The Story of OPC

CORE-MD Webinar
April 3, 2023

Gary Grunkemeier
Division of Cardiothoracic Surgery
Oregon Health & Science University
Portland, Oregon USA

The Story of OPC

1. OPC
   - FDA Workshop Bethesda – 1993
   - Heart Valve Guidance - 1994

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   - ISO meeting Portland - 2012
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Mitral Replacement: *

Clinical Experience with a Ball-Valve Prosthesis

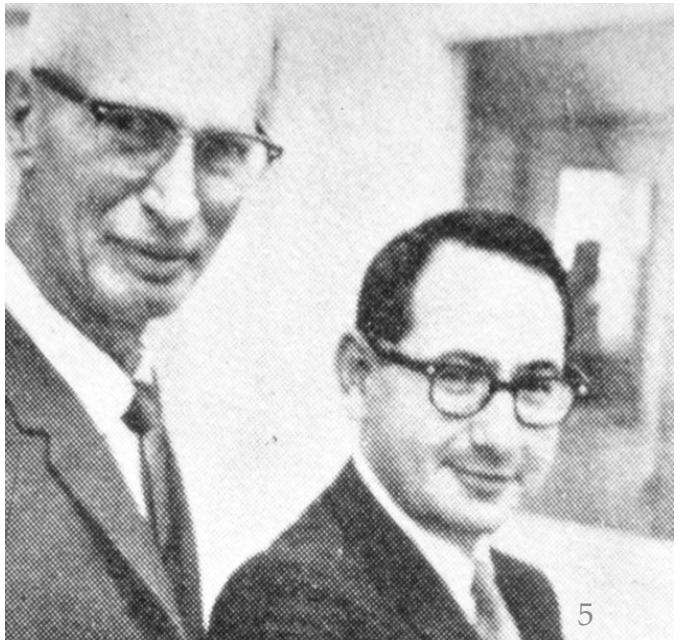
ALBERT STARR, M.D., M. LOWELL EDWARDS, B.S.

From the Department of Surgery and Division of Thoracic Surgery, University of Oregon Medical School, Portland, Oregon

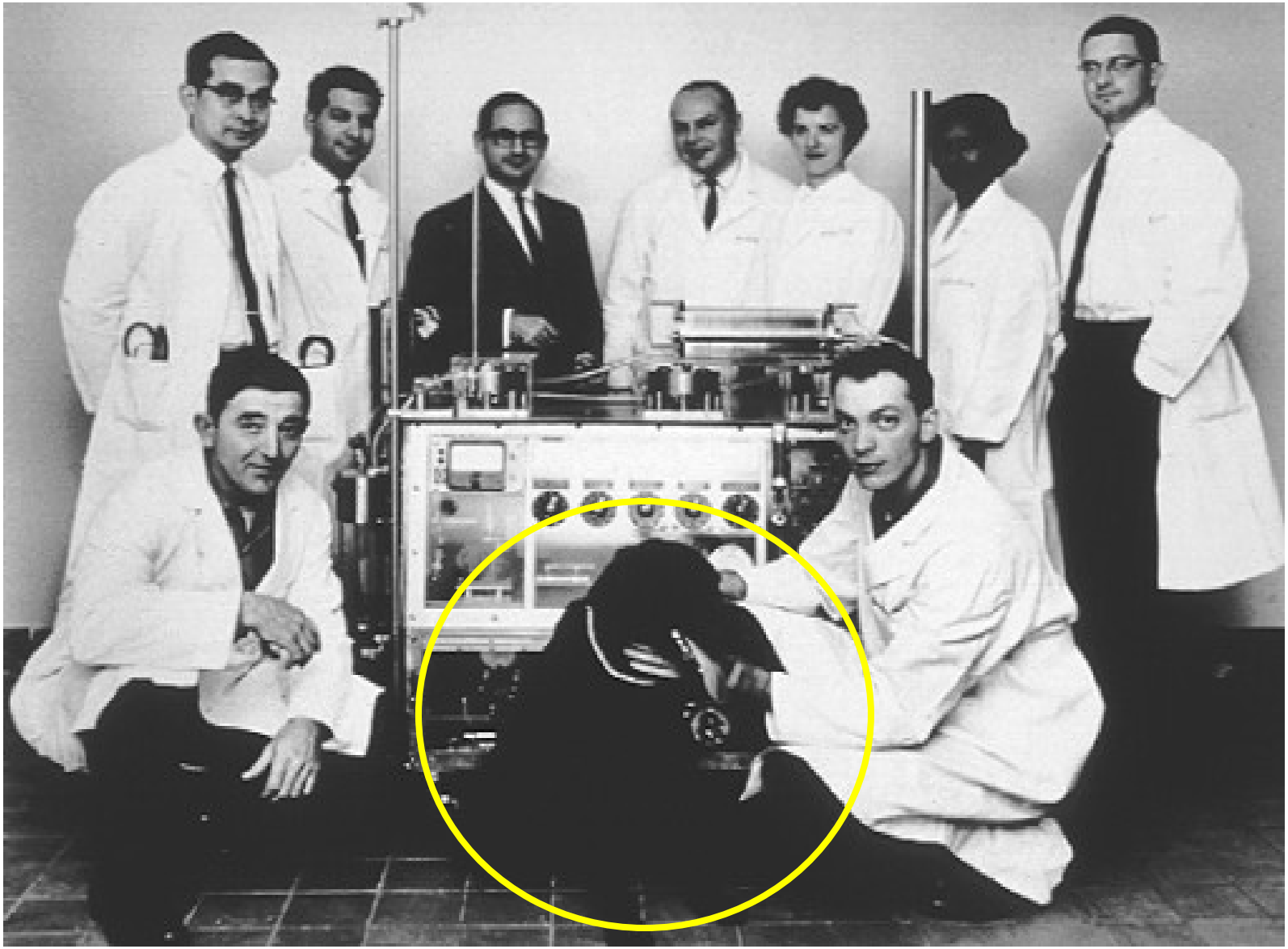
* Presented before the American Surgical Association, Boca Raton, Florida, March 21–23, 1961.

This work is supported in part by a grant-in-aid from the Oregon Heart Association.

Annals of Surgery 1961



Mitral Caged Ball Valves in Labrador Dogs

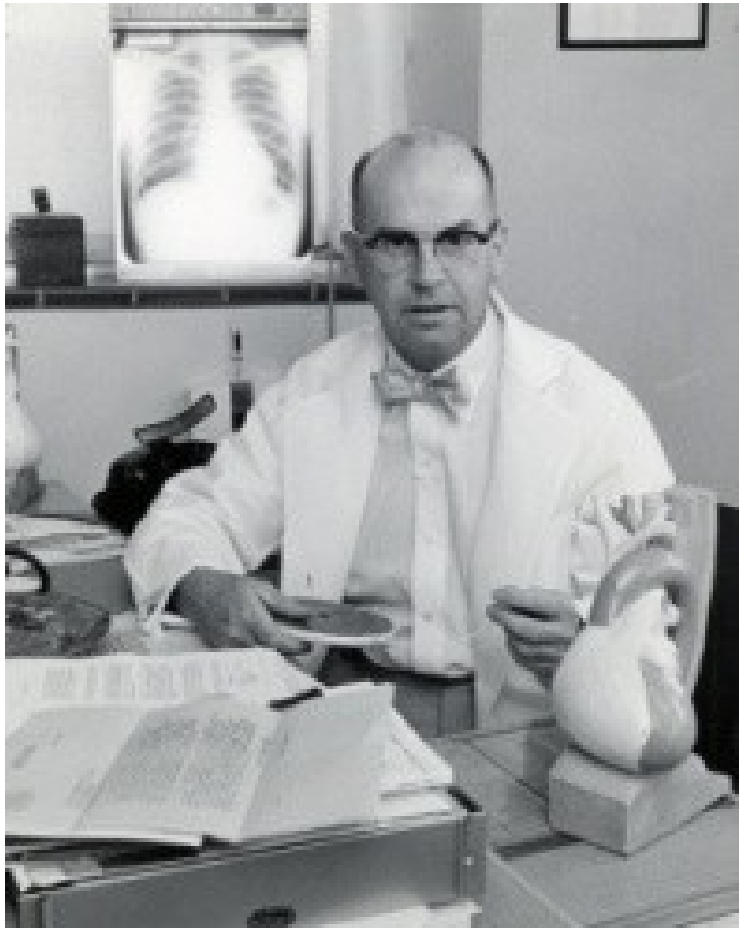


Animal to Man: Challenges

- Regulatory
  - No FDA or IRB
  - No informed consent
  - No ethical guidelines
- Technical
  - No surgical technique yet developed
  - No ICU
- Business
  - Name for the valve?
  - Manufacturing company?

Animal to Man?

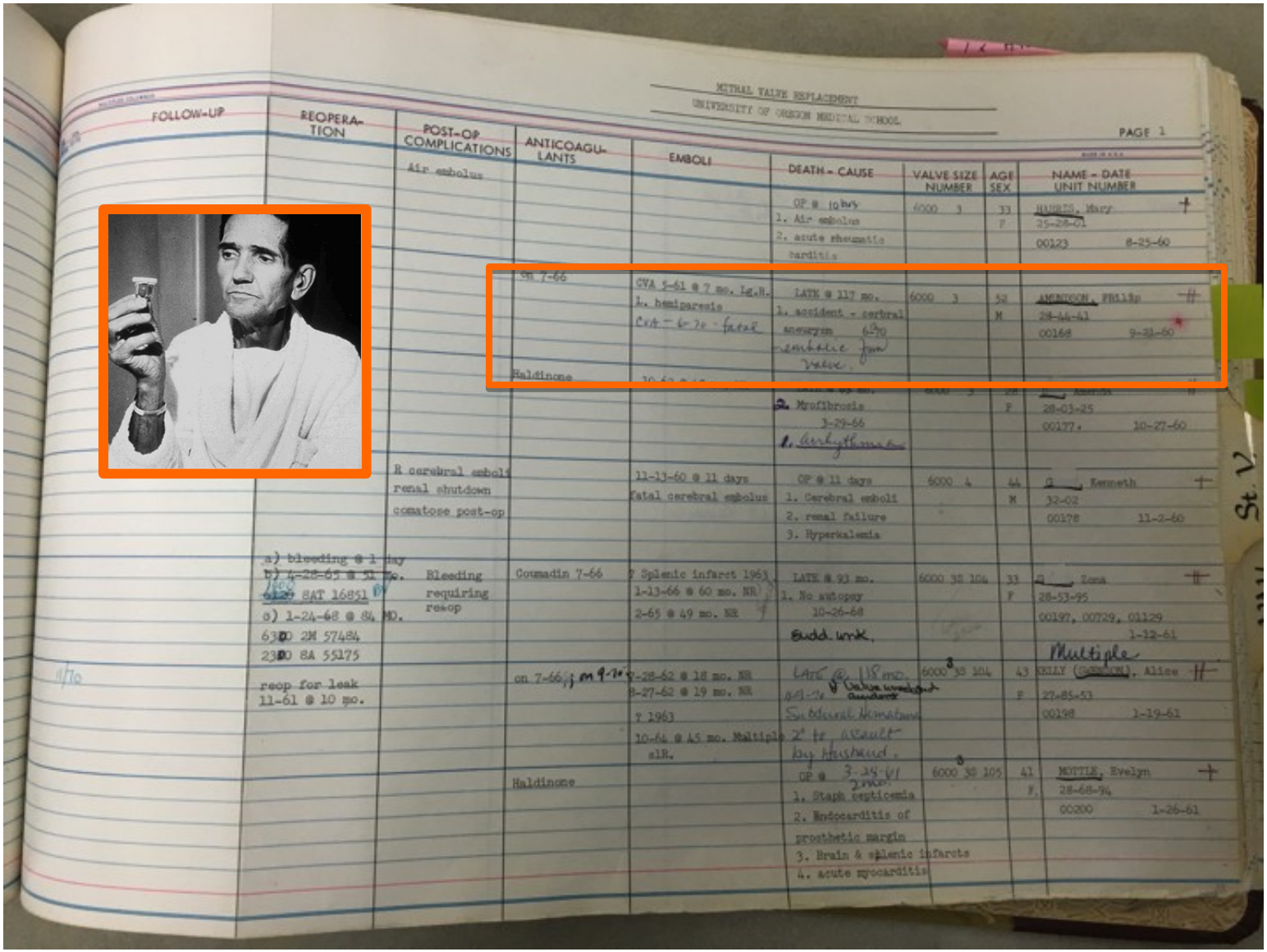
Chief of Cardiology



Blackie licks his hand

Animal to Man?
Mitral Disease Patients Dying

Dr. Starr introduced a life-time follow-up service, beginning with his very first patient.



In 1974, Starr obtained a 6 (3+3) year NIH grant to convert 3,000 patient records from flowsheet books to a mainframe database, to enable long-term follow-up.

StarrBase Follow-up Records (as/of 2016)

Patients	40,557
Procedures	45,798
Follow-up records	**256,729**
Follow-up years	326,548
Patients > 25 years	1,466
Patients > 40 years	37
Longest Follow-up	52 years

StarrBase → 85 publications . . .

. . . Including these papers, at "landmark" time points:

- **Ten-year** survival following aortic valve replacement: A multivariate analysis of coronary bypass as a risk factor. J Cardiovasc 1986
- The ultimate prognosis after valve replacement: an assessment at **twenty years**. Ann Thorac Surg. 1981
- **Twenty-five year** experience with Starr-Edwards heart valves: Follow-up methods and results. Can J Cardiol 1988
- Up to **thirty-year** survival after aortic valve replacement in the small aortic root. Ann Thorac Surg. 1995
- Heart valve replacement: A statistical review of **35 year** results. The Journal of Heart Valve Disease 1999
- **Forty-Year** Survival with the Starr-Edwards Heart Valve Prosthesis. The Journal of Heart Valve Disease 2004

AND . . .

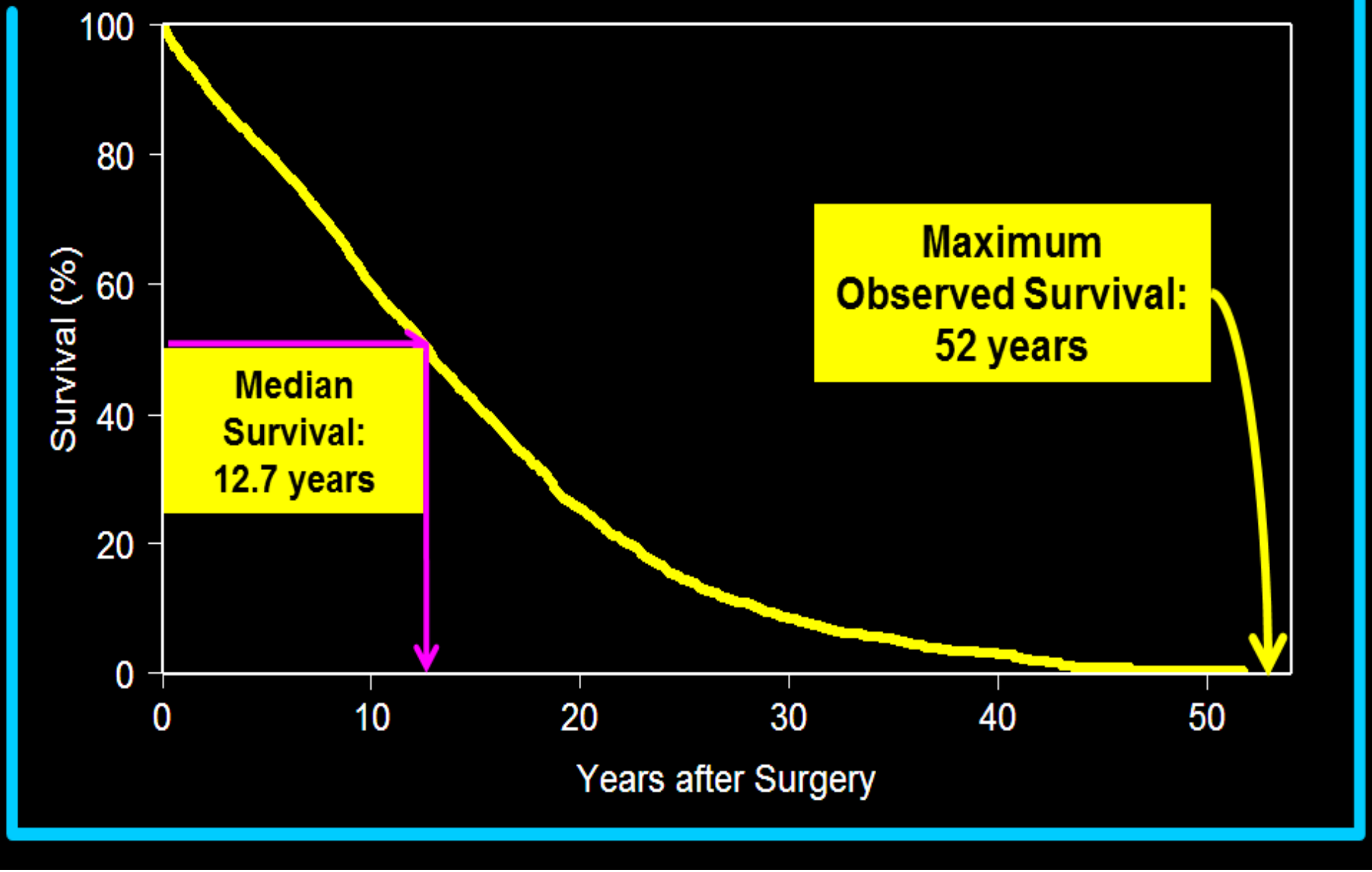
50-Year Follow-up of Mechanical Aortic Valve Replacement: Patient Survival and Prosthesis Durability

Tony Furnary, Mansen Wang, Chiu, Shih Ting,
Gary Grunkemeier, Albert Starr

Starr-Wood Cardiac Group
Medical Data Research Center, Providence Health & Services
Oregon Health & Sciences University
Portland, OR, USA

Society of Thoracic Surgeons 52nd Annual Meeting
Phoenix, AZ
January 26, 2016

Observed Survival: Mechanical AVR



Lasker Award for Clinical Medical Research

- Lasker Award
  - Called “America’s Nobel”
  - Given to 72 scientists who later received the Nobel Prize

- Starr and Carpentier (2007)
  - For prosthetic valves
  - In an era before the FDA regulated medical devices, Starr set up the infrastructure for conducting . . . *long-term patient tracking.*

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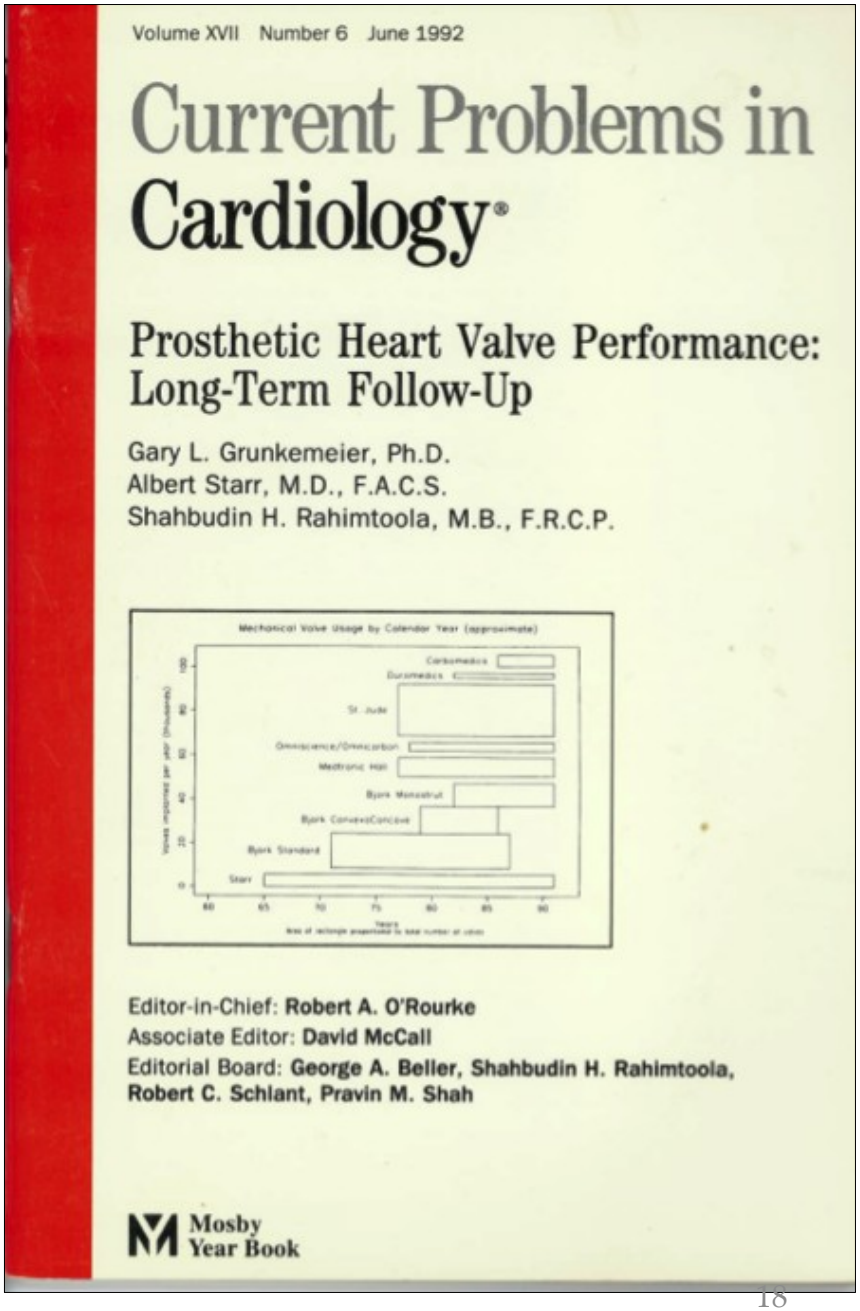
CPC 1992

Literature Review Inclusion Criteria

- published after 1984
- long term results
- written in English
- stratified by position
- most recent data
- statistically sound



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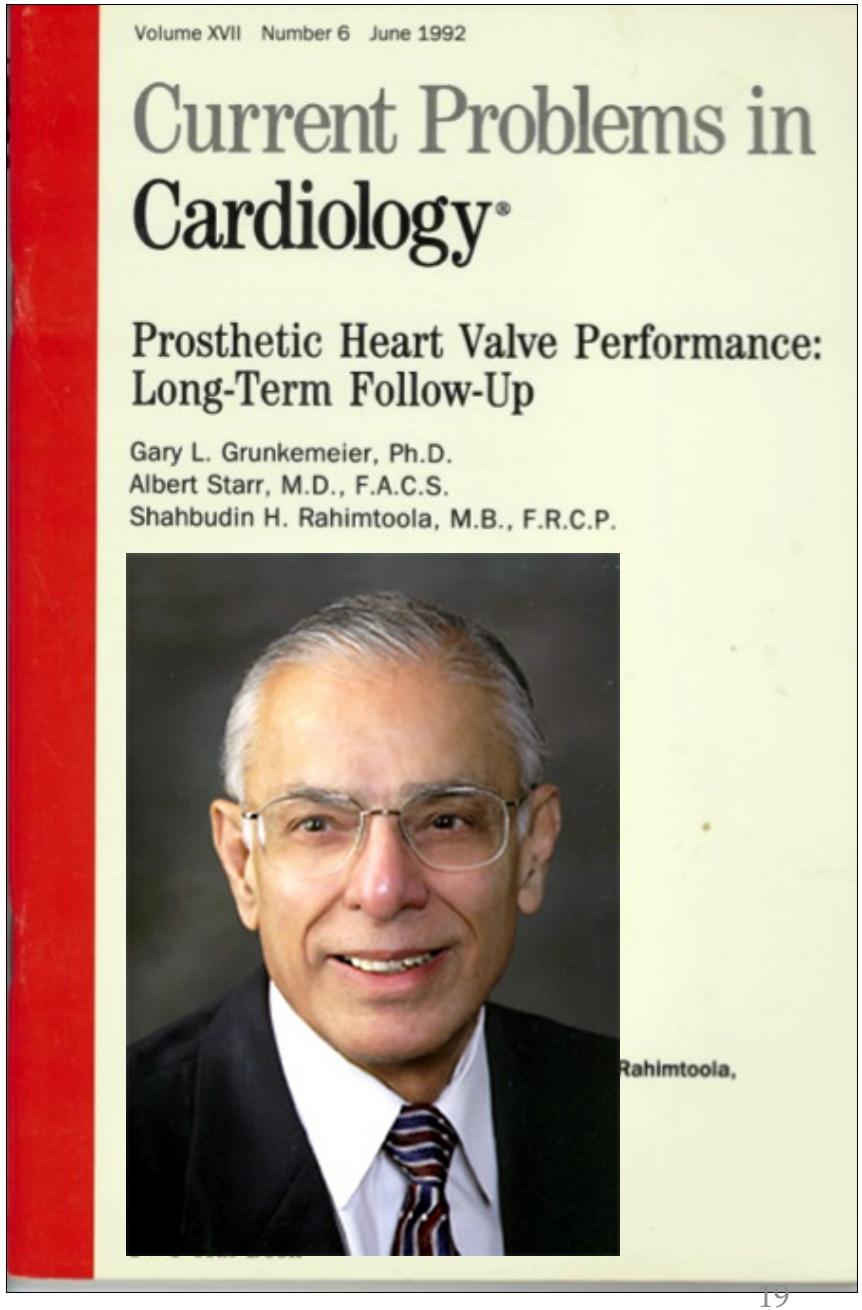
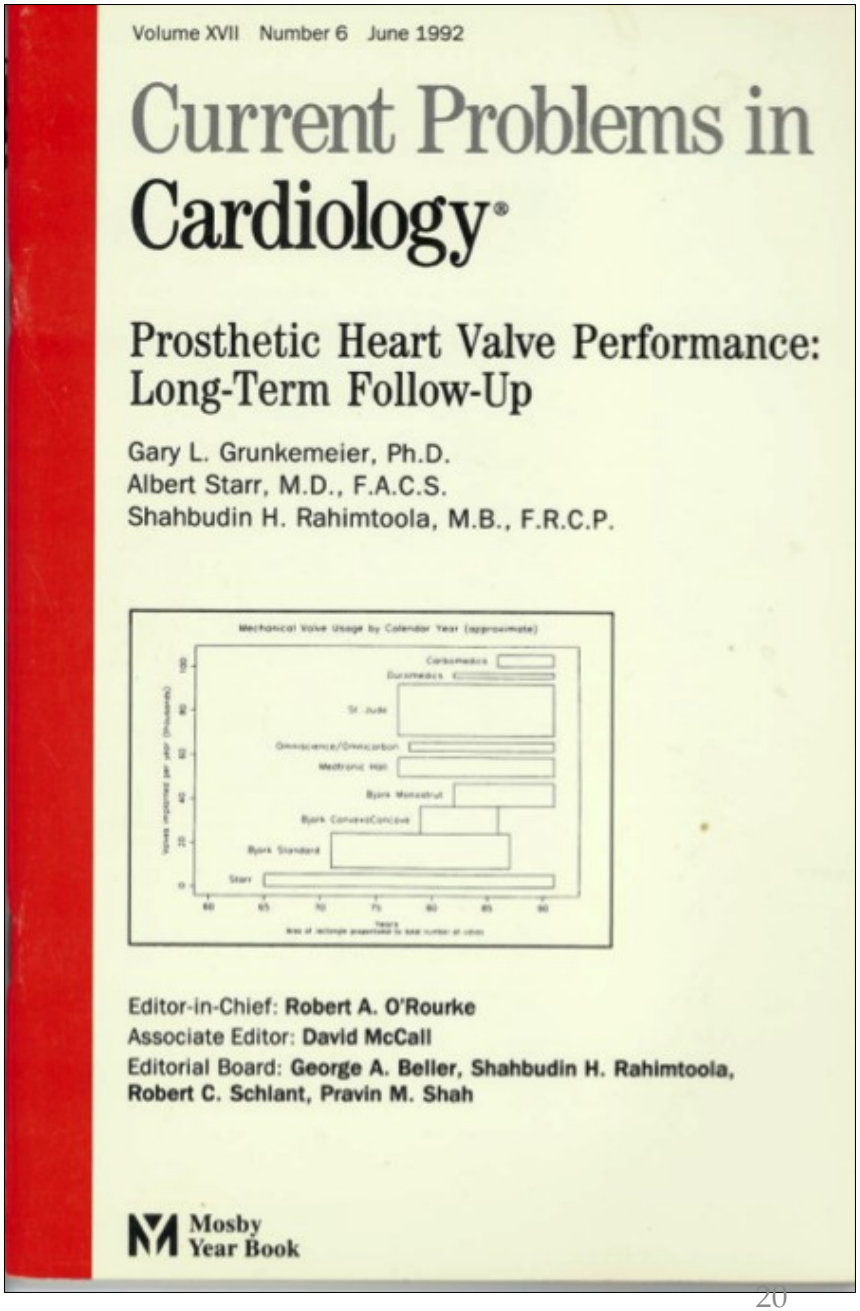
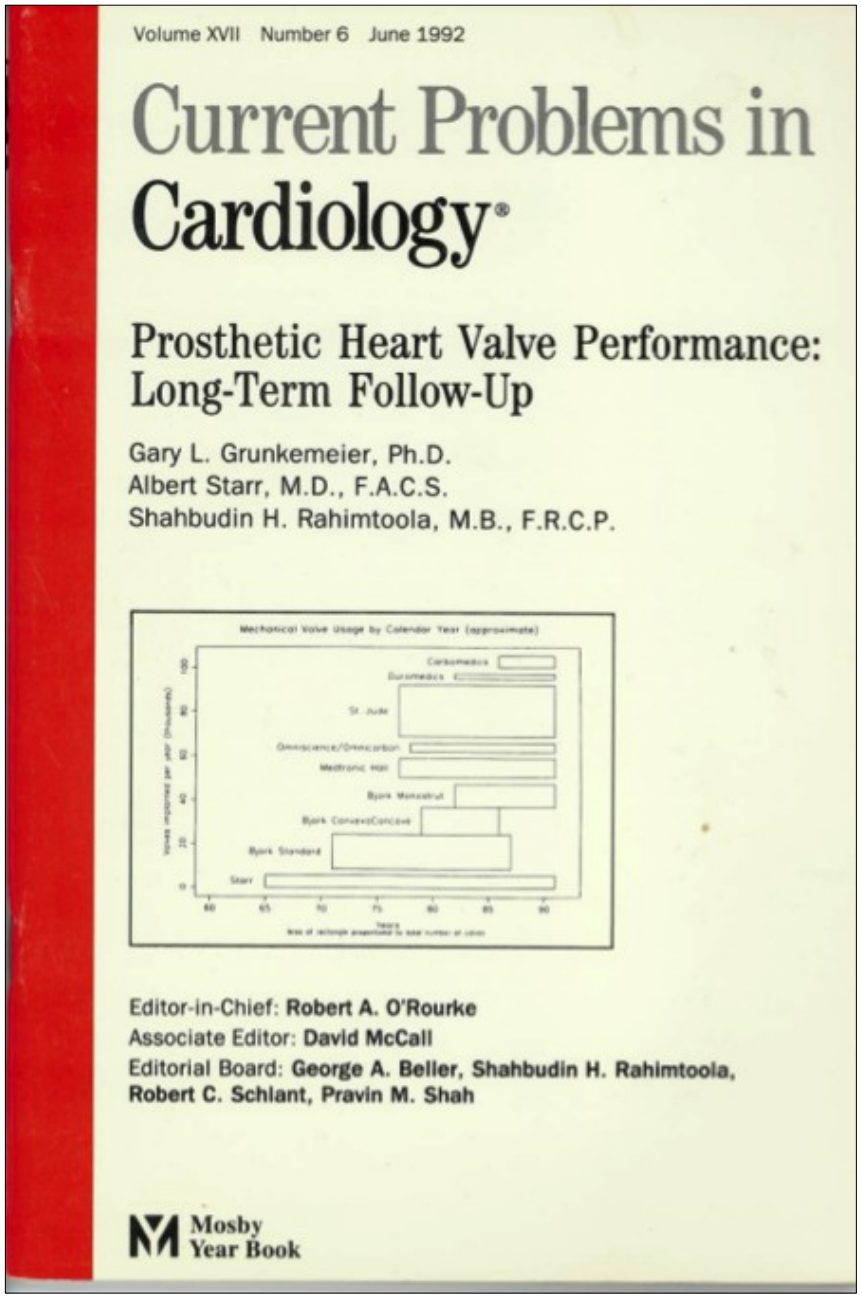


CPC 1992

Literature Review
Complications

- **Embolism**
- **Bleeding**
- **Thrombosis**
- **Leak**
- **Infection**
- **SVD**





CPC 1992

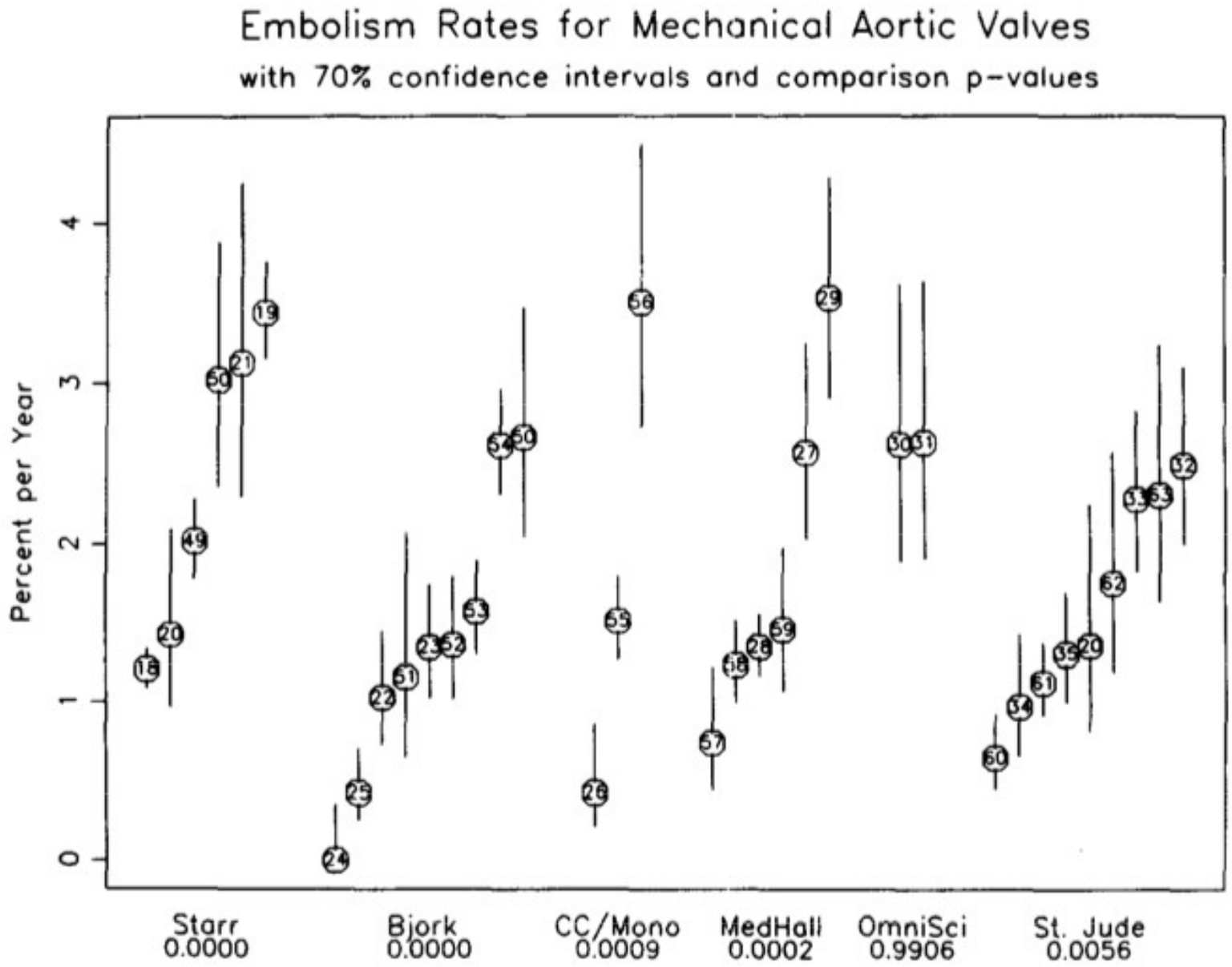
Valve replacements

- 81 publications
- Published 1985-1990

- 59,281 valves
- 54,271 patients

- 224,108 valve-years
- 204,078 patient-years

- 38 Figures
- 12 tables



CPC 1992 – Figure 23

Summary Statistic

- “Linearized” event rate
- Late events (> 1 month) only
- Assume constant risk (hazard)
  - Patient-years = Y
  - Count of events = N
  - Rate = N/Y x 100
    - events per 100 patient-years
    - “Percent per year” = %/year

J THORAC CARDIOVASC SURG 91:460-466, 1986

Editorial

Issues concerning the clinical evaluation of new prosthetic valves

Bernard J. Gersh, M.B., Ch.B., D.Phil., Lloyd D. Fisher, Ph.D., Hartzell V. Schaff, M.D., Shahbudin H. Rahimtoola, M.D., Guy S. Reeder, M.D., Robert W. M. Frater, M.B., Ch.B., and Dwight C. McGoon, M.D., *Rochester, Minn., Seattle, Wash., Los Angeles, Calif., and Bronx, N. Y.*

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"Arbitrary criteria for initial approval of a new valve would require documentation of event rates to be less than twice *the average of currently accepted values*."

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"Statistically this would require the use of one-sided 95% confidence intervals … "

Health Industry Manufacturers Association (HIMA)

- Convened a heart valve task force
- Advocated the method of Gersh et al.
- Introduced the term:

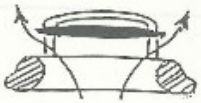
  "*Objective Performance Criteria*" (OPC)

- Meaning: *currently acceptable complication rates*

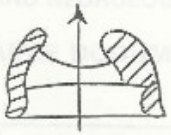
June 6, 1993 FDA Workshop

- NIH campus Bethesda
  - HIMA
  - AATS & STS
  - Physicians
  - Scientists
- FDA proposed RCT
- HIMA proposed OPC/Gersh
- Result: FDA to consider OPC

CAGED BALL



CAGED DISK

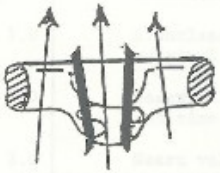


TISSUE

DRAFT

Replacement Heart Valve Guidance

134 pages

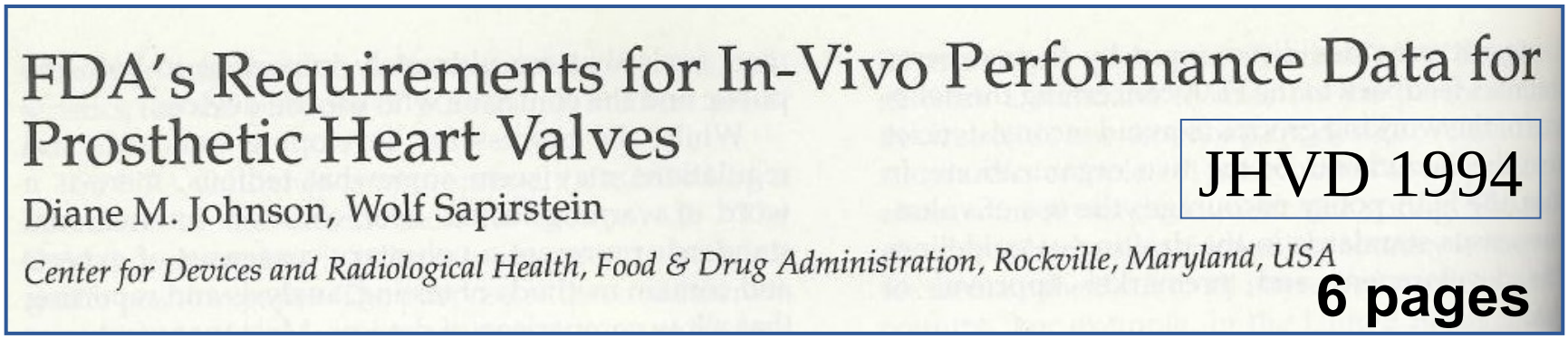


BILEAFLET

TILTING DISK

Division of Cardiovascular, Respiratory, and Neurological Devices
October 14, 1994

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health



FDA's Requirements for In-Vivo Performance Data for Prosthetic Heart Valves

JHVD 1994

Diane M. Johnson, Wolf Sapirstein

Center for Devices and Radiological Health, Food & Drug Administration, Rockville, Maryland, USA

6 pages

Data FDA Used for OPC

- CPC 1992 search updated to include all references published through mid-1993.
- Over 10,000 patients and 45,000 valve years
- Also included data from previously submitted PMA applications.

FDA's Requirements for In-Vivo Performance Data for Prosthetic Heart Valves

Diane M. Johnson, Wolf Sapirstein

Center for Devices and Radiological Health, Food & Drug Administration, Rockville, Maryland, USA

Table I: Optimum performance criterias (OPCs) for replacement valves.

Event	Mechanical %/patient-year	Tissue %/patient-year
Thromboembolism	3.0	2.5
Valve thrombosis	0.8	0.2
All bleeding	3.5	1.4
Major bleeding	1.5	0.9
All leakage	1.2	1.2
Major leakage	1.2	1.2

FDA's Requirements for In-Vivo Performance Data for Prosthetic Heart Valves

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Sample Size Requirement

- True rate of new valve significantly < 2 x OPC
- Hypothesis test setup

  Probability of Type 1 error = 5%

  Probability of Type 2 error = 20% (80% power)

- For OPC of 1.2%/year, requires **800 valve-years**

2005 - ISO Adopts FDA's 1994 OPC

ISO 5840, Annex R*:*
Cardiovascular implants -- Cardiac valve prostheses

Table R.1 — Objective performance criteria for heart valve substitutes

	Rigid	Flexible
Thromboembolism	3,0	2,5
Valve thrombosis	0,8	0,2
All haemorrhage	3,5	1,4
Major haemorrhage	1,5	0,9
All paravalvular leak	1,2	1,2
Major paravalvular leak	0,6	0,6
Endocarditis	1,2	1,2

Draft Guidance for Industry and FDA Staff

Heart Valves - Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: January 20, 2010

2010 FDA Heart Valve Draft Guidance

- "Control data … should include … literature-based objective performance criteria (OPCs)"

- "The control data … should be collected from studies published during the past 5 years"

- "FDA recommends the use of the OPCs as listed in Table R.1 of ISO 5840:2005 Annex R"

- "Sample size … is 800 patient-years"

Success of OPC Approach

VALVE NAME	APPROVED
Sorin Mitroflow Aortic Pericardial Heart Valve	2007
Medtronic ATS 3F Aortic Bioprosthesis, Model 1000	2008
St. Jude Medical Trifecta Valve	2011
Sorin Freedom SOLO Stentless Heart Valve and SOLO Smart Stentless Heart Valve	2014
Sorin Perceval Sutureless Heart Valve	2016
Edwards Intuity Elite Valve System	2016
Edwards Lifesciences Inspiris Resilia Aortic Valve	2017
Medtronic Avalus Bioprosthesis	2017

Success of OPC Approach

- Only one approved heart valve has been taken off the market because of postoperative complications.

- But that valve avoided the OPC test, being approved as a supplement to an original PMA. .
- A later analysis showed that it would not have passed the OPC test

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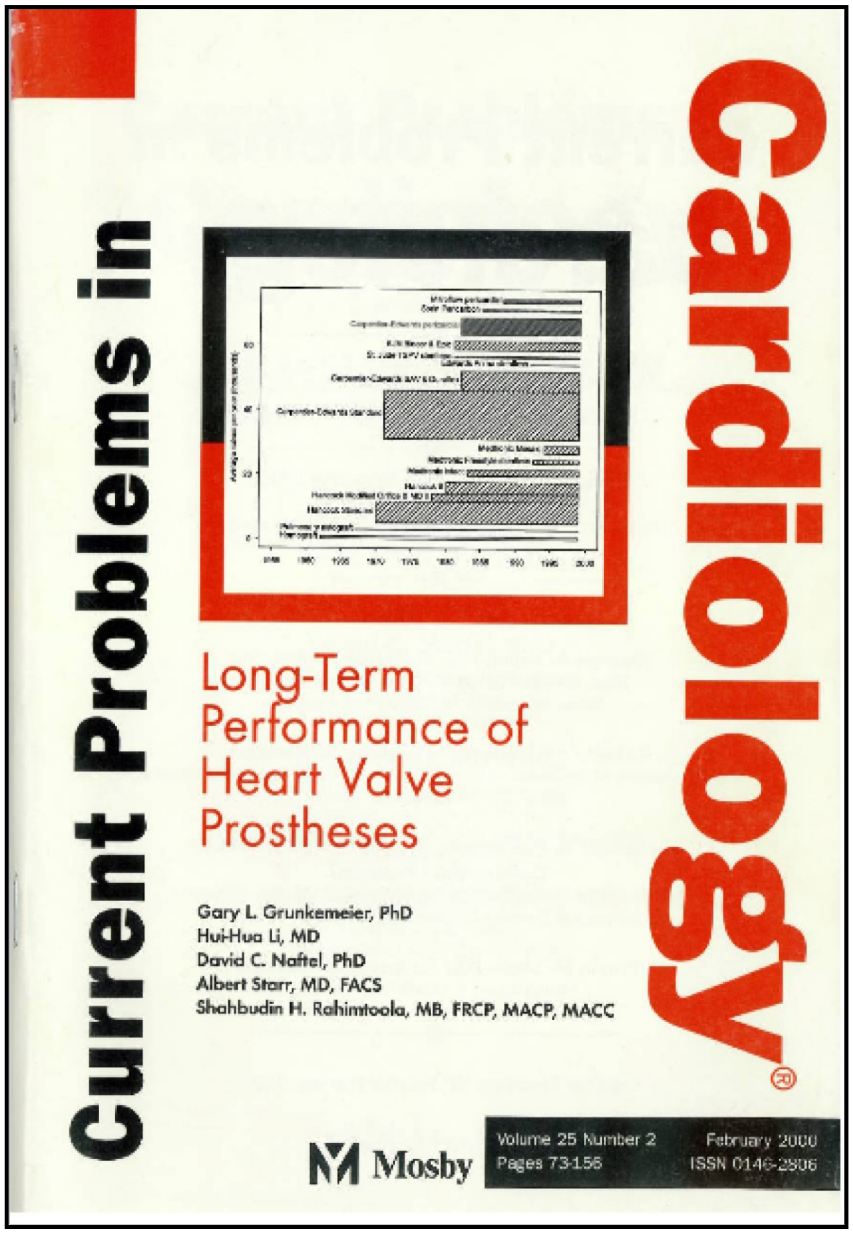
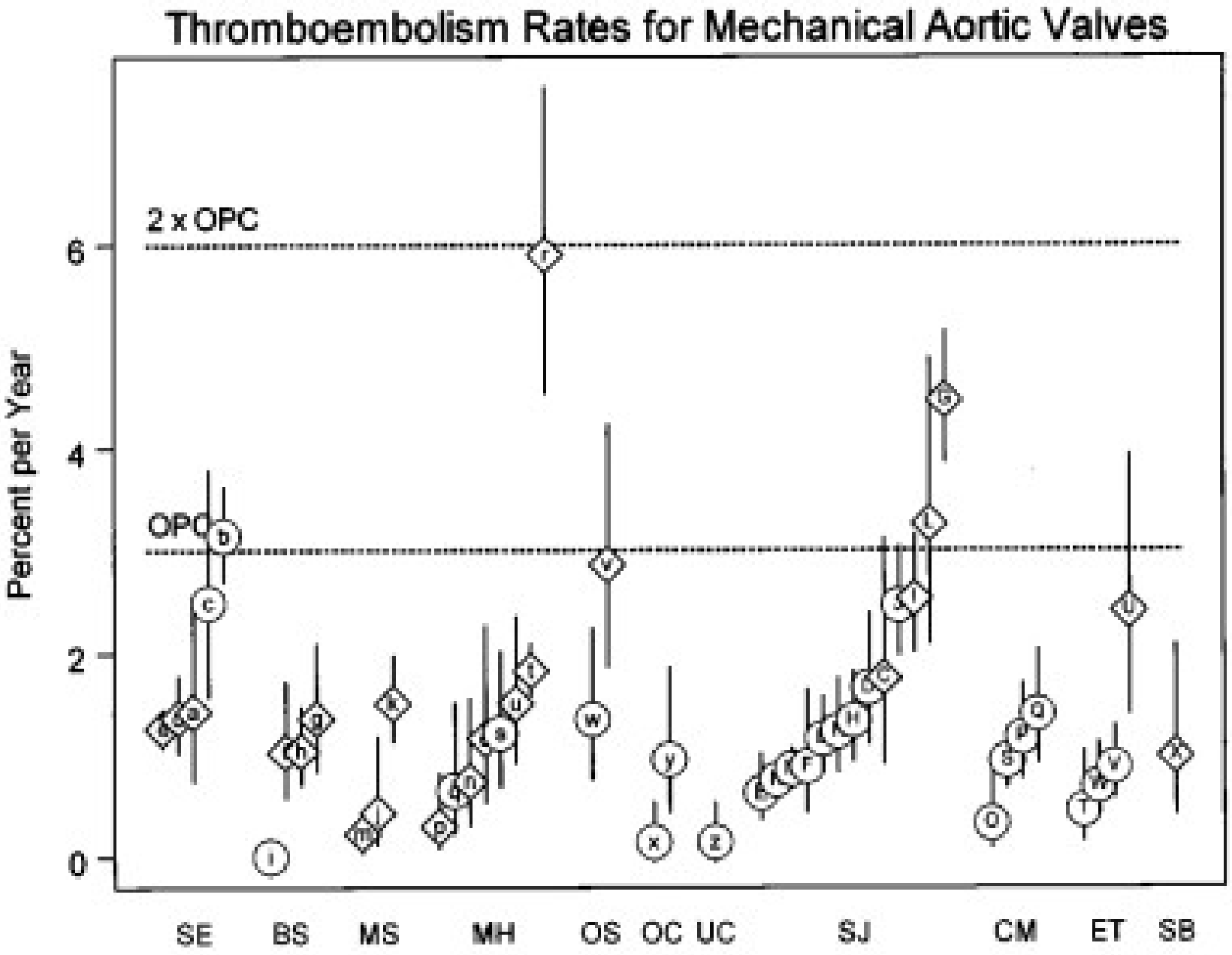


CPC 2000

Isolated Valve Replacement

- Published 1989-1999
- Mechanical
  - 95 series
  - 37,253 valves
  - 187,230 valve-years
- Biological
  - 70 series
  - 24,202 valves
  - 132,519 valve-years
- 46 figures
- 22 tables



CPC 2000 – Figure 15

2012 - ISO Request:

Update the Heart Valve OPC

- ISO International Task Force
  - Manufacturers
  - Independent Physicians
  - Statisticians
  - FDA
- FDA interested in adopting the ISO updates

Eric Butchart and the Heathman Hotel, Portland, Oregon

Meeting of the ISO 5840 Revision Committee WG

Nov. 14, 2012 - Heathman Hotel - Portland, Oregon

Data used for the ISO OPC Update

- Literature Review Series
  - Published from 1999 to 2012
  - 85 series from 56 literature articles
  - 38,788 valves and 208,585 patient-years

- FDA Summaries of Safety and Effectiveness (SSE)
  - 19 SSE reports with 31 series
  - 13,195 valves and 38,359 years of follow-up

Table 1. Original and Proposed New Objective Performance Criteria

	Mechanical Valve			Bioprosthetic Valve		
		Proposed New			Proposed New	
Adverse Event	Original OPC	Aortic	Mitral	Original OPC	Aortic	Mitral
Thromboembolism	3.0	1.6	2.2	2.5	1.5	1.3
Valve thrombosis	0.8	0.1	0.2	0.2	0.04	0.03
All hemorrhage	3.5			1.4		
Major hemorrhage	1.5	1.6	1.4	0.9	0.6	0.7
All paravalvular leak	1.2			1.2		
Major paravalvular leak	0.6	0.3	0.5	0.6	0.3	0.2
Endocarditis	1.2	0.3	0.3	1.2	0.5	0.4

OPC = objective performance criteria.

ISO Revised OPC

- What changed
  - The complications “all bleeding” and “all leak” were deleted, leaving only 5 of the original 7
  - OPC values all lowered
  - Separate OPC for the aortic and mitral positions
  - A new valve is required to have complication rates *numerically*, as opposed to “*statistically significantly*” lower than twice the OPC
- What didn’t change
  - 800 valve-years required

Clinical Evaluation of New Heart Valve Prostheses: Update of Objective Performance Criteria

YingXing Wu, MD, Eric G. Butchart, FRCS, Jeffrey S. Borer, MD, Ajit Yoganathan, PhD, and Gary L. Grunkemeier, PhD

Medical Data Research Center, Providence Health and Services, Portland, Oregon; Department of Cardiothoracic Surgery, University Hospital of Wales, Heath Park, Cardiff, United Kingdom; Division of Cardiovascular Medicine and the Howard Gilman Institute for Heart Valve Diseases, State University of New York Downstate Medical Center, Brooklyn, New York; and School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, Georgia

This article summarizes the long-term clinical results of the Food and Drug Administration–approved heart valves, provides current updates to the objective performance criteria (OPC) used to evaluate new heart valve prostheses, and documents the steps that the International Organization for Standardization Committee used to arrive at the updated OPC. Data were extracted from 19 Food and Drug Administration summaries of safety and effectiveness data reports (31 series) and 56 literature articles (85 series) published from 1999 to 2012. The OPC were calculated for five valve-related complications by valve type (mechanical and bioprosthetic) and valve position (aortic and mitral).

(Ann Thorac Surg 2014;98:1865–74)

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Albert Starr March 2023

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Thank You!