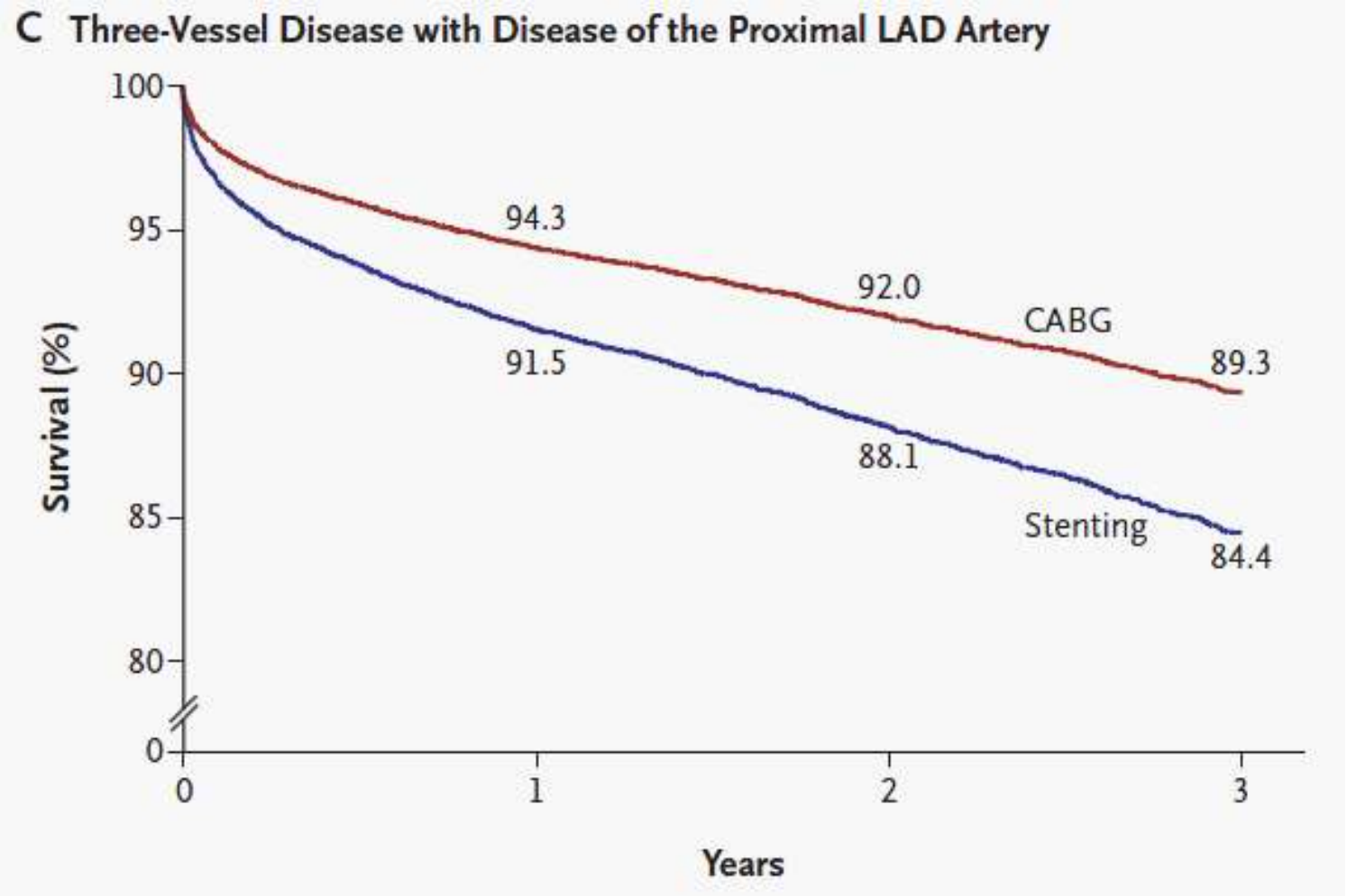
- Evidenz
- RCTs
- Registries
- Tierversuche
- Chirurgie
- Pharmazie vs Implantate vs ATMP

- Evidenz
- RCTs
- Registries
- Tierversuche
- Chirurgie
- Pharmazie vs Implantate vs ATMP

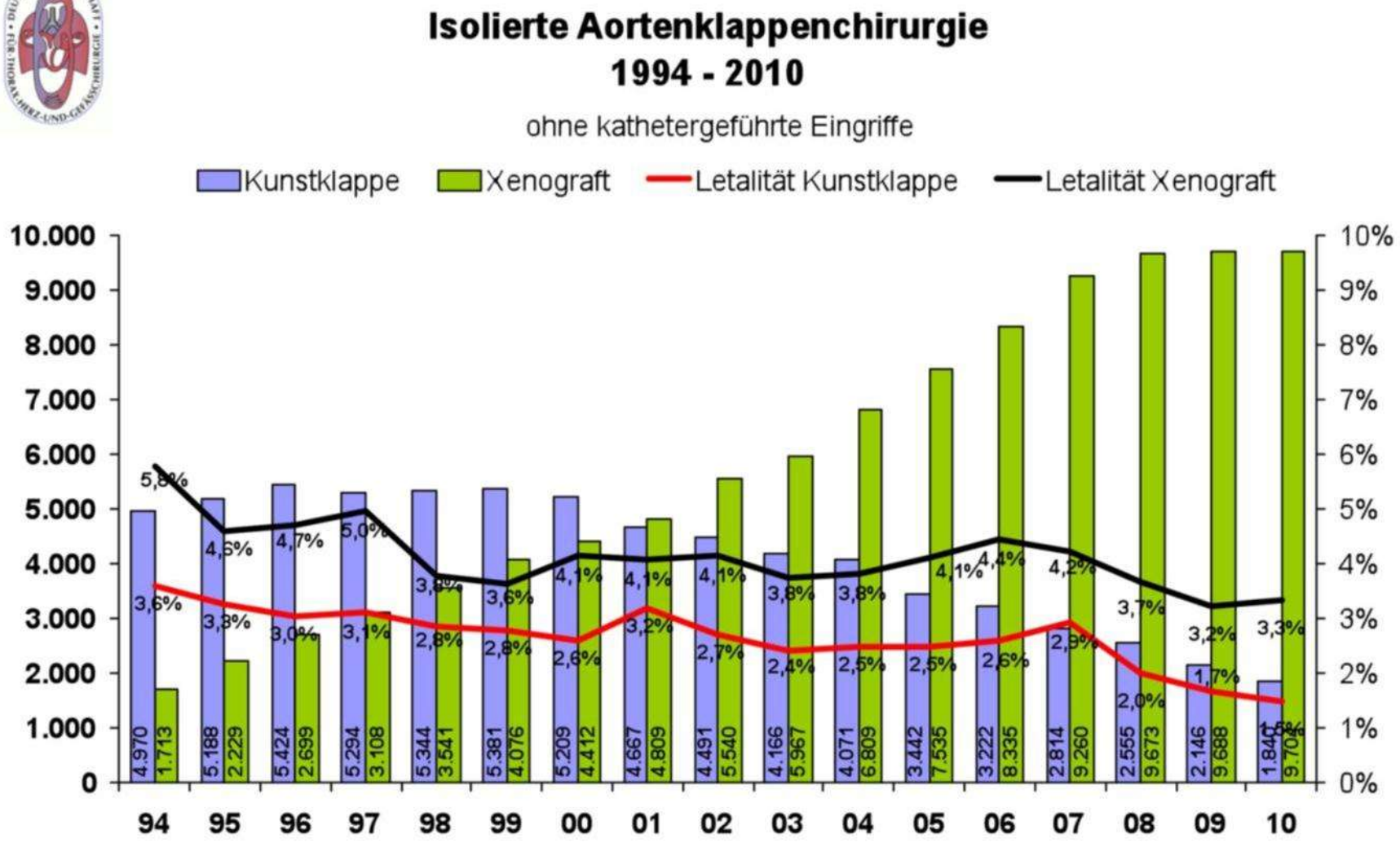
Langzeitergebnisse Bypass-Chirurgie vs PCI

(New York Registry, n = 46.000)

N Engl J Med 2005;352:2174-83.
Copyright © 2005 Massachusetts Medical Society

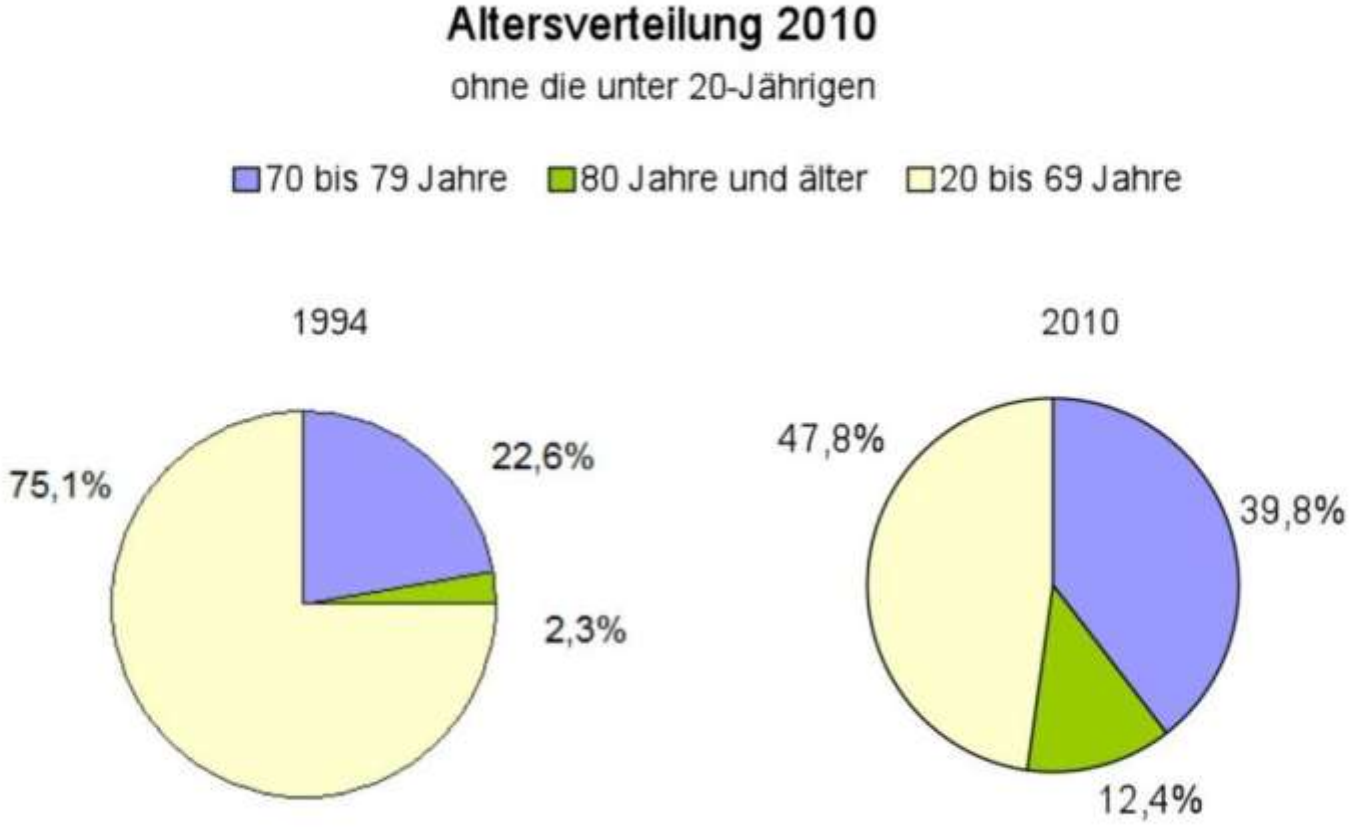


AVR in Germany (2010)



© DGTHG-Leistungsstatistik 2010

Cardiac Surgery Patients in Germany (2010): Age



Evidence-based Medicine

„ If you find that a study was not randomized, we`d suggest that you stop reading and go to the next article“

Sackett DL. Richardson WS. Rosenberg W. Haynes RB.
Evidence-based medicine: how to practice and teach EBM. New York: Churchill Livingstone; 1997

„ The popular belief that only randomized, controlled trials produce trustworthy results and that all observational studies are misleading does a disservice to patient care, clinical investigation, and the education of health care professionals.“

Concato J. Shah N. Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs.
N Engl J Med 2002;342:1887-92

Organtransplantation

Herz- Lunge

MHH

Herz-, Thorax-, Transplantations-
und Gefäßchirurgie

Organkonservierung

Thorac. cardiovasc. Surgeon 34 (1986) 368–376
© Georg Thieme Verlag Stuttgart · New York

Improved Lung Preservation using Euro-Collins Solution for Flush-perfusion

A. Haverich[1], S. Aziz[2], W.C Scott[2], S.W. Jamieson[2], and N.E. Shumway[2]

[1] Division of Thoracic and Cardiovascular Surgery, Hannover Medical School, Hannover, FRG
[2] Department of Cardiovascular Surgery, Stanford University, Palo Alto, CA, USA

Pädiatrie ?

Pädiatrie ?

<u>Lung growth after experimental pulmonary transplantation.</u>
Haverich A, Dammenhayn L, Demertzis S, Kemnitz J, Reimers P.
J Heart **Lung** Transplant. 1991 Mar-Apr;10(2):288-95.

- Evidenz
- RCTs
- Registries
- Tierversuche
- Chirurgie
- Pharmazie vs Implantate vs ATMP

NIERENARTERIEN ABLATION

Krum H, Schlaich MP, Böhm M, Mahfoud F, Rocha-Singh K, Katholi R, Esler MD. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet*. 2013; 140:62192–62193.

INTERPRETATION: Changes in blood pressure after RDN persist long term in patients with treatment-resistant hypertension, with good safety.
FUNDING: Ardian LLC/Medtronic Inc

Is renal sympathetic denervation effective in the long-term? - Reduction in blood pressure by renal denervation seems to be placebo effect].
[Article in German] Middeke M., 2014

Bilateral Renal Artery Stenosis After Renal Denervation

Fernando Jaén Águila, Juan Diego Mediavilla García, Eduardo Molina Navarro, Jose Antonio Vargas Hitos, Celia Fernández-Torres

NIERENARTERIEN ABLATION

Krum H, Schlaich MP, Böhm M, Mahfoud F, Rocha-Singh K, Katholi R, Esler MD. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet*. 2013; 140:62192–62193.

INTERPRETATION: Changes in blood pressure after RDN persist long term in patients with treatment-resistant hypertension, with good safety.
FUNDING: Ardian LLC/Medtronic Inc

Is renal sympathetic denervation effective in th - Reduction in blood pressure by renal den is to be placebo effect].
[Article in German] Middeke M., 2

Eine (!) Serie Tierversuche, eine publizierte Histologie einer Nierenarterie

Bilateral Renal Artery Stenosis After Renal Denervation

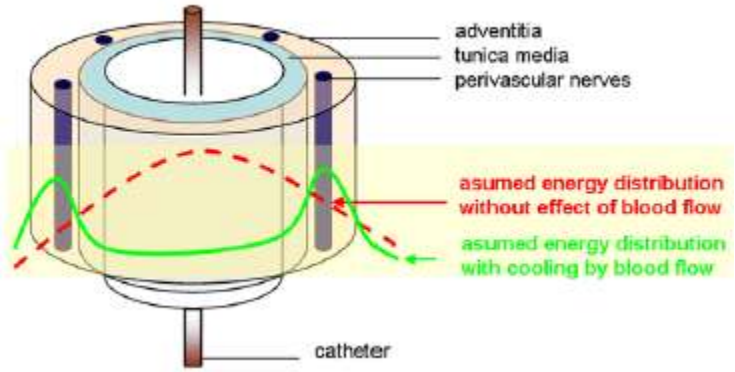
Fernando Jaén Águila, Juan Diego Mediavilla García, Eduardo Molina Navarro, Jose Antonio Vargas Hitos, Celia Fernández-Torres

NIERENARTERIEN ABLATION

bei intraktabler Hypertension

- **Early Effects in Perivascular Nerves and Arterial Media**
- **Following Renal Artery Denervation** ***(in pigs)***
- Franziska Schlegel*, Sait Sebastian Daneschnejad*, Mikhail Mavlikeev, Sara Klein, Marcel Vollroth,
- Aida Salameh, Bruno Andrea, Friedrich Wilhelm Mohr, Gerd Hindricks, Stefan Dhein, **Leipzig**

- März 2014



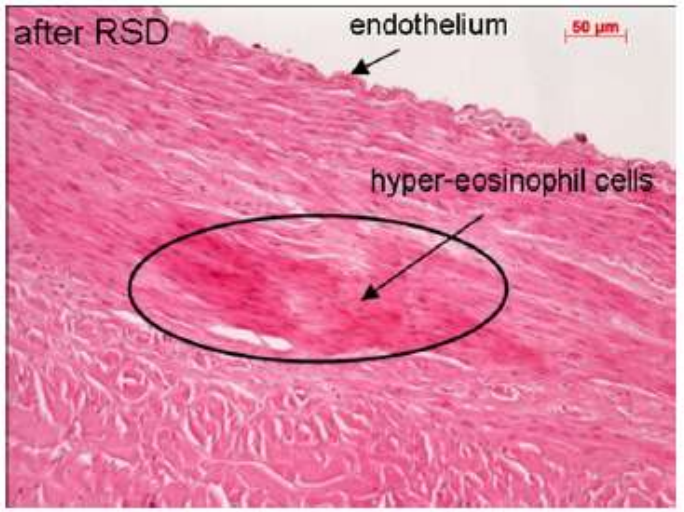


Figure 3. Hematoxylin and eosin staining of media after renal sympathetic denervation (RSD) indicated unmodified endothelium and hyper-eosinophilic cells in media.

Decellularized Heart Valves - first clinical results

- 38 patients – received decellularized
- pulmonary valve allograft

- Age 4.6 - 21.9 years mean (12.7±4.8) years

- Tetralogy of Fallot, d-TGA+Pulmonary stenosis, Ross operation, degeneration of previous conduit

- TE Valve implantation since 2002,
- Decellularized Valve Implantation since 2005

Clinical Implantation of Tissue Engineered Heart Valves

(May, 2002)

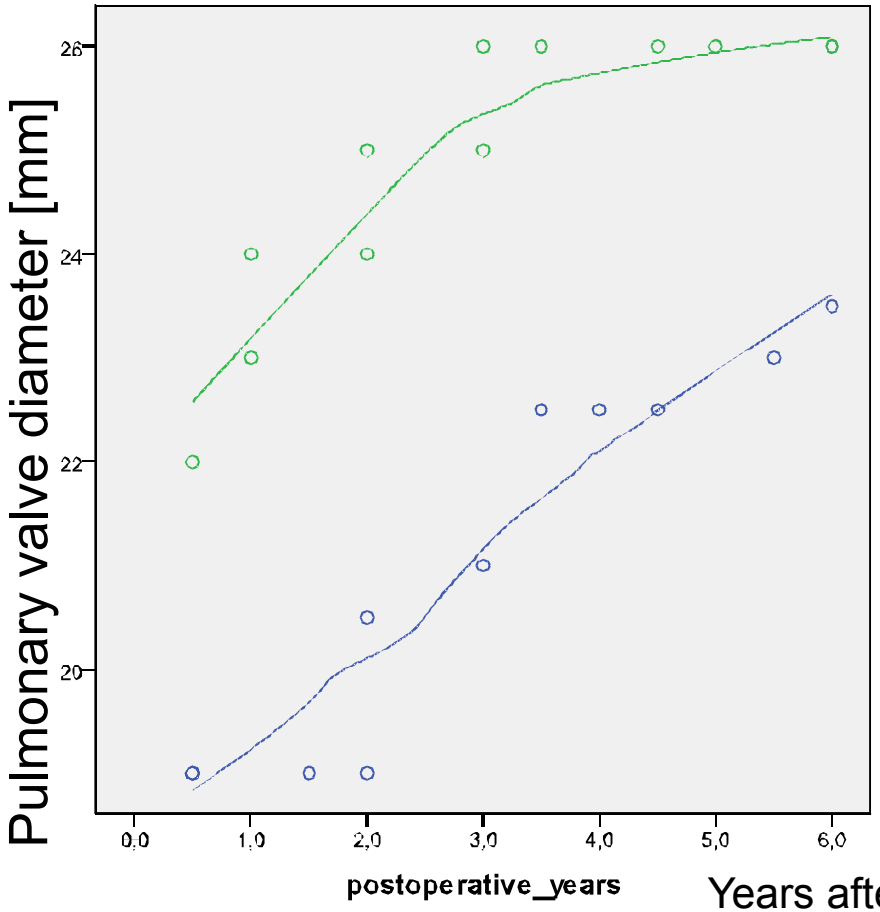
- Girl

  (13 years old)
  Tetralogy of Fallot with Pulmonary Atresia

- Boy

  (11 years old)
  Aneurysm of the Right Ventricle after radical correction of TF.

Development of 2 Reseeded Pulmonary Valve Grafts



Boy,
10 Years old

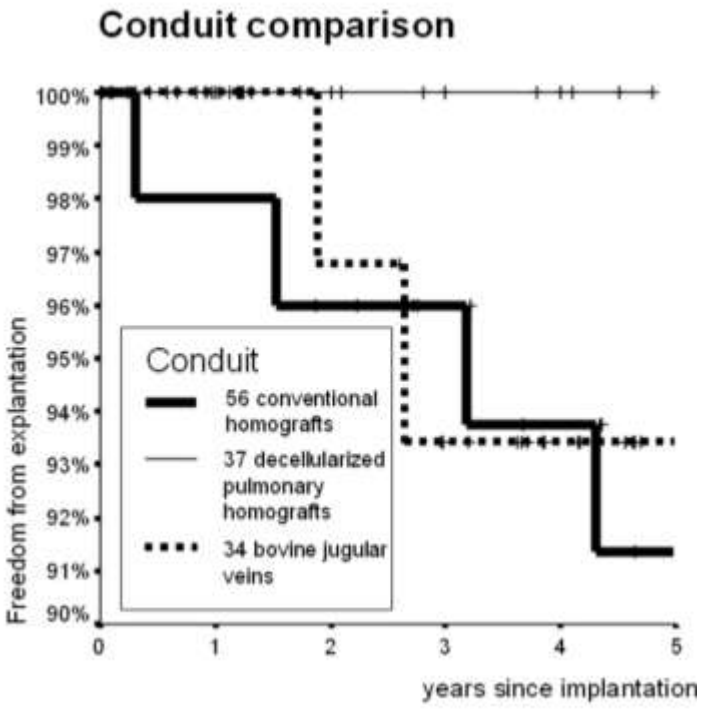
Girl,
13 Years old

Years after Implantation

8 Years Follow-up

Decellularized valves versus „Contegra“ and versus cryopreserved Homografts

37 „decellularized valves“ Patients were matched according to age and pathology with 34 „Contegra“- and 56 „Cryopreserved Homografts“ patients.



Five-year-freedom from explantation:

100% for Decellularized pulmonary allografts
93 ± 4% for Bovine Jugular Vein
91 ± 4% for Cryopreserved Homografts

The ESPOIR consortium

www.espoir-clinicaltrial.eu

Prof. Dr. Axel Haverich,
PD Dr. Samir Sarikouch, Hannover

Mr. Victor Tsang, London

Prof. Mark Hazekamp, Leiden

Prof. Pascal Vouhé, Paris

Prof. René Prêtre, Zürich

Prof. Dr. Bart Meyns, Leuven

Prof. Dr. Anatol Ciubotaru, Chisinau

Prof. Giovanni Stellin, Padua

Dr. Massimo Padalino, Padua

Dr. Michael Harder, Hannover

Martin Börgel, Hannover

Dr. Ramadan Jashari, Brussels

Sonja Kress, Hannover

Hospitals
- Chisinau
- Hannover
- Leiden
- London
- Padua
- Paris
- Leuven
- Zürich

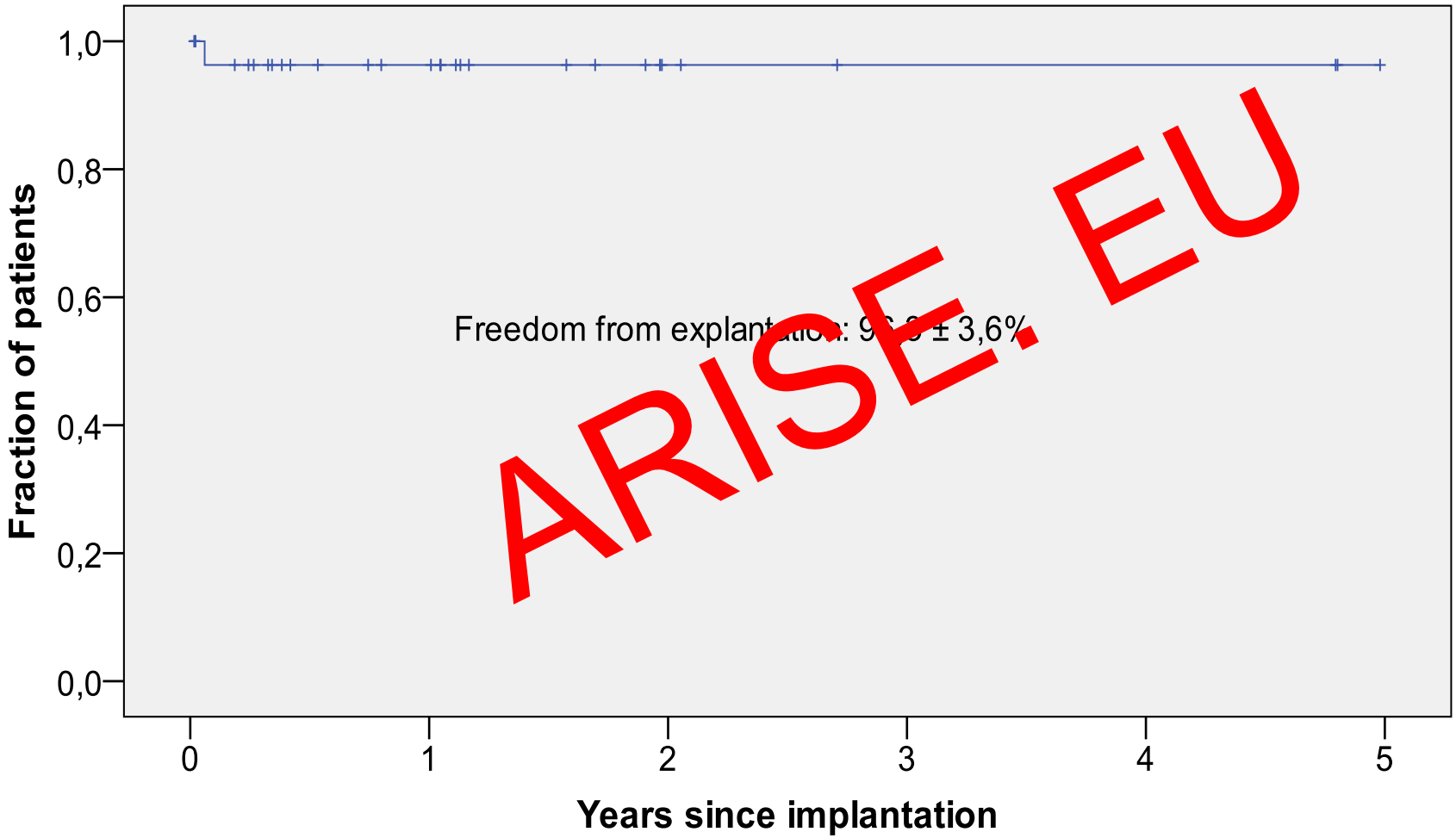
Tissue Banks
- EHB, Brussels
- DGFG, Hannover

Processing
- corlife, Hannover

E·S·P·O·I·R

Herz-, Thorax-, Transplantations- und Gefäßchirurgie

Hannover results – Aortenklappen (n=46)



Vascular: Abstracts 16:15–17:45 Room 113

Total aortic arch replacement with frozen elephant trunk: 10-year single center experience

Mahekh Shrestha, Andreas Martens, Felix Fleissner, Fabio Ius and Axel Haverich Hannover Medical School

Objective

Combined pathology of the aortic arch and the descending aorta (aneurysms and Dissection) remains a surgical challenge. Different techniques have been proposed. In a two stage operation, at the first stage, the aortic arch is replaced through a median sternotomy and during the second stage, the descending thoracic aorta is replaced through a lateral thoracotomy. Professor Hans Borst and colleagues introduced so called 'Elephant trunk' technique in 1982 at our center, greatly simplifying this two stage technique. However, a major disadvantage of this approach was the need for two operations with its associated mortality and morbidity as well as the fact that at least some mortality in the interval between the two operations due to the rupture of the untreated segment of aorta.

With the 'frozen elephant technique' (FET), the aortic arch is replaced conventionally and an endovascular stent-graft is placed into the descending aorta in antegrade manner through the open aortic arch, thereby potentially allowing for a 'single –stage' operation, especially in pathologies limited to the proximal descending aorta. Publications with Long term follow-up results are sparse. We present our 10 year results.

Methods

Between 2001- 01/2012, FET was implanted in 131 patients (95 males, 61±13 years). The indications included 91 aortic dissections (Type A (acute and Chronic): n= 78, type B (acute and chronic): n=13) and aortic aneurysms (n=40), respectively. Median follow-up was 42 ± 37 months. 40 patients had undergone previous cardiac operations. Concomitant procedures included 25 Bentall, 26 CABG, 17 David, 5 Yacoub and 8 aortic root repairs, respectively.

Three different FET prostheses, custom-made (n=66), Jotec-E®-vita (n=30) and Vascutek (n=35) prosthesis were used. The cerebral protection was done moderate hypothermic circulatory arrest (MHCA) and selective antegrade cerebral perfusion (SACP).

Results

Intra-operative mortality was 1.6%(n=2) and in-hospital mortality was 14.17% (n=20). CPB, X-clamp, MHCA and SACP times were 238±70, 137 ±51, 58±24, and 69±31 minutes respectively. Complications included re-thoracotomies 18% (n=24), acute renal failure leading to Dialysis 16% (n=21), paraparesis 3.1% (4) and stroke 14.7% (n=19).

Thirty-six patients underwent follow-up procedure on the downstream aorta, either endovascular (n=16), open surgery (n=20), respectively.

One, five and ten-year survival was 82±3, 72±5 and 58±8 years, respectively.

Conclusion

FET concept adds to the armament of the surgeon in the treatment of complex and diverse aortic arch pathology. The initial learning curve, acute dissections, re-do and concomitant procedures partially explains the higher mortality rate. Nevertheless, our experience demonstrates acceptable short and long-term results in treating this complex disease cohort. Our series shows that in carefully selected patients with combined pathology of the aortic arch and the proximal descending aorta, the FET procedure allows for a 'single-stage' procedure.

Vascular Coupling System

Akute Aortendissektion

50 Implantationen im Minipig

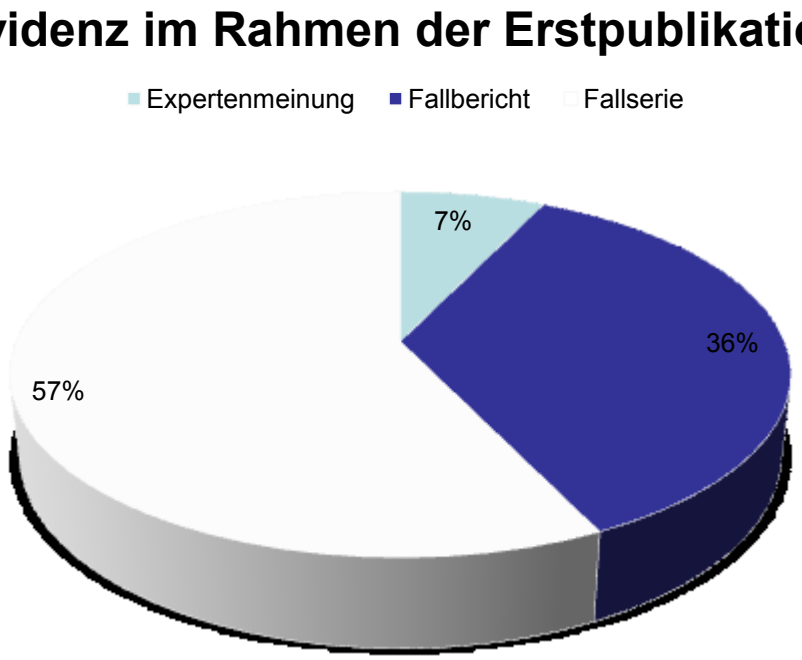
BEFARM Zulassungsstudie (konstruiert für elektive Ops)

März 2014 Unterbrechung wegen Komplikationen Kontrollgruppe

- Evidenz
- RCTs
- Registries
- Tierversuche
- Chirurgie
- Pharmazie vs Implantate vs ATMP

= Rolle der Fachgesellschaften

Bahnbrechende Chirurgische Innovationen in Deutschland



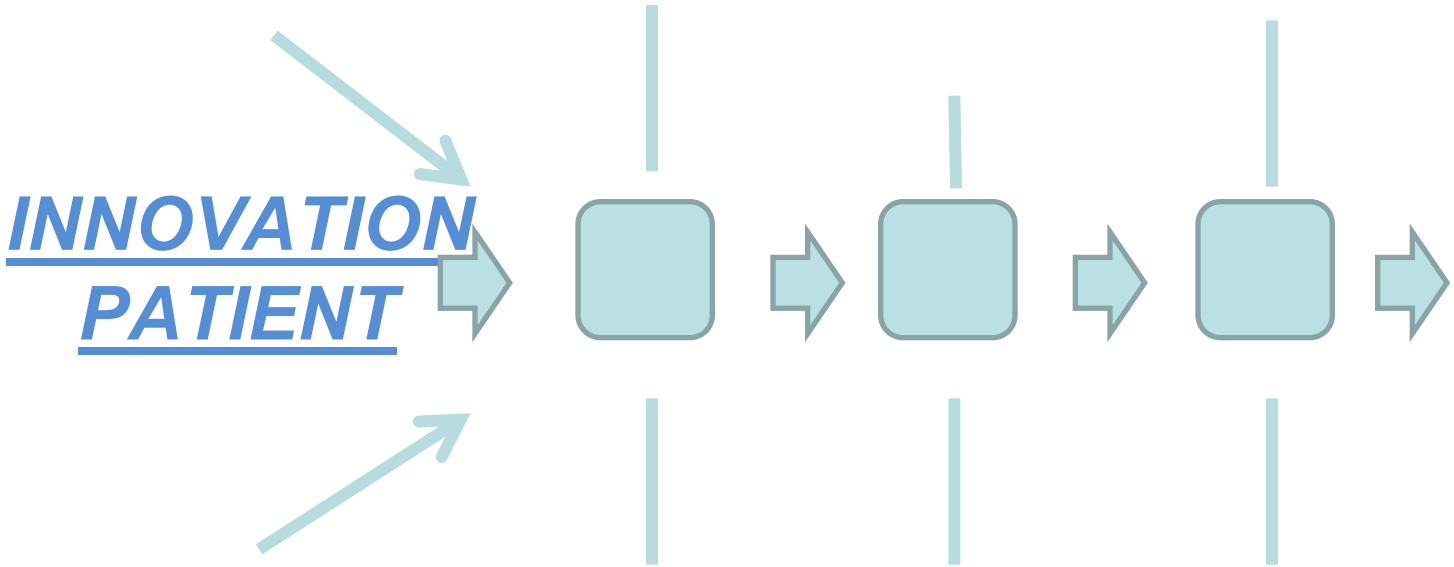
Innovations-Netze in der Chirurgie

- Industrie
- (Implantat)

Bench
Tierversuch

Studie
- Klinik
- ambulant

GBA
Kostenträger



- Chirurg
- (Verfahren)

Forschung
Entwicklung

Evaluation

Finanzierung

Anno 2030
NSF
NSF
NSF
NSF
$
$
$
$
ARENA
Personalized Medicine