

FDA Analysis of Cardiac Valvular Dysfunction with Use of Appetite Suppressants

Data from Case Reports

Summary of Case Reports (I)

Single reports received through August 29, 1997

Fenfluramine + phentermine	85
Fenfluramine alone	3
Dexfenfluramine alone	9
Fen + phen/Dexfen + phen	4

(includes 24 cases from Mayo article)



Summary of Case Reports (II)

Analysis of 61 single reports with fenfluramine-phentermine use received through August 29, 1997

	<u>Mean</u>	<u>Range</u>
% Female	97	
Age	44.9	22-67
Weight (lb)	200	129-350
Fen dose (mg/d)	56	10-120
Duration (mos)	11.9	2-39

(does not include 24 cases from Mayo article)



Echocardiographic “Research” Case Definition for Valvulopathy with Appetite Suppressants

- Aortic Regurgitation (AR)
 \geq Mild

and/or

- Mitral Regurgitation (MR)
 \geq Moderate



Summary of CARDIA Study*

- Random selection
- Healthy adults
- Age 23-35
- 2-D and doppler echocardiography
- N = 4532
- AR = 1.2%
- MR = 1.0%

*Circulation 90 (4, part 2): i-282, 1994



Summary of Case Reports (III)

Analysis of 38 reports with fenfluramine-phentermine use meeting FDA case definition

	<u>Number</u>	<u>Percentage</u>
Aortic	28	74
Mitral	27	71
A + M	18	47
Surgery	12	32
Death	2	5
<u>Based on 33 cases with data</u>		
CHF/SOB	20	61
New murmur	8	24
No symptoms/signs	5	15

(does not include 24 cases from Mayo article)



Data from Echocardiographic Screening of Asymptomatic Patients

Overview of Surveys with Fenfluramine-Phentermine

	<u>n</u>	<u>% F</u>	<u>Median Age</u>	<u>Mean Initial Wgt (lb)</u>	<u>Fen Dose (mg/d)</u>	<u>Treatment Duration (mos)</u>	
Bowen, FL	122	89	48.5	202.3	20	11	Asymptomatic. Convenience sample.
Khan, MN	47				60	12-24	NIH protocol. Random ascertainment; full ascertainment planned. BMI-matched controls.
Glicklich, WI	50	94	47.8		60	> 12	Asymptomatic. Convenience sample.
Rasmussen, IN	31	77	47.0	234		6	Asymptomatic. Response to community hospital screening program.
Wadden, PA	21	100	48.0	222	20-60	24	Asymptomatic. Full ascertainment of patients in long-term study.



Counts of Subjects and Cases from Echo-Prevalence Surveys

<u>Fen-phen</u>	Number with <u>Echocardiograms</u>	Cases with <u>Valvulopathy</u>	Aortic Regurgitation <u>(at least mild)</u>	Mitral Regurgitation <u>(at least moderate)</u>
Bowen	122	35	29	7
Khan	47	18	16	8
Glicklich	50	15	14	3
Rasmussen	31	11	11	1
Wadden	21	7	6	2
Overall	271	86	76	21
<u>Dexfen+/-phen</u>				
Khan	20	6	4	2

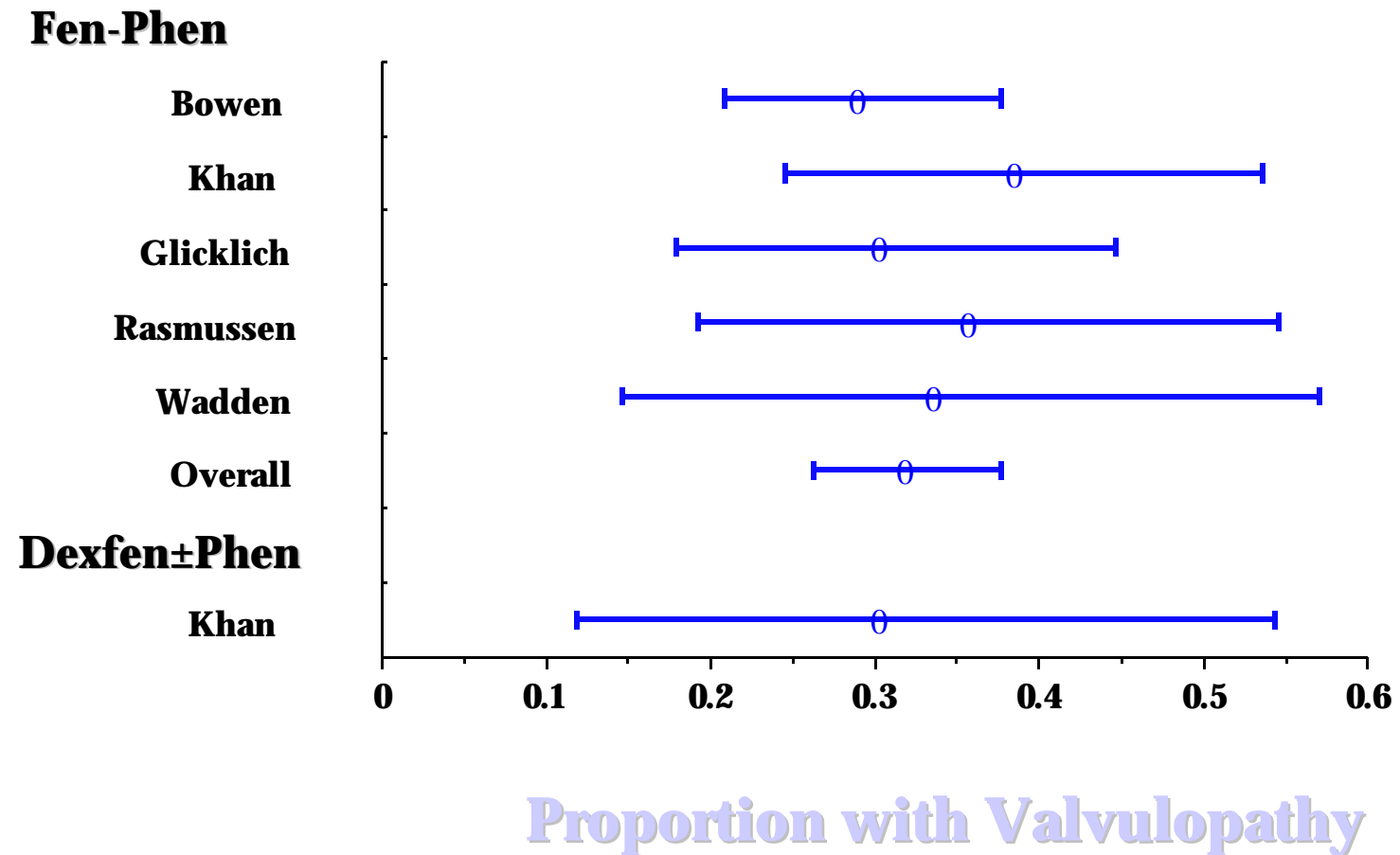


Absolute Risk of Valvulopathy from Echo-Prevalence Surveys

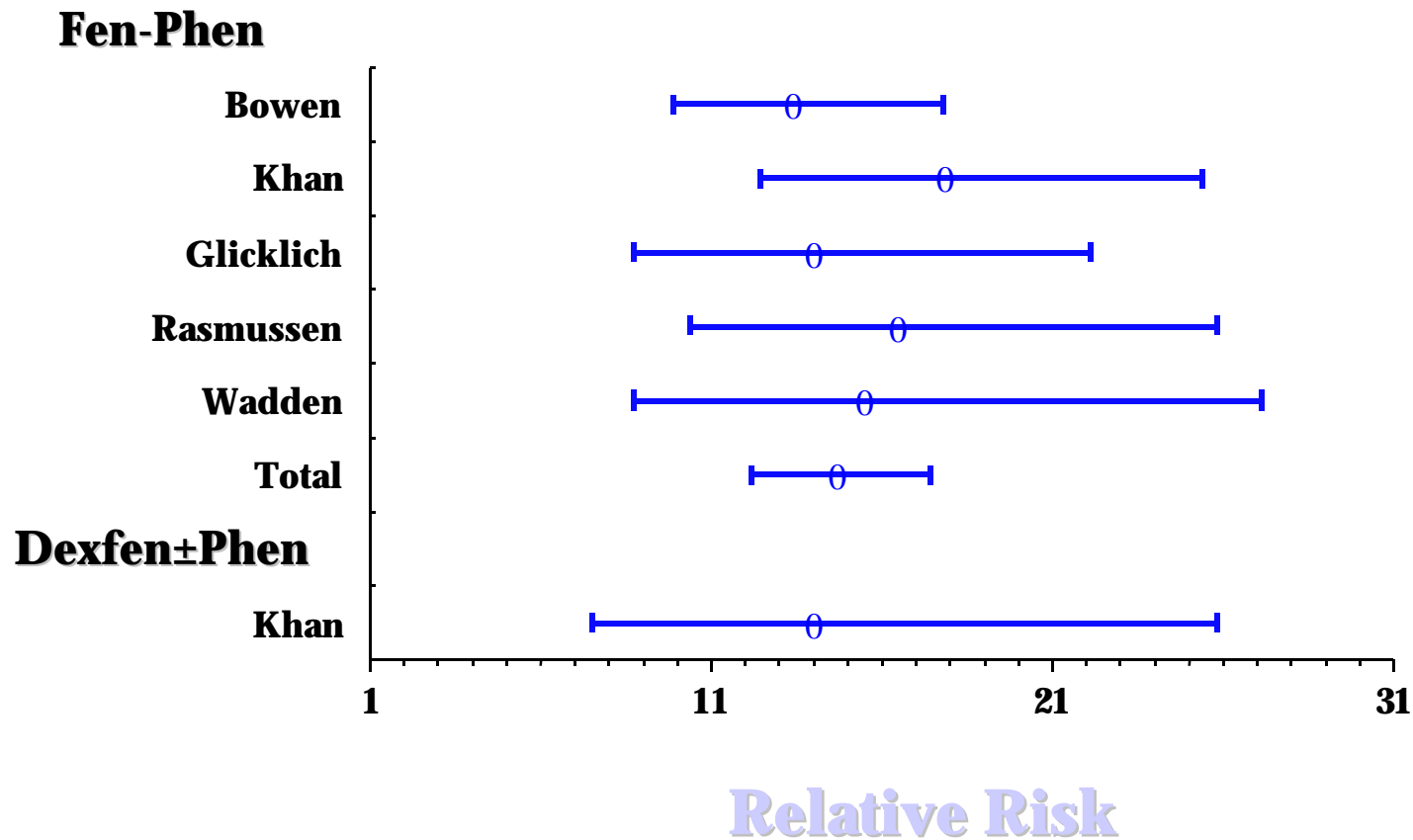
<u>Fen-phen</u>	Number with <u>Echocardiograms</u>	<u>Mean</u>	<u>95% CI</u>
Bowen	122	.287	.208 - .376
Khan	47	.383	.245 - .536
Glicklich	50	.300	.179-.446
Rasmussen	31	.354	.192-.546
Wadden	21	.333	.146-.570
Overall	271	.317	.262-.376
<u>Dexfen+ /-phen</u>			
Khan	20	.300	.119 - .543



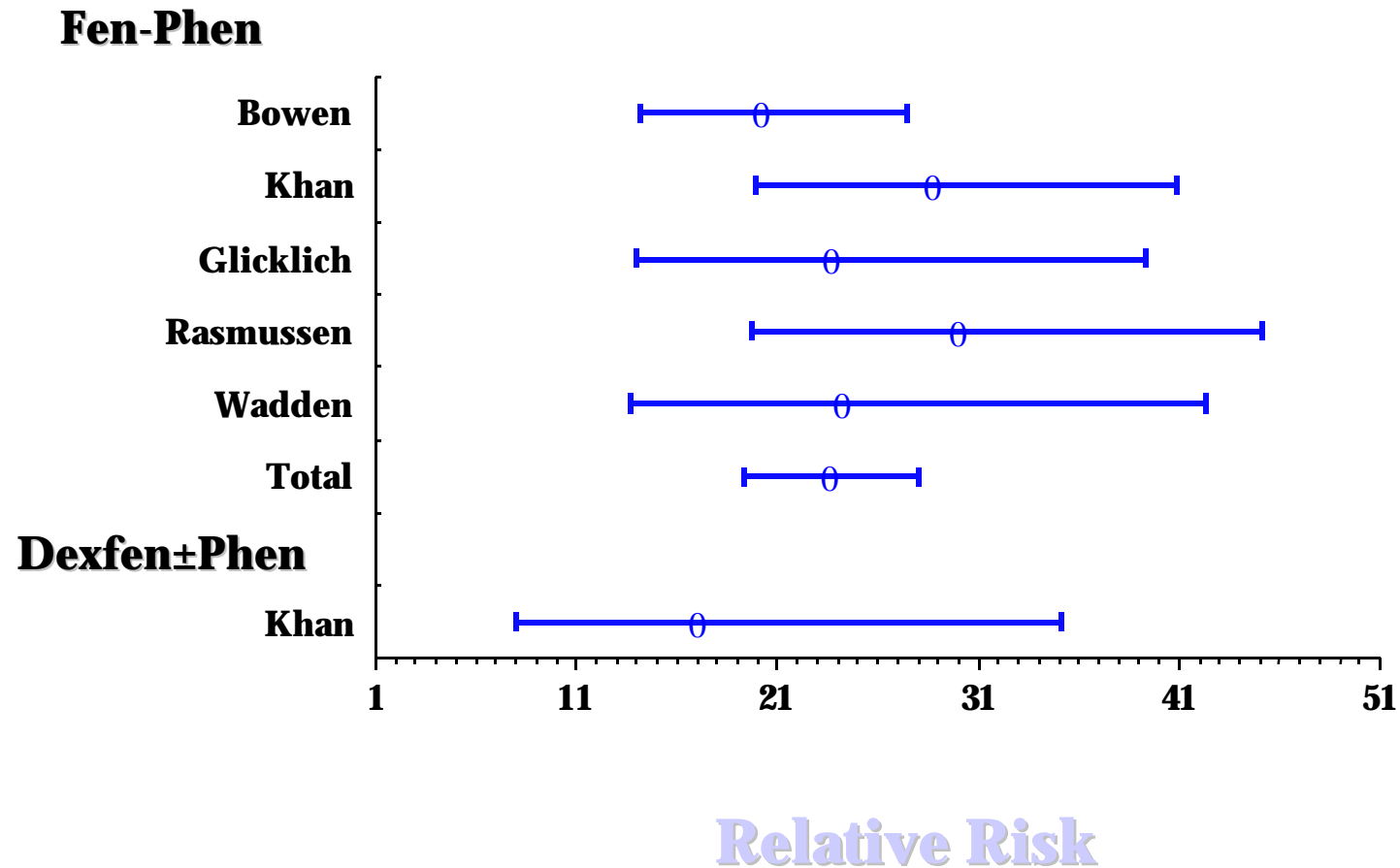
Absolute Risk of Valvulopathy from Echo-Based Prevalence Surveys



Relative Risk of Valvulopathy from Echo-Based Prevalence Surveys; CARDIA as Reference



Relative Risk of Aortic Valvulopathy from Echo-Based Prevalence Surveys; CARDIA as Reference



Epidemiologic Study of Valvulopathy with Fenfluramine Use in an HMO

- Cohort: 793 subjects on fen-phen
142 subjects on fenfluramine
- Echo Results*:
Pre-treatment: 0/25 cases
Post-treatment: 4/9 cases p = .003

*Pre- and post-treatment echocardiograms were in different subjects from the same cohort



Summary of Echo Data on Obese Subjects - Obtained Prior to Suppressant Therapy

	<u>Number of subjects with Echocardiograms</u>	<u>Number of cases with valvulopathy</u>
HMO Study	25	0
Khan	8	0
Khan (controls)	5	0
Glicklich	3	0
Rasmussen	2	0
Bowen	5*	0
Total	48	0

* 3 echos were obtained at 1wk, and 1 at 3wks after initiating therapy

