



CORE-MD Webinar April 3, 2023

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



OHSU



1. OPC

- FDA Workshop Bethesda 1993
- Heart Valve Guidance 1994

1. OPC

- FDA Workshop Bethesda 1993
- Heart Valve Guidance 1994

2. ISO OPC update

- ISO meeting Portland 2012
- Publication 2014

- 1. Albert Starr
 - First successful heart valve -1960
 - Lifetime follow-up service

2. OPC

- FDA Workshop Bethesda 1993
- Heart Valve Guidance 1994

3. ISO OPC update

- ISO meeting Portland 2012
- Publication 2014

Mitral Replacement: *

Clinical Experience with a Ball-Valve Prosthesis

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

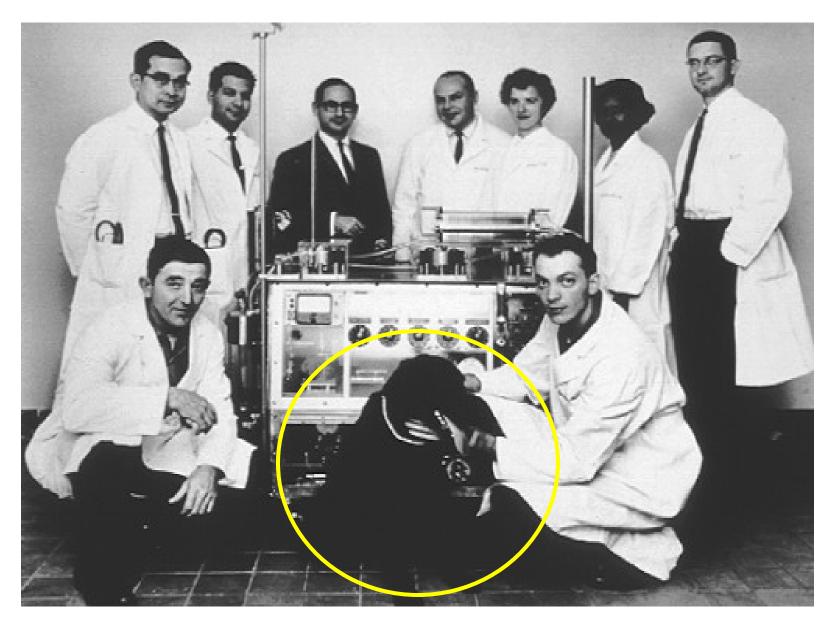
From the Department of Surgery and Division of Thoracic Surgery, University of Oregon Medical School, Portland, Oregon

• 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

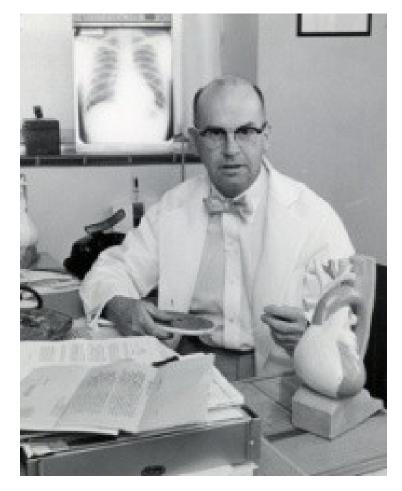


Animal to Man: Challenges

- 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 <u>life-time follow-up</u> <u>service</u>, beginning with his very first patient.

| FOLDAUL REGRET FORMULT INTERMENT FORMULT INTERMENT FORMULT INTERMENT ALT. REDUCES | the latent | | | | MITHAL TAI | OTE REPLACEMENT | | | |
|--|------------|--|--|--------------------|--|---|----------------|------------|--|
| NUME COMPLEXITION ANIECOACU EMOLIA OLATE CAUSE CAUSE <thcause< th=""> CAUSE</thcause<> | FOLLOW-UP | REOPERA | | | ORTAXESILL OF | ORRECT MEDICAL DOMOG. | | - | |
| Als. meloline Control Other CASE VALVESSE Control Diversity Image: Control of the contr | 10 | TION | COMPLICATION | ANTICOAGU | | | | - | |
| NUMBER SXX UNIT NUMBER 0.7 # 1285 SXX UNIT NUMBER 1000000 137 1000000 | | | Air scholms | LANTS | EMBOLI | DEATH- CAUSE | VALVE SIZE | Incel | The second se |
| 1 All methods 1 <td< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td>NUMBER</td><td>SEX</td><td>UNIT NUMBER</td></td<> | | | | | | | NUMBER | SEX | UNIT NUMBER |
| 37.760 38.760 36.760 38.760< | | | | | | | 4000 3 | | |
| 37.766 37.766< | | | | | | | | 2 | |
| In Desting rest, lack 1488 8 20 ms. lack 1100 | | | | | | | | | 00123 8-25-60 |
| In Desting rest, lack 1488 8 20 ms. lack 1100 | | 3 | | ST 7-66 | 1984 | | | | |
| Chr. Chr. <th< td=""><td></td><td>9</td><td></td><td></td><td>L hants</td><td>LATE @ 117 mo.</td><td>6000 3</td><td>32</td><td>AMINIDON, PRALAD -H</td></th<> | | 9 | | | L hants | LATE @ 117 mo. | 6000 3 | 32 | AMINIDON, PRALAD -H |
| Raltinge Notice South | | | | | Cret = (= 2e = (/ 2 | A. accident - certral | | | |
| Raldings Press | | | | | the pre- parae | | | | 00168 9-21-60 |
| Baldines Defense < | | | | | and the second second | | | | |
| Image: Source of the state of the | | | - | Haldinone | 10.62.0.0 | Panto . | - | | |
| Image: Source of the state of the | | | | | | 2. Mroftbrosts | - aw - 3 | 20 | towning in |
| R. accelinal schole 12-33-50.8 11 days S. Build days < | | | | | | | | 100 | |
| Penal shrutdeen Atal cardenal exploits 1. Cardenal exploits 2000 4 2. According to the second cardenal exploits a) bloeding # 1 asy | | 14 - | | | and the second sec | 1. arrhythman | | | and the second s |
| Penal shrutdsen stal careford sekolu 1. Careford sekolu 2001 % 208 constose post-op stal careford sekolu 1. Careford sekolu 2. read failure 00178 11260 a) bloeding # 1 av 3. Hyperkalenia 00178 11260 a) bloeding # 1 av 3. Hyperkalenia 00178 11260 b) -265 # 31 p. Riesding Counadia 766 Splenic infares 1965. LATE # 93 m. 6000 38 106 53 2 2ms 1 22-56 a) 12468 # 63, 0. requiring 113-66 # 60 m. RN 3. How methods 1 22-58 1 22-58 a) 12458 # 63, 0. requiring 113-66 # 60 m. RN 3. How methods 1 22-58 1 22-58 a) 22458 # 63, 0. reaop 255 # 49 m. RN 3 300 methods 1 22-58 a) 22458 m. m. A 80 methods 1 22-58 1 22-58 a) 12458 m. m. R 88 1 22-58 1 22-58 a) 22458 m. | | 14 | P annubul 1 ann | | | 0 | | | |
| Construint Constru | | | renal shutdown | | | | 6000 4 | 44 | G Renneth 7 |
| a) blooding e 1 bay au au <td></td> <td></td> <td>and the second sec</td> <td></td> <td>fatal carebral empolus</td> <td></td> <td></td> <td>×</td> <td></td> | | | and the second sec | | fatal carebral empolus | | | × | |
| a) blooding e 1 hy counadin 7-65 3 Splenic infares 1953 LAIX & 91 mo. 6000 35 L04 33 2 Jama 1 11 : 22:557 m 51 counadin 7-65 3 Splenic infares 1953 LAIX & 91 mo. 6000 35 L04 33 2 Jama 1 11 : 22:557 m 51 counadin 7-65 3 Splenic infares 1953 LAIX & 91 mo. 6000 35 L04 33 2 Jama 1 10 : 24.468 @ 03, 20, 28 5725 counadin 7-65 3 Splenic infares 1953 LAIX & 91 mo. 6000 35 L04 33 2 Jama 1 10 : 2300 84 55375 con 7-66; m 97* 5-265 & 18 mo. NR LAIX @ UR mo. 6000 35 L04 43 Counadin 7-66 1 < | | | commences boar-ob | | and the second second | | - | - | 00178 11-2-60 |
| b) 4-22-65 m 51 mo. Electing Counsadin 7-66 3 plante infaret 1963. LATE # 23 mo. 6000 38 108 33 2 2 mag 4 4500 8AT 16851 requiring 1-33-66 # 60 mo. NRI 1. No subcopy N 28-53-55 001 38 108 33 2 2 mag - 0) 1-24-68 8. 00. recop 2-65 # 49 mo. NR 10-26-68 001 38 108 33 2 2 mag - - 2 mag - 2 mag - 2 mag - - 2 mag 2 mag | | | | | | 3. Hypersalenia | | | |
| Aless sar 16831 requiring recop 1-33-66 % 60 mo. NR) 1. No subopy F 26-33-95 0) 1-24-68 @ 84, 90, 6300 2M 57484 90, 2-65 @ 49 mo. NR 10-26-68 00197, 00729, 01129 2300 8A 55175 500 7 - 66 j; m 97* 5-28-52 @ 18 mo. NR L475 @ 18 mo. 600 38 104 43 52121 (scalable), Alice f 10 recop for leak 11-61 @ 10 mo. 0n 7-66 j; m 97* -28-52 @ 18 mo. NR L475 @ 18 mo. 6000 38 104 43 52121 (scalable), Alice f 10 recop for leak 11-61 @ 10 mo. 0n 7-66 j; m 97* -28-52 @ 18 mo. NR D61 - 21 0 mo. 6000 38 104 43 52121 (scalable), Alice f 10 10-64 @ 45 mo. NR D61 - 21 0 mo. 00198 00198 1-12-61 10 10 mo. 10 mo. NR D61 - 21 0 mo. 00198 00198 1-12-61 10 10 mo. 10 mo. 10 mo. NR D61 - 21 0 mo. 100 00 38 104 3001712, D19-61 10 10 mo. 10 mo. 10 mo. | | | | Cormadan 7-66 | Colimbo Informer 1060 | | 200000000000 | | - |
| 0) 1-24-68 @ 84, 0. 0. resop 2-65 @ 49 mo. NR 10-25-68 00137, 00729, 01129 6300 28 57128 2300 8A 55175 500 70 1000, 10000, 1000, 1000, 1000, 1000, 1000, 1000, 1000, 1000, 1000, 1000, 1 | | | | openeter 1-00 | 1-13-66 # 60 mo. NR | the second se | 5000 35 10 | 6 133 F | |
| 6300 24 57484 Budd unk, 1-12-61 2300 84 55175 on 7-66,3 m97* 2-38-62 0 18 no. Nil L47* 8. 118 no. 600* 30 104 43 KELLY (Section), Alsee - 10 reop for leak on 7-66,3 m97* 2-38-62 0 18 no. Nil L47* 8. 118 no. 600* 30 104 43 KELLY (Section), Alsee - 11-61 0 10 so. y 2963 Subdenet Kinnahme 9 27-85-53 00398 1-19-61 10-64 0 45 no. Naltiple 27 to 8 5 no. Naltiple 27 to 8 5 no. Naltiple 21 to 7 100 to 100 100, Alsee - 10-9-61 10-64 0 45 no. Naltiple 27 to 8 5 no. Naltiple 27 to 8 5 no. Naltiple 21 to 7 100 to 100 100, Alsee - 10-64 0 45 no. Naltiple 21 to 7 100 to 100, Alsee - 9 27-85 - 53 00398 1-19-61 10-64 0 45 no. Naltiple 21 to 7 100 to 100, Alsee - 9 27-85 - 53 00398 1-39-61 10-64 0 45 no. Naltiple 21 to 7 100 to 100, Alsee - 9 27-85 - 33 00398 1-39-61 10-64 0 45 no. Naltiple 21 to 7 100, Alsee - 10 | | and the second s | 1000 000 | a formation and | | | and the second | 1 | |
| 2380 8A 55175 on 7-66,5 m97 -28-62 a 18 mo. Nil LATT & LIS mo. South and the second and the secon | | | NA | and the second | | Fund unk | 1 Start | | |
| To reop for leak or. 7-66; for 97 - 22.52 ± 18 mor. NR Left & Lift & Lift & Lift & Sourt (Section), Alice - 11-61 ± 10 po. 27.62 ± 29 mo. NR 3.27.62 ± 29 mo. NR 3.43.73 F 27.65.53 10-64 ± 45 mor. MR 10-64 ± 45 mor. MR 10-64 ± 45 mor. MR 001-73 F 27.65.53 10-64 ± 45 mor. MR 10-64 ± 45 mor. MR 10-64 ± 45 mor. MR 001 mor. MR 00198 1-29-61 10-64 ± 45 mor. MR 00198 1-29-61 10-64 ± 45 mor. MR 10-64 ± 10 mor. | | | | | | | | 100 | Multiple |
| 11-61 @ 10 mo. 27-62 @ 19 mo. NA pdf-74 P 27-85-53 11-61 @ 10 mo. 9 1963 Subdivisit Mirmature 00130 1-19-61 10-64 @ 45 mo. Nattiple 2' tr account 00130 1-19-61 10-64 @ 45 mo. Nattiple 2' tr account 00130 1-19-61 10-64 @ 45 mo. Nattiple 2' tr account 000 % 105 41 MITTLE 10-64 @ 45 mo. Statiple 2' tr account 0000 % 105 41 MITTLE Evelym 10-64 @ 45 mo. Statiple 2' tr account 1 1-29-61 1 10-64 @ 45 mo. Nattiple 2' tr account 1 1 1-29-61 10-70 0' a 3-29' WI 6000 % 105 41 MITTLE Evelym 10 10-80 1 2' transmitter 1 00000 1-26-61 10 10 1 2'' transmitter 1 00000 1-26-61 10 10 1 1 1 00000 1-26-61 | Ito | | | 10 7 16 2 00 9-70. | -28-62 # 18 mo. MR | LATE R. 118 mg. | | 4 | |
| 1001 0 20 get 10060 0 45 mo. 00196 1-19-63 10060 0 45 mo. 10060 0 45 mo. 10060 0 20 tr 10000 00 30 105 10060 0 45 mo. 10060 0 45 mo. 1000 00 30 105 10000 00 30 105 10060 0 40 mo. 10000 00 30 105 10000 00 30 105 10000 00 30 105 10060 0 40 mo. 10000 00 30 105 10000 00 30 105 10000 00 1000 10000 0 1000 0 1000 10000 00 1000 10000 0000 10000 0000 10000 0 1000 10000 0 1000 100000 10000 0000 10000 0 1000 10000 0 1000 100000 10000 10000 0 1000 10000 10000 10000 10000 0 1000 10000 10000 10000 10000 0 1000 10000 10000 10000 10000 0 1000 10000 10000 10000 10000 0 1000 10000 10000 10000 10000 0 1000 10000 10000 10000 10000 0 1000 10000 10000 10000 10000 0 1000 10000 10000 10000 10000 0 1000 10000 10000 10000 10000 0 1000 10000 10000 10000 10000 0 1000 10000 10000 10000 1 | | reop for leak | | | 8-27-62 @ 19 mo. NR | 15-11 V Calve was | deput | 1 | 27-85-53 |
| all. big highered. Haldinge 02 a. 3-29-07 Haldinge 1. Stap. switchenda 2. Endoarditis of 00000 1-26-61 3. Brain & splenic infarets | | TT-OT & TA MA. | | | 2 2963 | | | | 20198 1-19-61 |
| BlR. Dag Hushkuid. Bladinace Haldinace OP a 3.24-V/1 6000 30 105 41 Haldinace 1. Staff explored a 8. 28-68-94 28-68-94 2. Endocarditis of 00200 1-26-61 9. Bridge angle 3. Brain & splenic inforets | | | | | | 10.2" to assault | | _ | |
| Haldingee de la State de la Ministrie de la Mi | | | | | | by Husband. | 1 | | |
| 1. Staph regitionia 7. 28-00-76 2. Endocarditis of 00200 groathetis margin 3. Brain & splenic informatis | | | | Waldingen | | 0P 0 3-24-11 | 6000 30 | | |
| 2. Mainedernitis on prosthetic margin 3. Brain & splenic ipfarots | | | | THE CARTERY | | 1. Staph cepticent | | | and in case of the second se |
| 3. Brain & splenic infarots | | | | | | 2. Endocarditis of | E | - | 00200 1-26-61 |
| 3. Brain & splenic infarots | | Section and the | | | and the second second | prosthetic margin | - | - | |
| 4. acute mycoarditis | | | | | | 3. Brain & spleni | e infarcts | | |

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

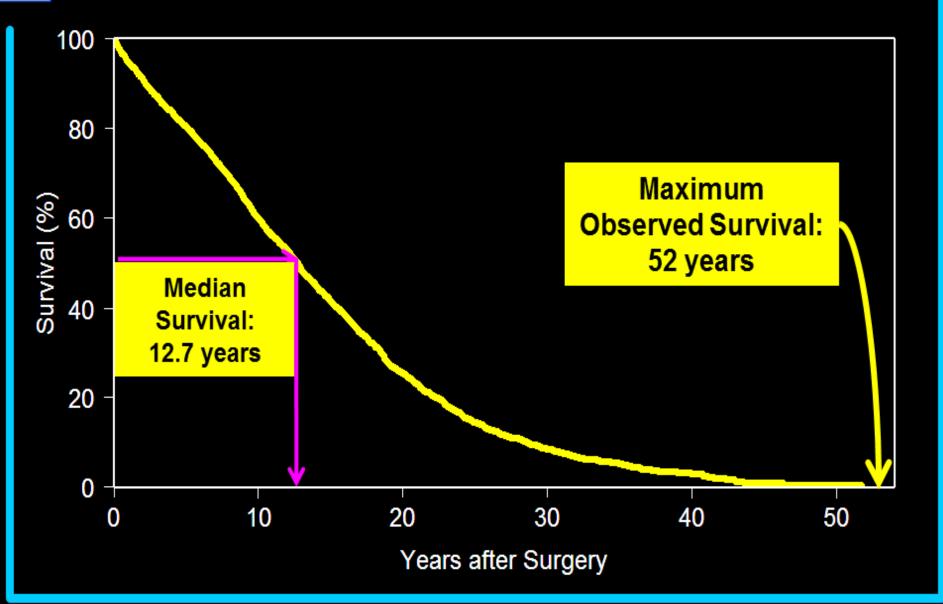
Tony Furnary, Mansen Wang, Chiu, Shih Ting, Gary Grunkemeier, Albert Starr

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.*



1Albert Starr 1First successful heart valve -1960 2Lifetime follow-up service

2OPC 1FDA Workshop Bethesda – 1993 2Heart Valve Guidance - 1994

3ISO OPC update 1ISO meeting Portland - 2012 2Publication - 2014

CPC 1992

Literature Review Inclusion Criteria

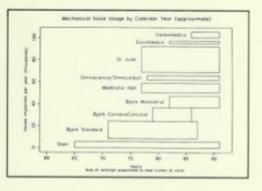
- published after 1984
- long term results
- written in English
- stratified by position
- most recent data
- statistically sound

Volume XVII Number 6 June 1992

Current Problems in Cardiology[®]

Prosthetic Heart Valve Performance: Long-Term Follow-Up

Gary L. Grunkemeier, Ph.D. Albert Starr, M.D., F.A.C.S. Shahbudin H. Rahimtoola, M.B., F.R.C.P.



Editor-in-Chief: Robert A. O'Rourke Associate Editor: David McCall Editorial Board: George A. Beller, Shahbudin H. Rahimtoola, Robert C. Schlant, Pravin M. Shah

CPC 1992

Literature Review Inclusion Criteria

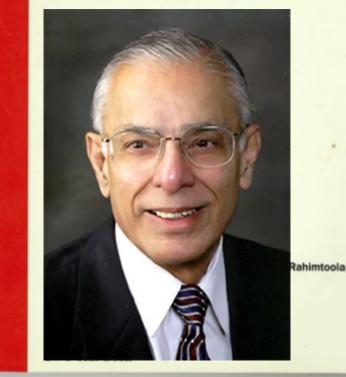
- published after 1984
- long term results
- written in English
- stratified by position
- most recent data
- statistically sound

Volume XVII Number 6 June 1992

Current Problems in Cardiology[®]

Prosthetic Heart Valve Performance: Long-Term Follow-Up

Gary L. Grunkemeier, Ph.D. Albert Starr, M.D., F.A.C.S. Shahbudin H. Rahimtoola, M.B., F.R.C.P.



CPC 1992

Literature Review Complications

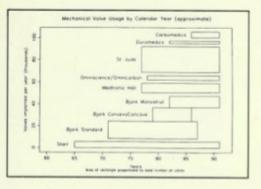
- Embolism
- Bleeding
- Thrombosis
- Leak
- Infection
- SVD

Volume XVII Number 6 June 1992

Current Problems in Cardiology[®]

Prosthetic Heart Valve Performance: Long-Term Follow-Up

Gary L. Grunkemeier, Ph.D. Albert Starr, M.D., F.A.C.S. Shahbudin H. Rahimtoola, M.B., F.R.C.P.

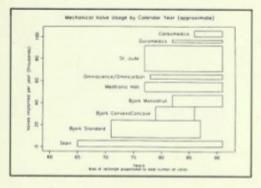


Editor-in-Chief: Robert A. O'Rourke Associate Editor: David McCall Editorial Board: George A. Beller, Shahbudin H. Rahimtoola, Robert C. Schlant, Pravin M. Shah Volume XVII Number 6 June 1992

Current Problems in Cardiology[•]

Prosthetic Heart Valve Performance: Long-Term Follow-Up

Gary L. Grunkemeier, Ph.D. Albert Starr, M.D., F.A.C.S. Shahbudin H. Rahimtoola, M.B., F.R.C.P.



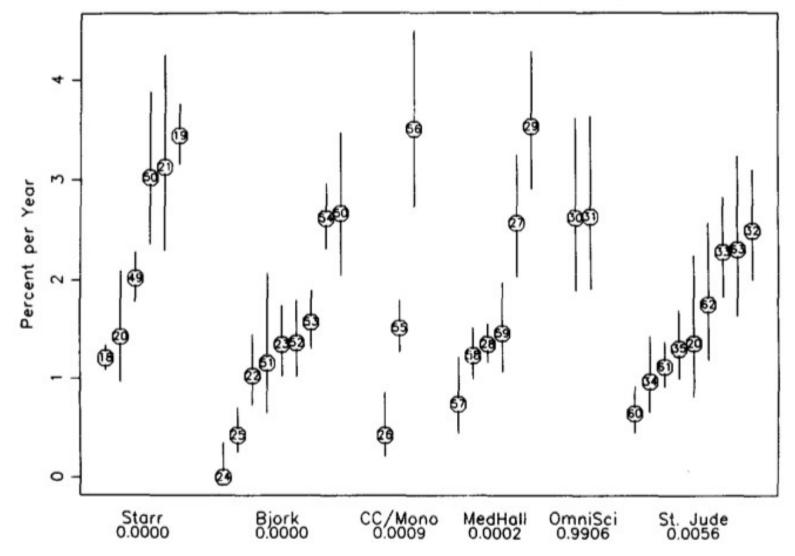
Editor-in-Chief: Robert A. O'Rourke Associate Editor: David McCall Editorial Board: George A. Beller, Shahbudin H. Rahimtoola, Robert C. Schlant, Pravin M. Shah

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

Embolism Rates for Mechanical Aortic Valves with 70% confidence intervals and comparison p-values



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



Editorial Issues concerning the clinical evaluation of new prosthetic values

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.



Editorial Issues concerning the clinical evaluation of new prosthetic values

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. J THORAC CARDIOVASC SURG 91:460-466, 1986

Editorial Issues concerning the clinical evaluation of new prosthetic values

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.

"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." J THORAC CARDIOVASC SURG 91:460-466, 1986

Editorial Issues concerning the clinical evaluation of new prosthetic values

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.

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

Health Industry Manufacturers Association (HIMA)

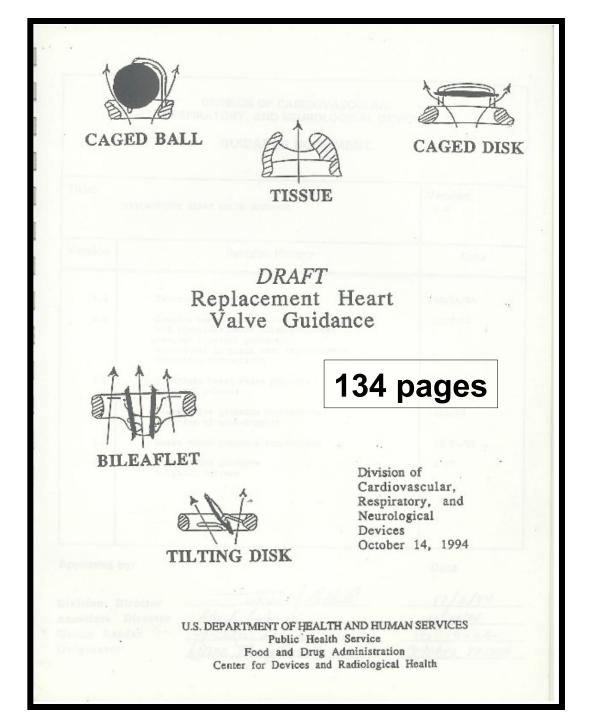
- Convened a heart valve task force
- Advocated the method of Gersh et al.
- Introduced the term:

"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



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

Diane M. Johnson, Wolf Sapirstein

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

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 ... literaturebased 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 37 |

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

The Story of OPC

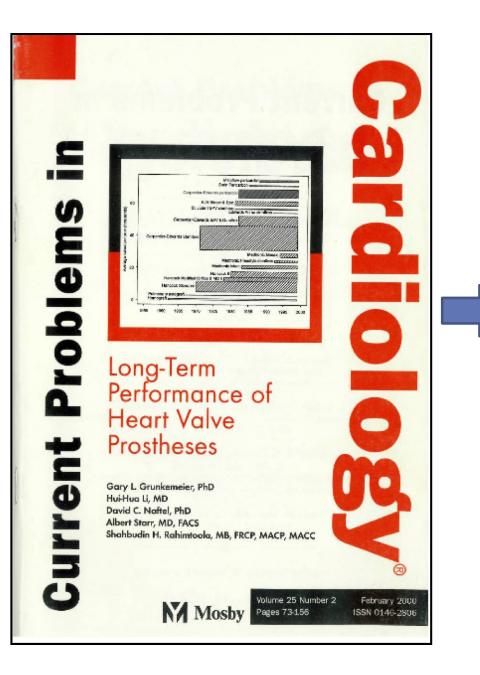
- 1. Albert Starr
 - First successful heart valve -1960
 - Lifetime follow-up service

2. OPC

- FDA Workshop Bethesda 1993
- Heart Valve Guidance 1994

3. ISO OPC update

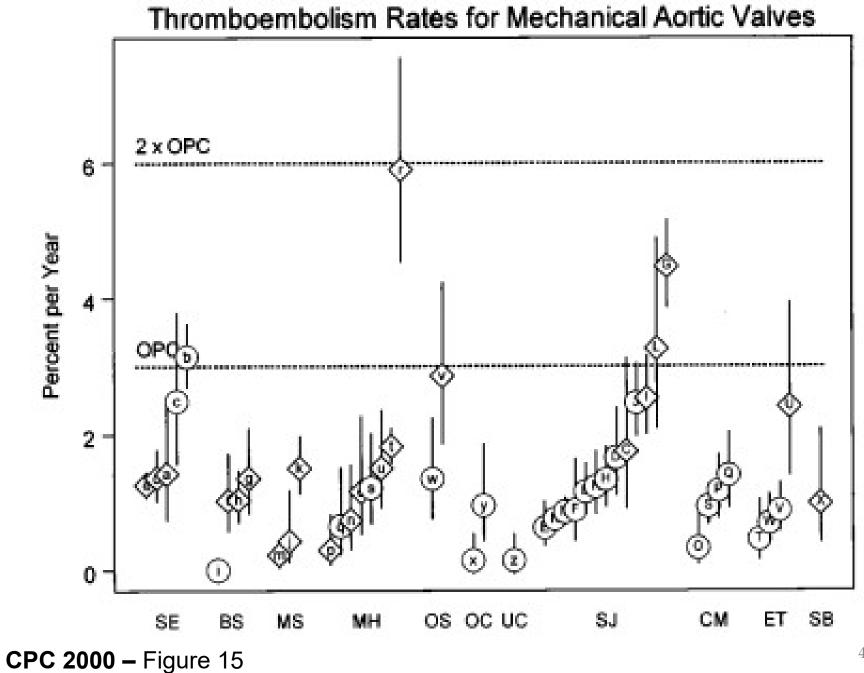
- ISO meeting Portland 2012
- Publication 2014



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



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

| Adverse Event | Mechanical Valve | | | Bioprosthetic Valve | | |
|-------------------------|------------------|--------------|--------|---------------------|--------------|--------|
| | Original OPC | Proposed New | | | Proposed New | |
| | | 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 |

Table 1. Original and Proposed New Objective Performance Criteria

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 value 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) © 2014 by The Society of Thoracic Surgeons

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) © 2014 by The Society of Thoracic Surgeons





The Story of OPC



Thank You!

OHSU



