

# **Survival: Reality, Hopes and Pitfalls**

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# Survival

- **Probability of survival from a specific starting time to a specific event**
- **Survival does not just mean death, but it can be time to any event**

# Starting Times

- **Need to determine best starting time**
  - Time of onset of first symptom
  - Time of onset of first non-Raynaud's symptom
  - Time of diagnosis of SSc
  - Time of first visit
  - Time of diagnosis of a specific event (survival from renal crisis)
  - Time from the first DLCO <50% predicted

# Events

- **‘Survival’ is time to an event**
  - **Death**
  - **Time to Renal Crisis**
  - **Time to an FVC of 60% predicted**
  - **Time to an improved skin score by 50%**
  - **Time to anything**

# Survival Analysis Advantages

- **Could compare mean times to event between groups by t-test**
  - Ignores censoring
- **Could compare proportion of events using logistic regression.**
  - Ignores time
- **Survival analysis accounts for censored observations and time**

# Censoring Observations

**Censoring – Incomplete observations of time of event.**

- **Right censoring - no event recorded during time**
  - **Missing data, inadequate data collection**
  - **Lost to follow up, didn't come to clinic, moved away, too sick to come**
  - **Death from an independent, non scleroderma related cause**

# Censoring Observations

- **Left truncation – events occurring before starting time**
  - Long disease duration so events occurred before starting time
  - Diffuse disease deaths are early so if disease duration is long at starting time many may have died before starting.

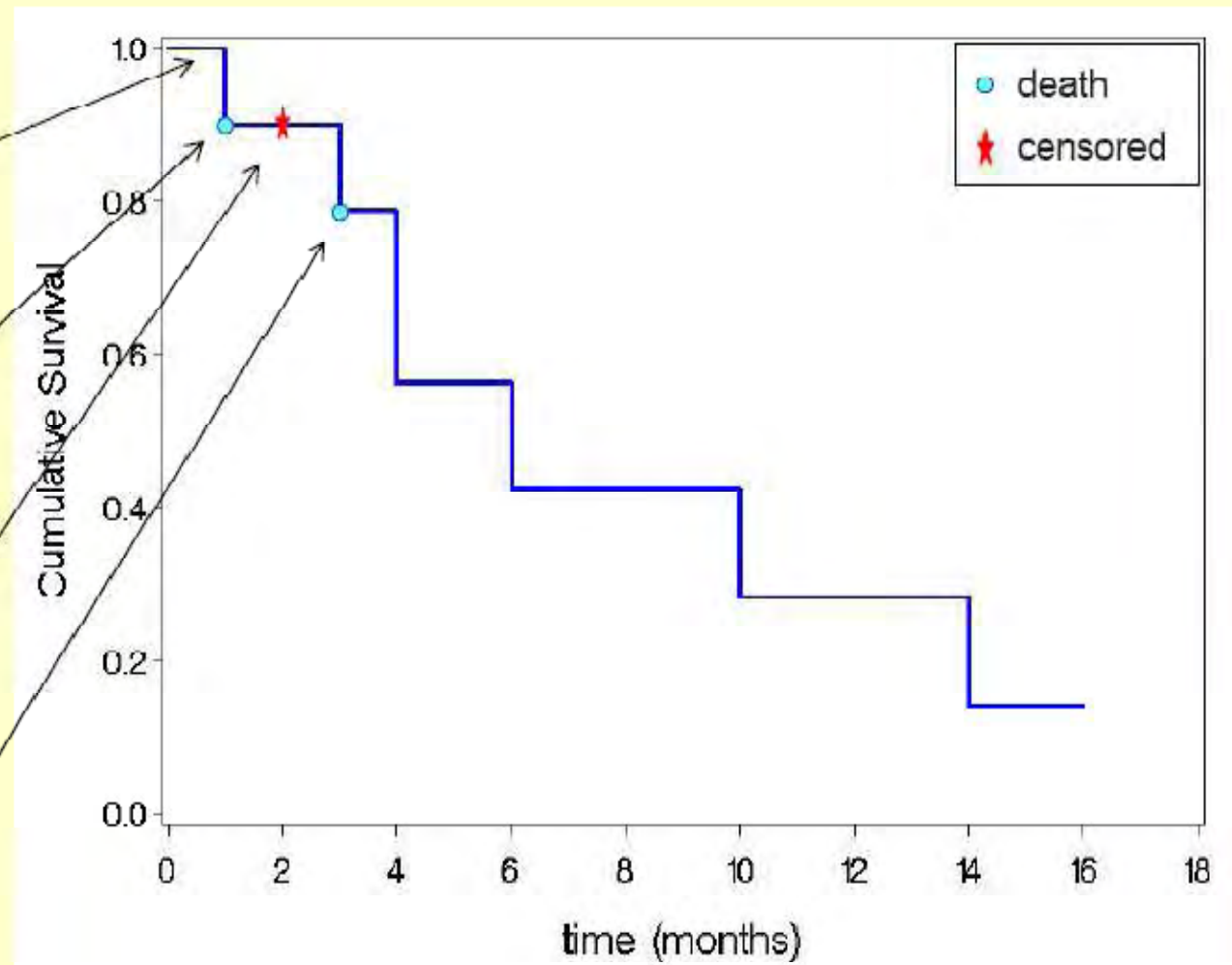
# Kaplan - Meier Survival Curve

N° subjects **at risk** for death = 10  
Fraction surviving before 1 month =  $10/10 \Rightarrow 100\%$

Subject dies at 1 month  
**Hazard** =  $1/10$   
**Fraction surviving** =  $9/10$

Subject drops out of the study at 2 months.  
Subjects at risk for death = 8

Subject dies at 3 months  
**Hazard** =  $1/8$   
**Fraction surviving** =  $7/8$



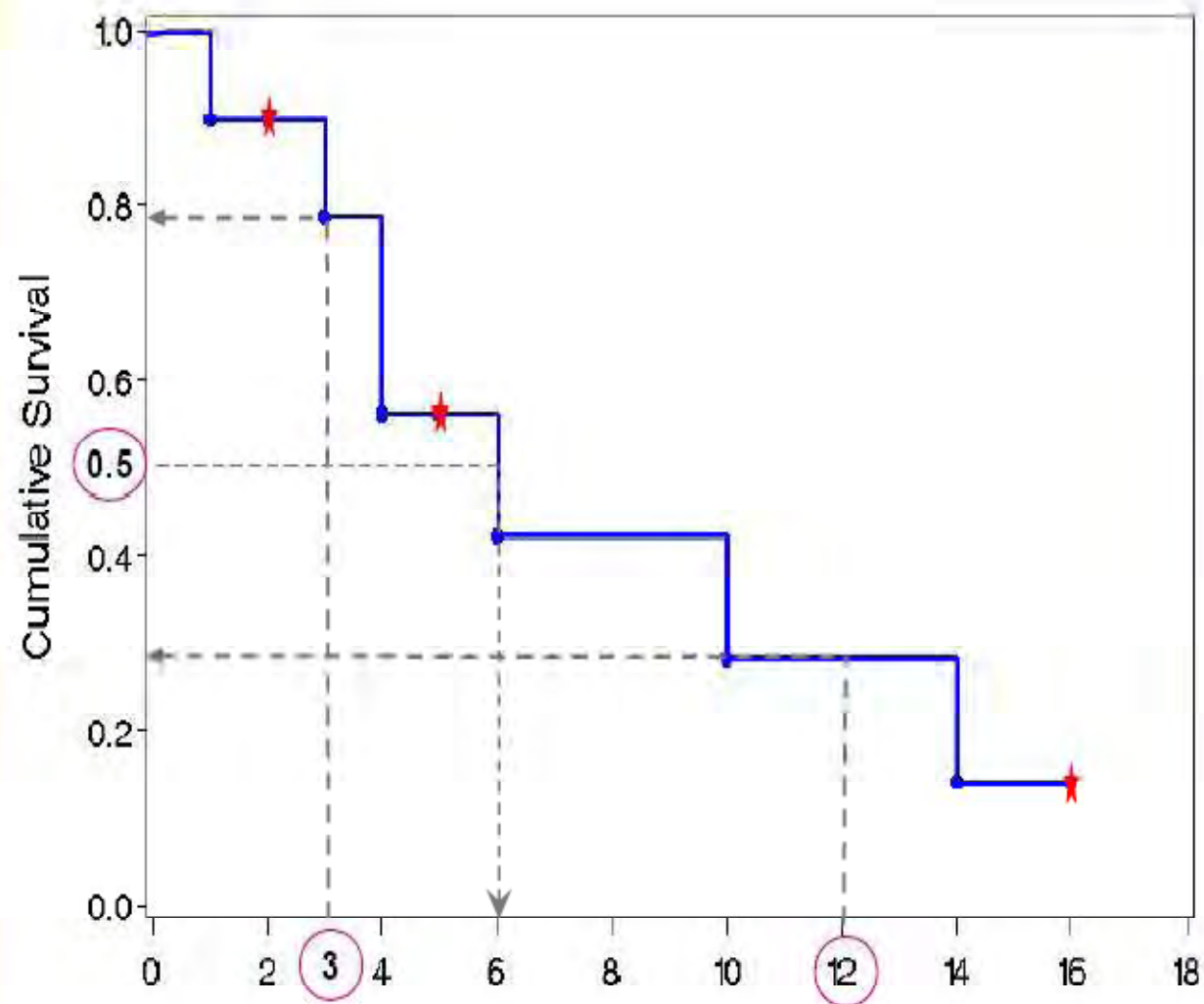
# Kaplan - Meier Survival probability

Survival probability  
at 3 months

$$= 9/10 * 7/8 = 0.788$$

1-year  
survival rate  $\approx 28\%$

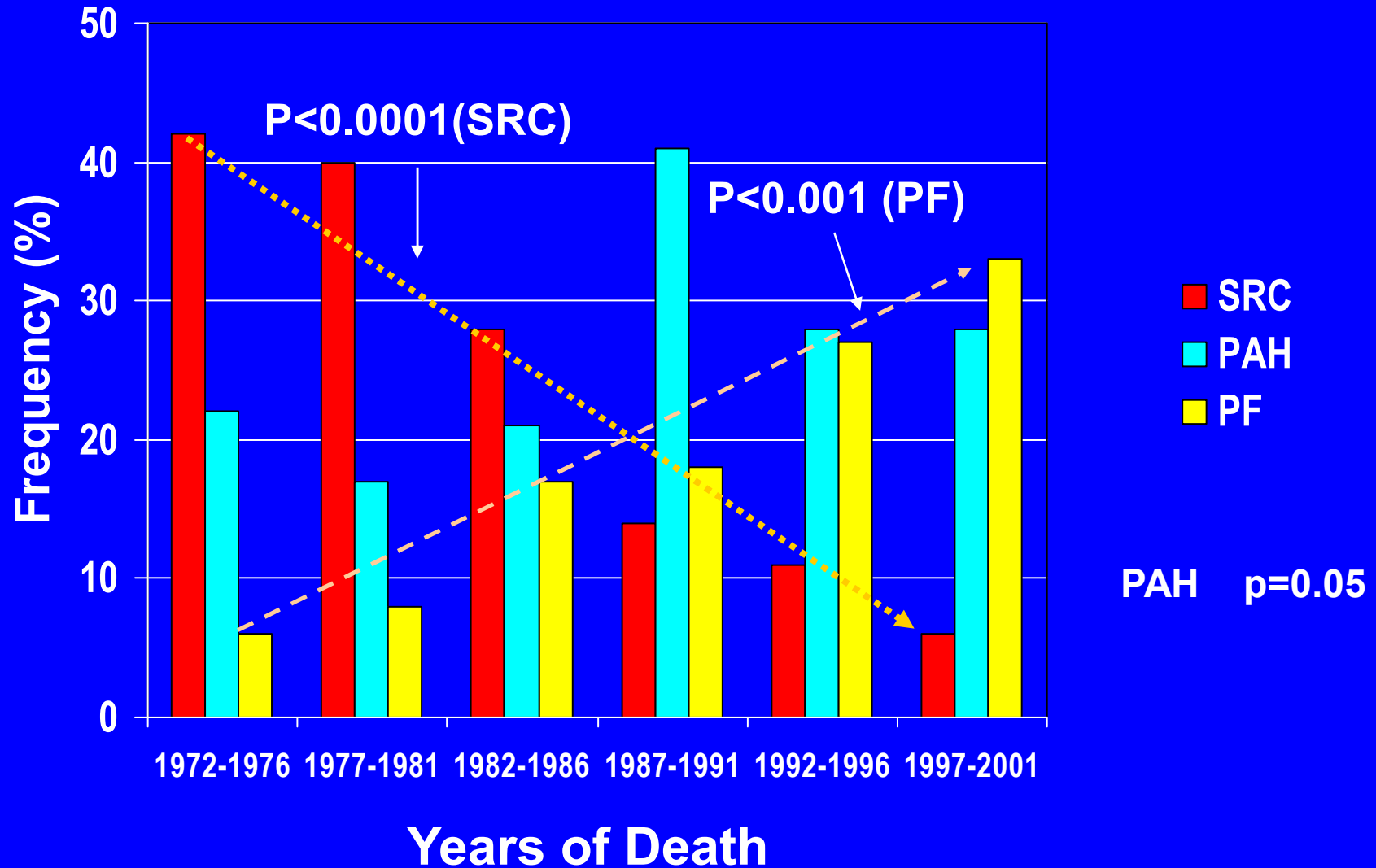
**Median survival  
time = 6 months**



# Causes of Death

- **Death – easy to determine**
- **Cause of death – much more difficult**
  - **Can't use death certificates or hospital discharge summaries**
  - **Need to review hospital records, doctors records and discuss event with family**
  - **Need to define causes of death before analysis, Primary vs secondary, etc.**
  - **Need to have a small number of people reviewing records and determining cause**

# CHANGES IN SCLERODERMA DEATHS OVER TIME



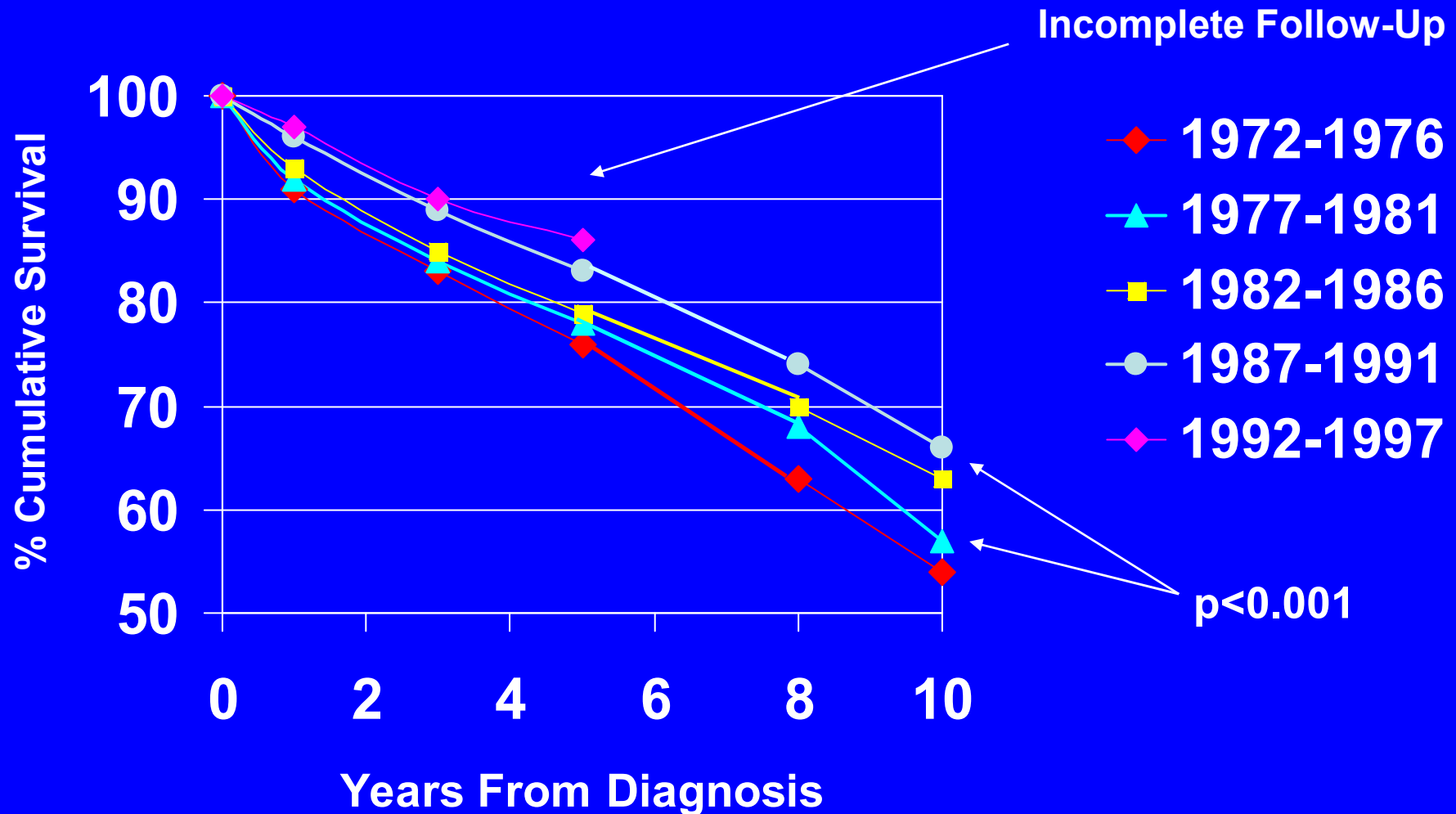
# PATIENT FEATURES AT FIRST VISIT IN TIME PERIODS

	<u>1972-76</u>	<u>1977-81</u>	<u>1982-86</u>	<u>1987-91</u>	<u>1992-96 *</u>
<u>Number</u>	221	323	392	534	655
Sex (%male)	21	20	15	21	19
Age (diagnosis)	46	48	47	46	47
<u>SSc subtype</u>					
(% diffuse SSc)	40	47	49	44	47
<u>Disease duration (years)</u>					
First visit	8.2	6.7	7.0	7.3	6.9
Last study visit	15.1	14.7	14.7	14.2	11.1

- NO significant demographic differences across times

\*incomplete followup

# Survival in Systemic Sclerosis over the last 30 years



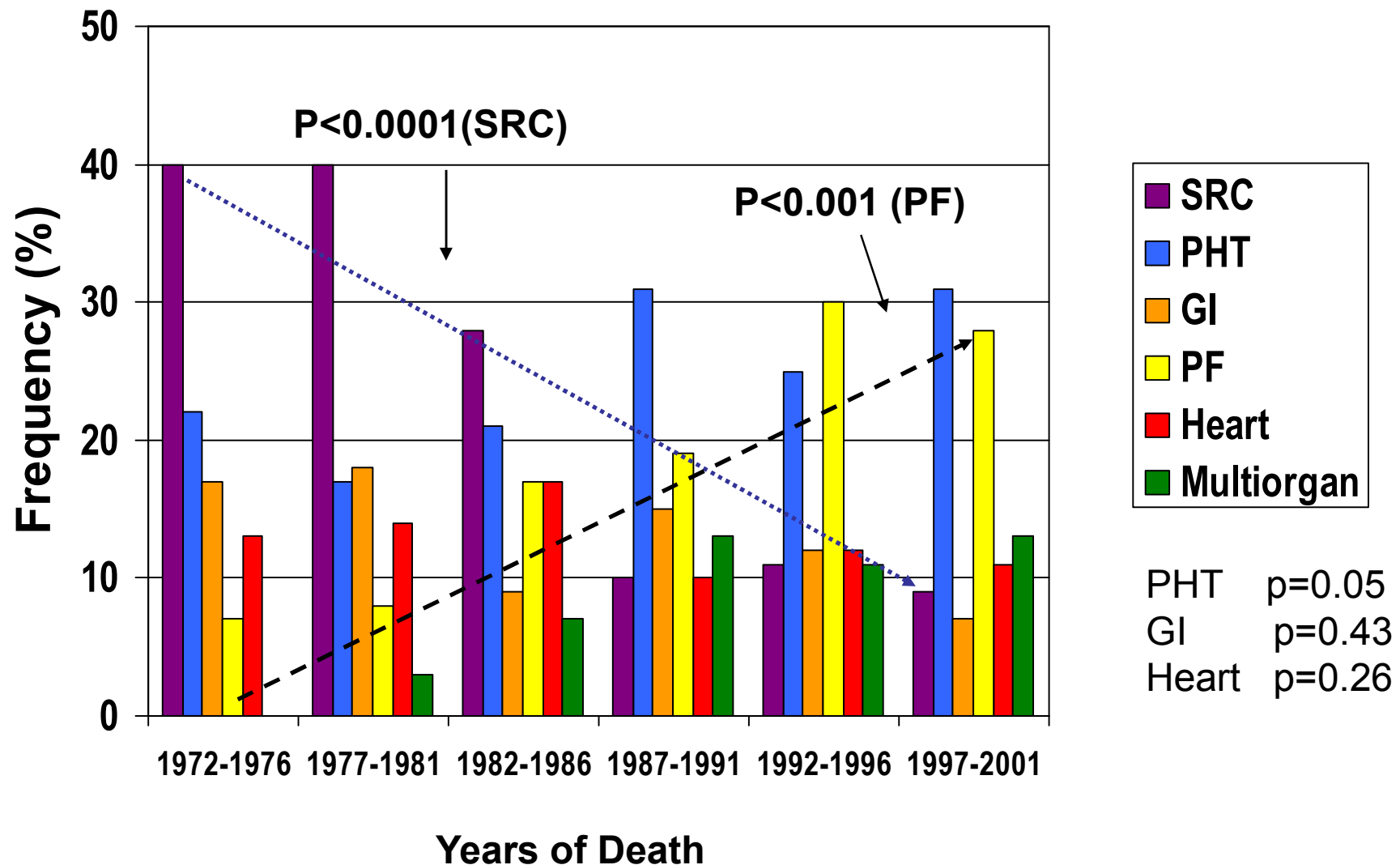
# Demographics of SSc patients at onset of these times periods

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	<u>1972-76</u>	<u>1977-81</u>	<u>1982-86</u>	<u>1987-91</u>	<u>1992-96</u>	<u>1997-01*</u>
<b>Number</b>	<b>221</b>	<b>493</b>	<b>768</b>	<b>1153</b>	<b>1460</b>	<b>1508</b>
<b>Deaths (%)</b>	<b>19</b>	<b>21</b>	<b>19</b>	<b>18</b>	<b>20</b>	<b>24</b>
<b>Sex (%M)</b>	<b>21</b>	<b>20</b>	<b>18</b>	<b>18</b>	<b>19</b>	<b>17</b>
<b>% Diffuse</b>	<b>41</b>	<b>47</b>	<b>49</b>	<b>47</b>	<b>49</b>	<b>45</b>
<b>Age (yrs)</b>	<b>48</b>	<b>50</b>	<b>51</b>	<b>51</b>	<b>51</b>	<b>55</b>
<b>Duration</b>	<b>8.4</b>	<b>8.4</b>	<b>9.2</b>	<b>10.6</b>	<b>11.2</b>	<b>14</b>
<b>Dead-SSc</b>	<b>70%</b>	<b>68%</b>	<b>58%</b>	<b>53%</b>	<b>57%</b>	<b>50%</b>

\* Time period without new patients, so older, longer disease, more deaths, excluded from ANOVA analysis.

# CHANGES IN CAUSES OF SSc RELATED DEATHS OVER TIME



# Lung Disease as Cause of Death in Scleroderma

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<u>Cause of death</u>	<u>All SSc</u>
All SSc causes	687
PAH (% SSc causes)	25%
Pulmonary Fibrosis	23%
Kidney	14%
Heart	14%
GI	11%

# Changes in non-SSc causes of Death in SSc patients

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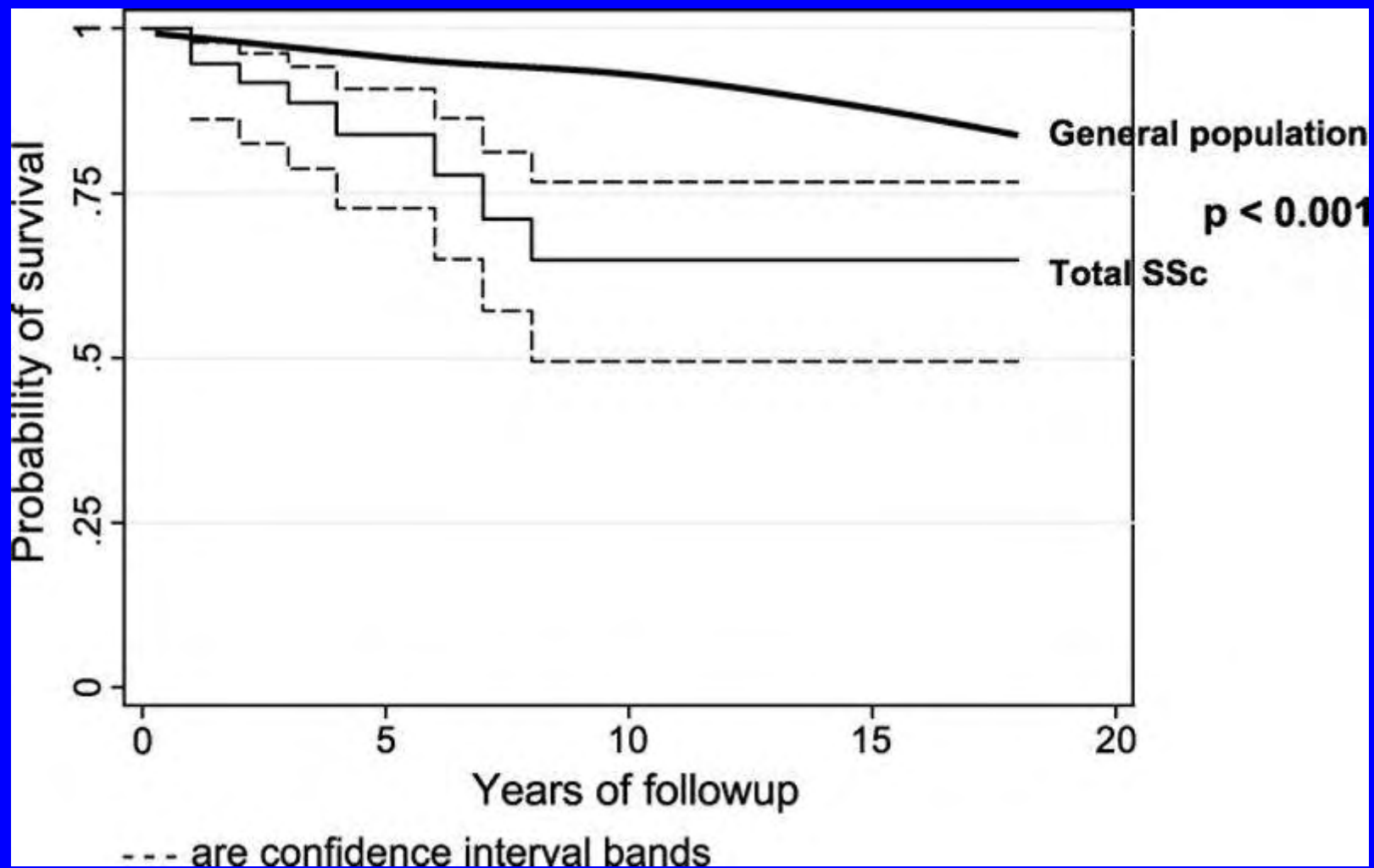
	<u>1972-76</u>	<u>1977-81</u>	<u>1982-86</u>	<u>1987-91</u>	<u>1992-96</u>	<u>1997-01*</u>
Number	42	105	148	211	289	364
Cancer (%)	10%	10	10	15	11	7
ASD	3	4	8	8	6	2
Infection	2	3	6	7	9	5
Non-CTD	7	8	12	10	10	12
Unknown	9	7	6	7	8	10
Pending	0	0	0	1	1	13

\* Time period without new patients, so older, longer disease, more deaths, excluded from ANOVA analysis.

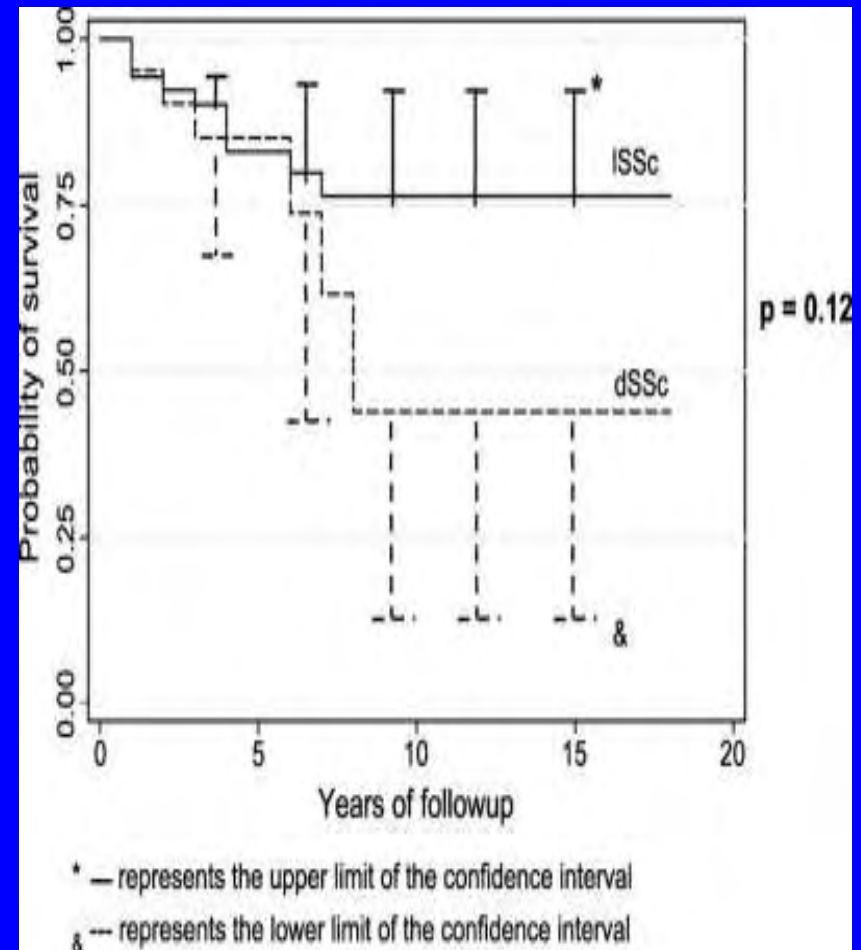
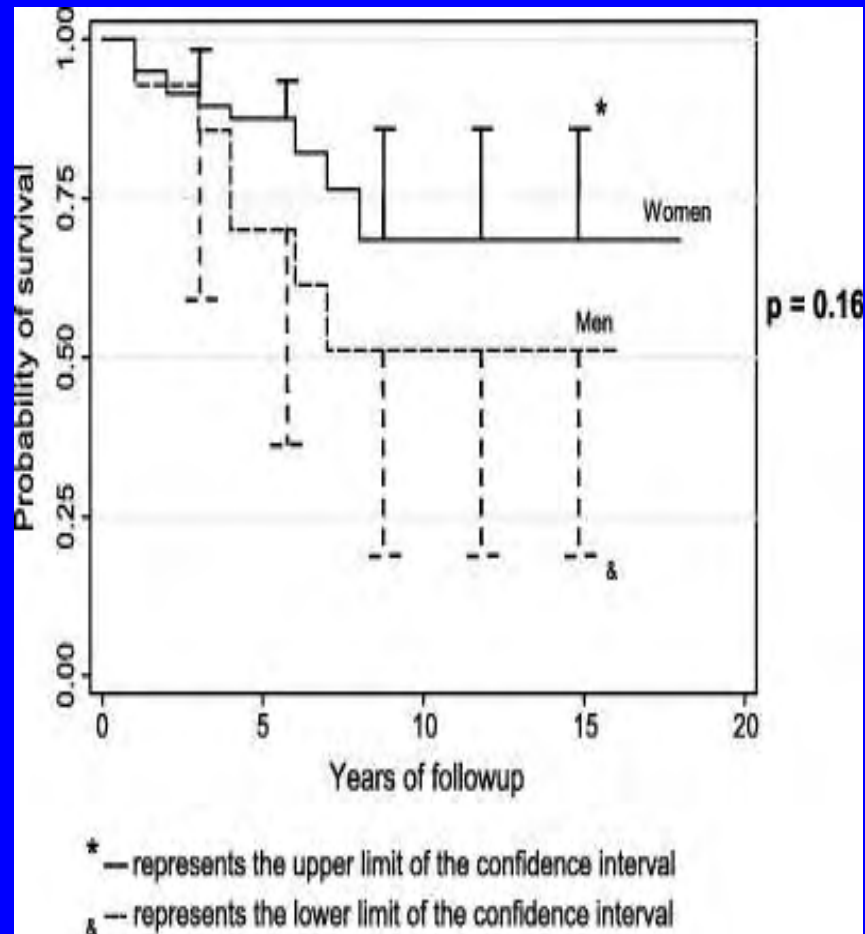
# Survival in Spain

- **78 patients**
- **80% female, Age at diagnosis 59.9 years**
- **70% limited**
- **Disease duration at time of diagnosis 8.3 years**
- **Mean disease follow-up 6.6 years**

# Survival from First Visit



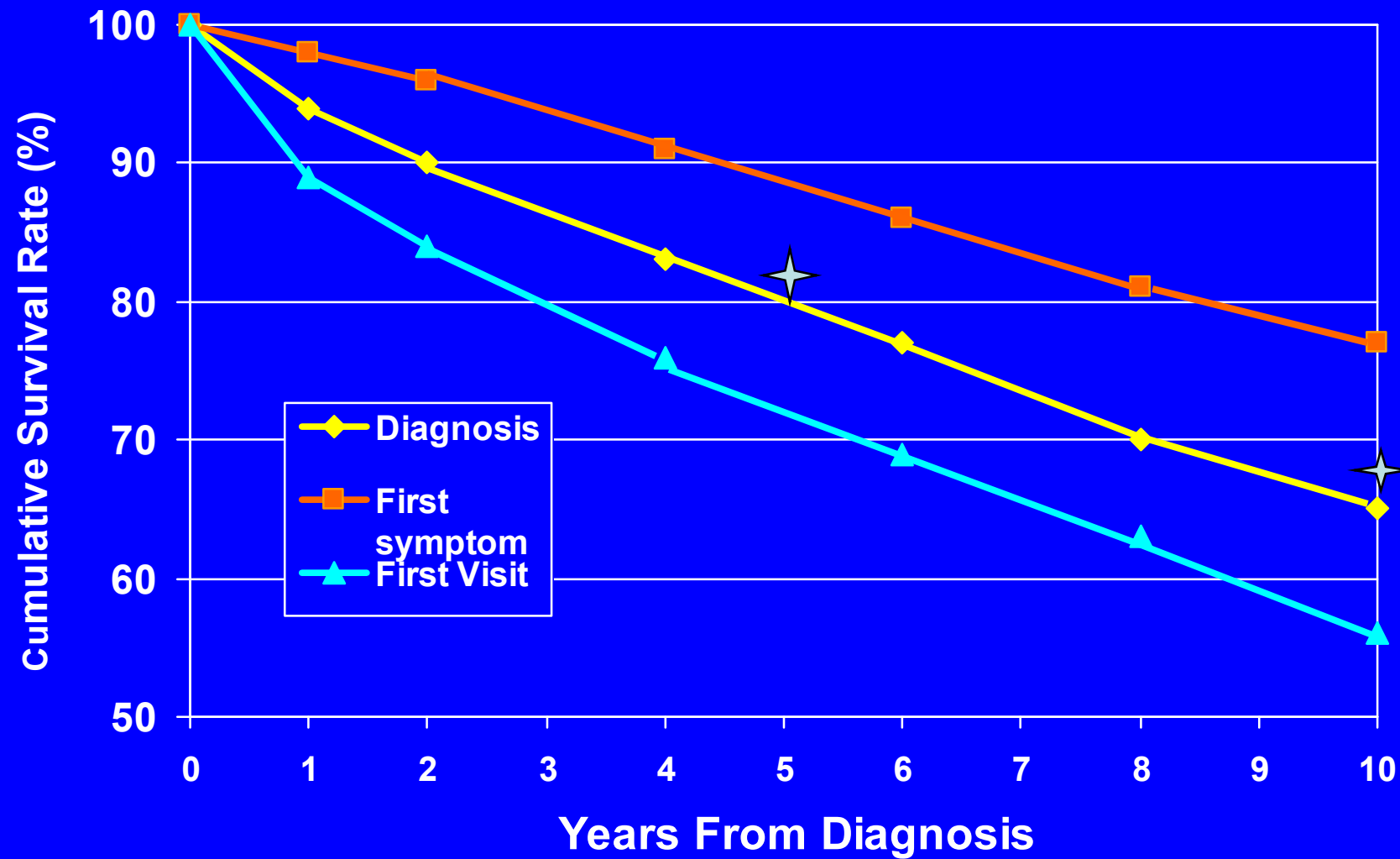
# Survival in Sexes and Subsets



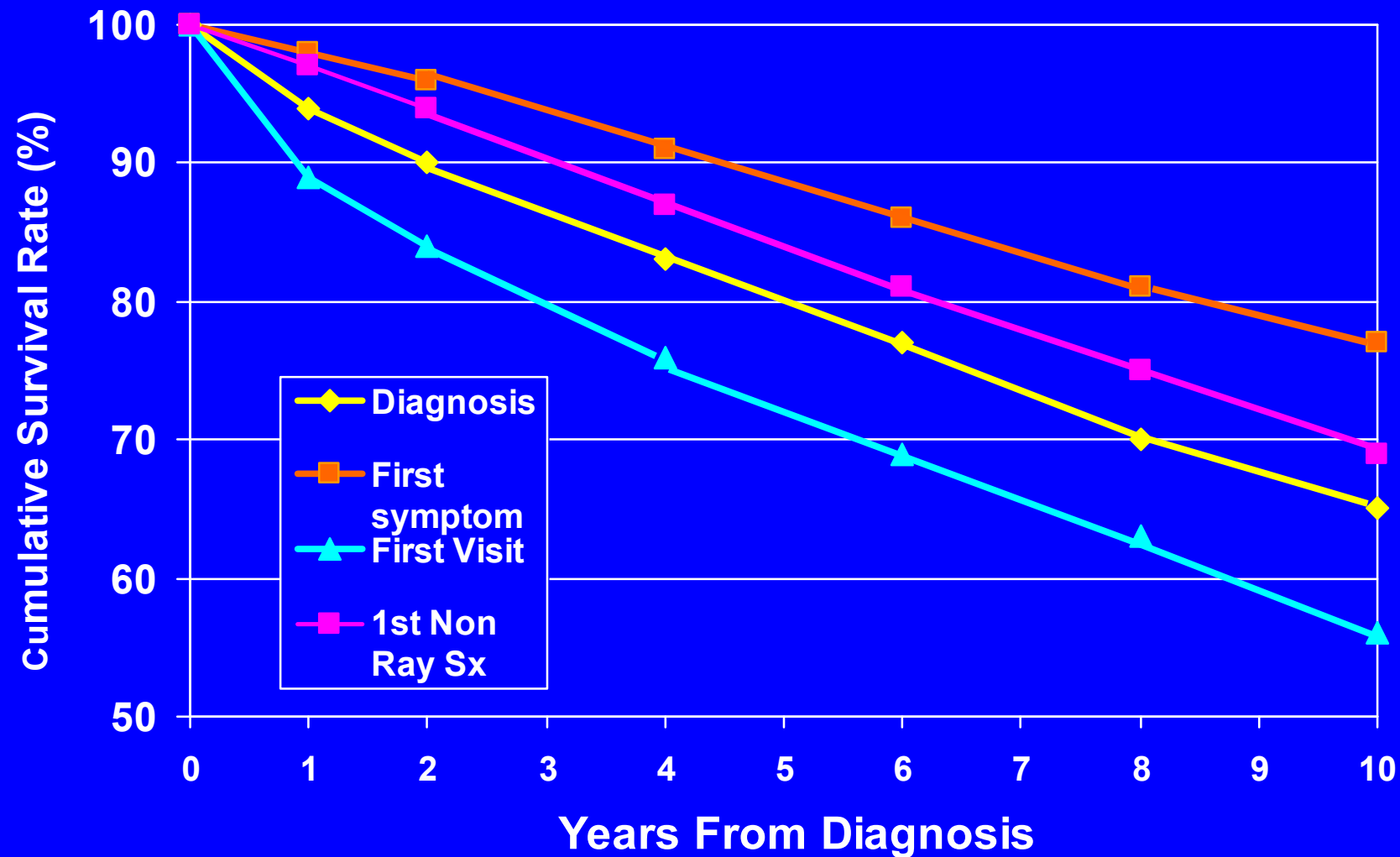
# Survival in Spain

- Plateau out to 20 years not meaningful since only followed for 6.6 years
- Sex and type, look much different except since the numbers were small they were not significant.
- Disease duration at diagnosis was 8.3 years, but not known how long disease was at first visit to their site.
- Survival was from first visit.

# Survival in SSc depending on Starting Times



# Survival in SSc depending on Starting Times



# Disease Duration at First Visit

	<u>Any 1<sup>st</sup> Sx</u>	<u>1<sup>st</sup> Non Raynaud's Sx</u>
<b>All</b>	<b>7.2 yrs</b>	<b>3.9 yrs</b>
<b>Limited</b>	<b>11.2 yrs</b>	<b>5.9 yrs</b>
<b>Diffuse</b>	<b>3.4 yrs</b>	<b>2.3 yrs</b>

# Canadian Survival

- 158 patients
- 85% female, Age at diagnosis 49 years
- 63% limited
- Diagnosis duration at time of last follow up or death 9.1 years, ? Total disease duration??
- Unknown duration of diagnosis at time of initial evaluation, assume diagnosis made at time of first visit??.

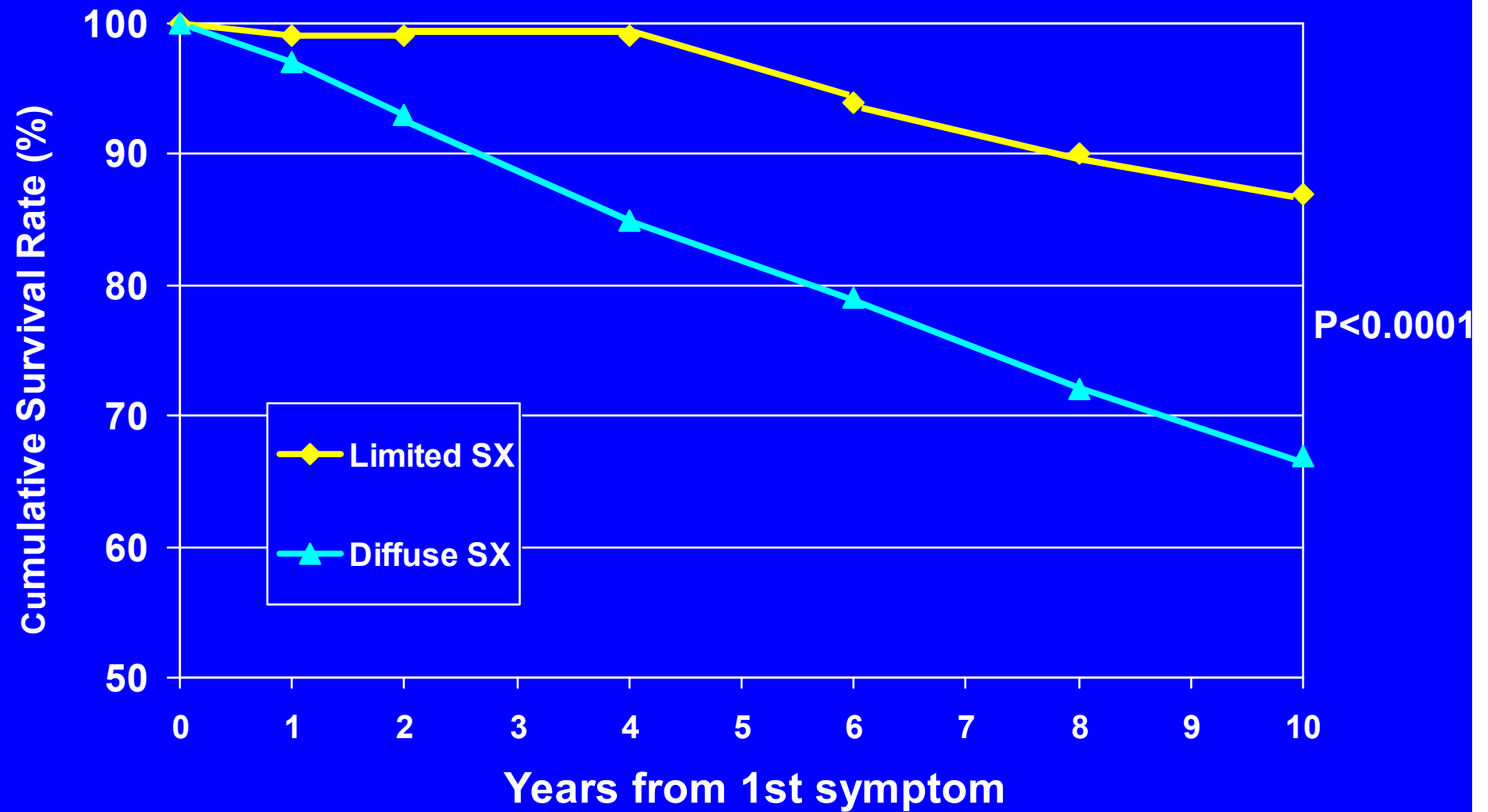
# Canadian Survival

	<u>5 year</u>	<u>10 year</u>	
Canada	90%	82%	
Diffuse	81%	65%	P<0.001
Limited	95%	95%	
Men	91%	82%	P=NS
Women	90%	81%	
SRC	70%	70%	P=NS
No SRC	94%	85%	

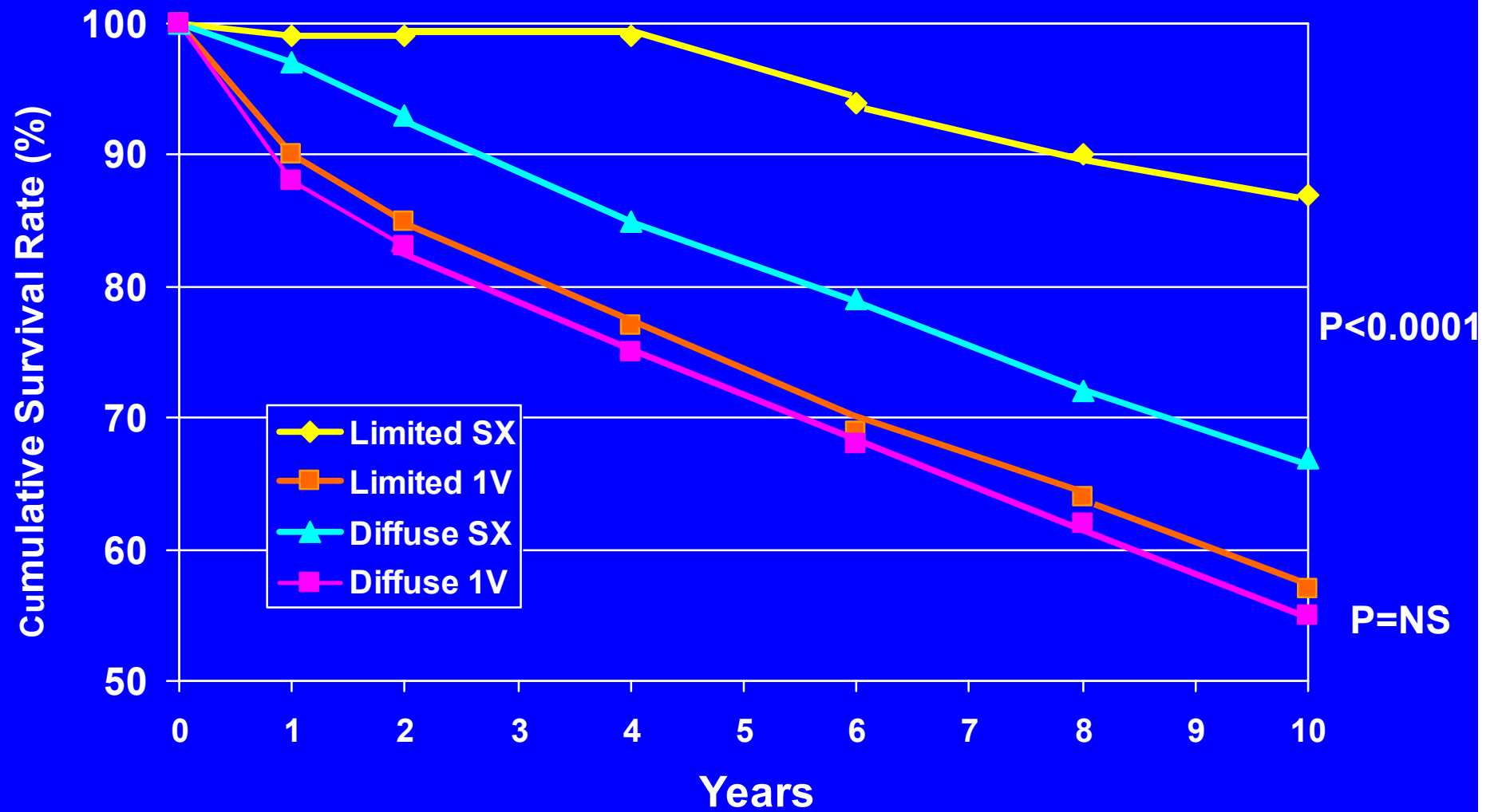
# Canadian Survival Studies

- **Survival Rates- Not probability of survival and methods do not indicate that they used a Kaplan-Meyer analysis, so can't compare them to other studies**
- **Causes of death confirmed in 33/42 deaths, PAH-5, renal 9 (and yet only 4 had renal crisis), ILD 10, Cardiac 9 (can't tell whether it was scleroderma related or not)**

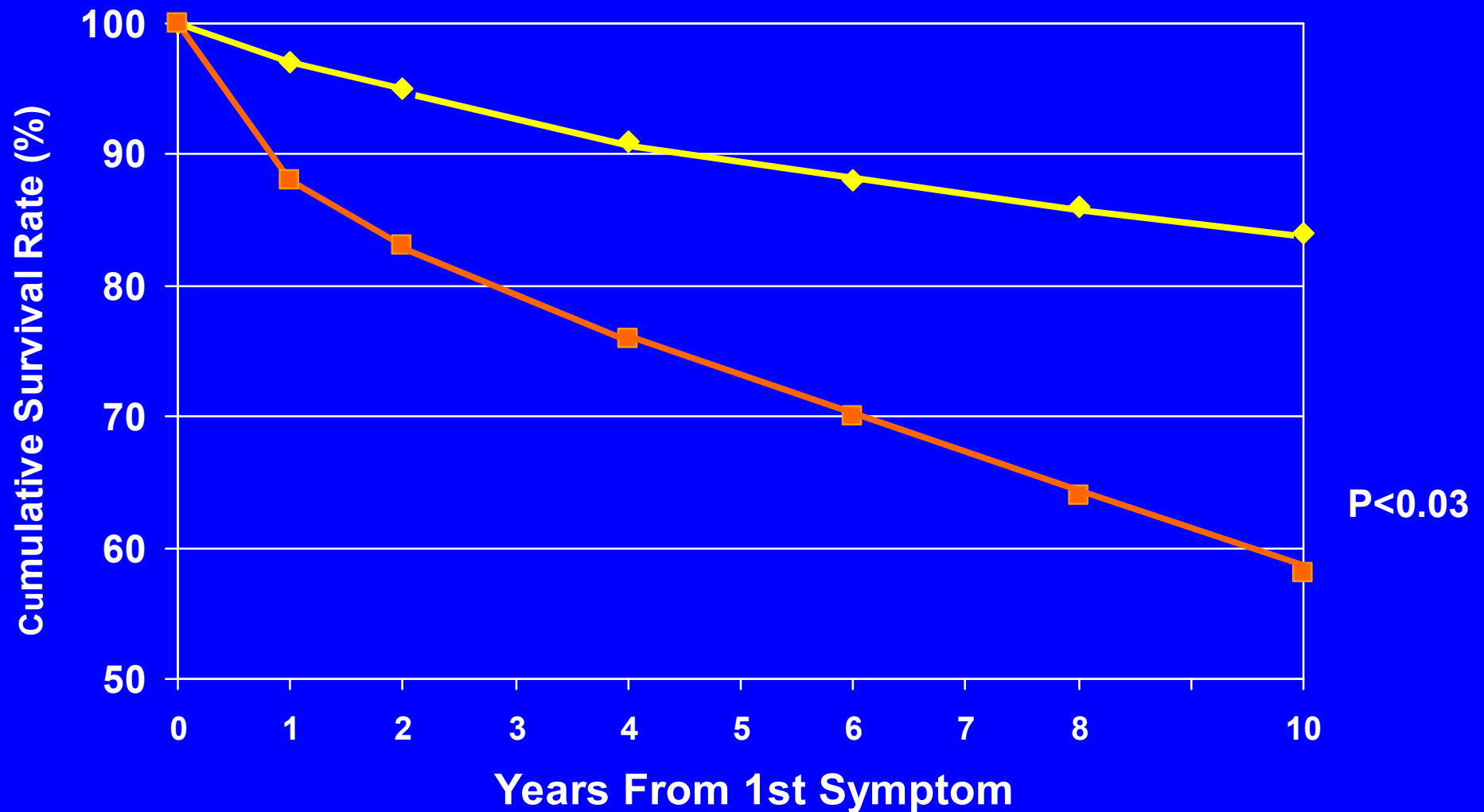
# Limited vs Diffuse SSc at 1<sup>st</sup> Sx



# Limited vs Diffuse SSc at 1<sup>st</sup> Sx and 1<sup>st</sup> Visit



# Limited vs Diffuse SSc with less than 3 years of symptoms at 1<sup>st</sup> visit



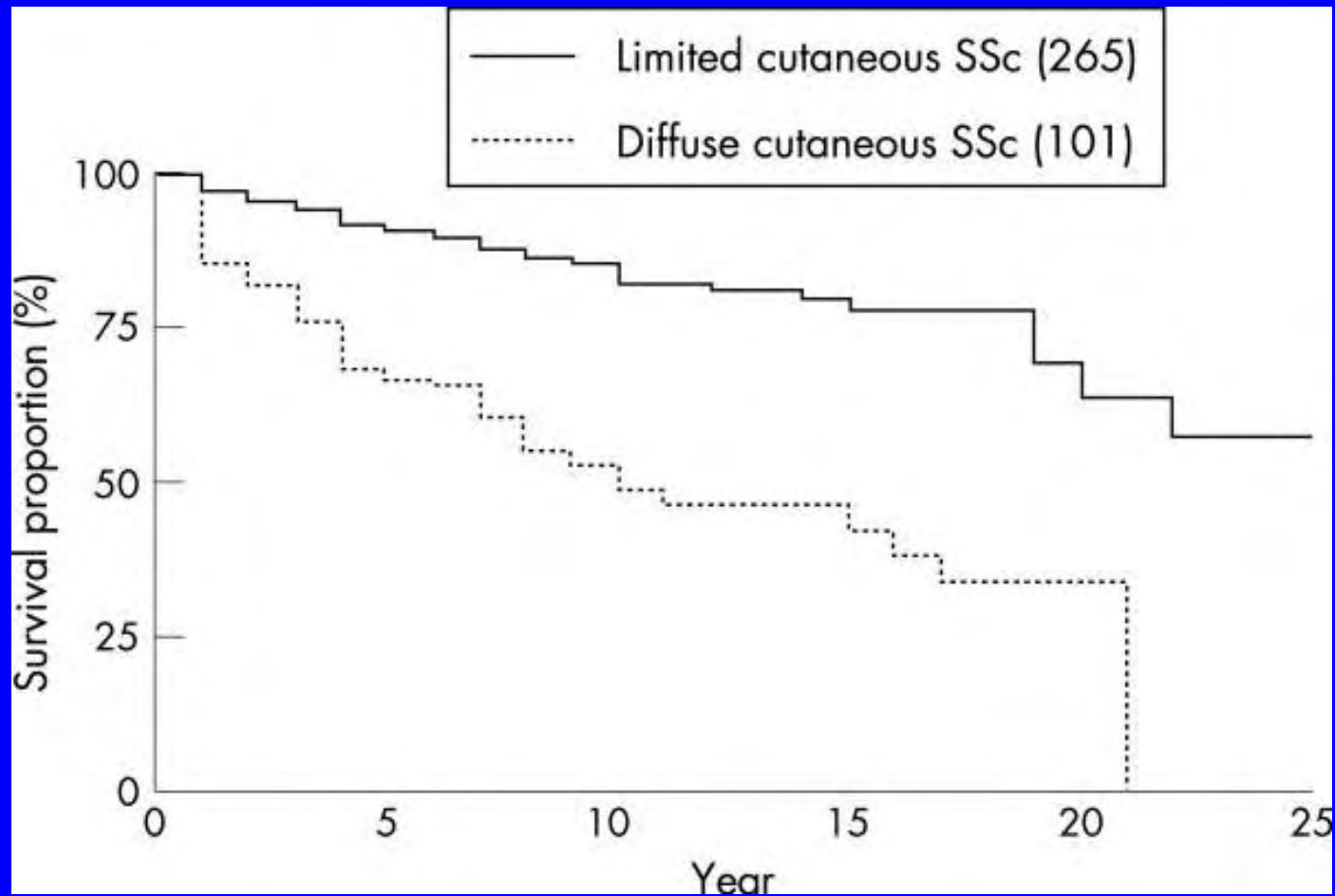
# Hungarian Survival

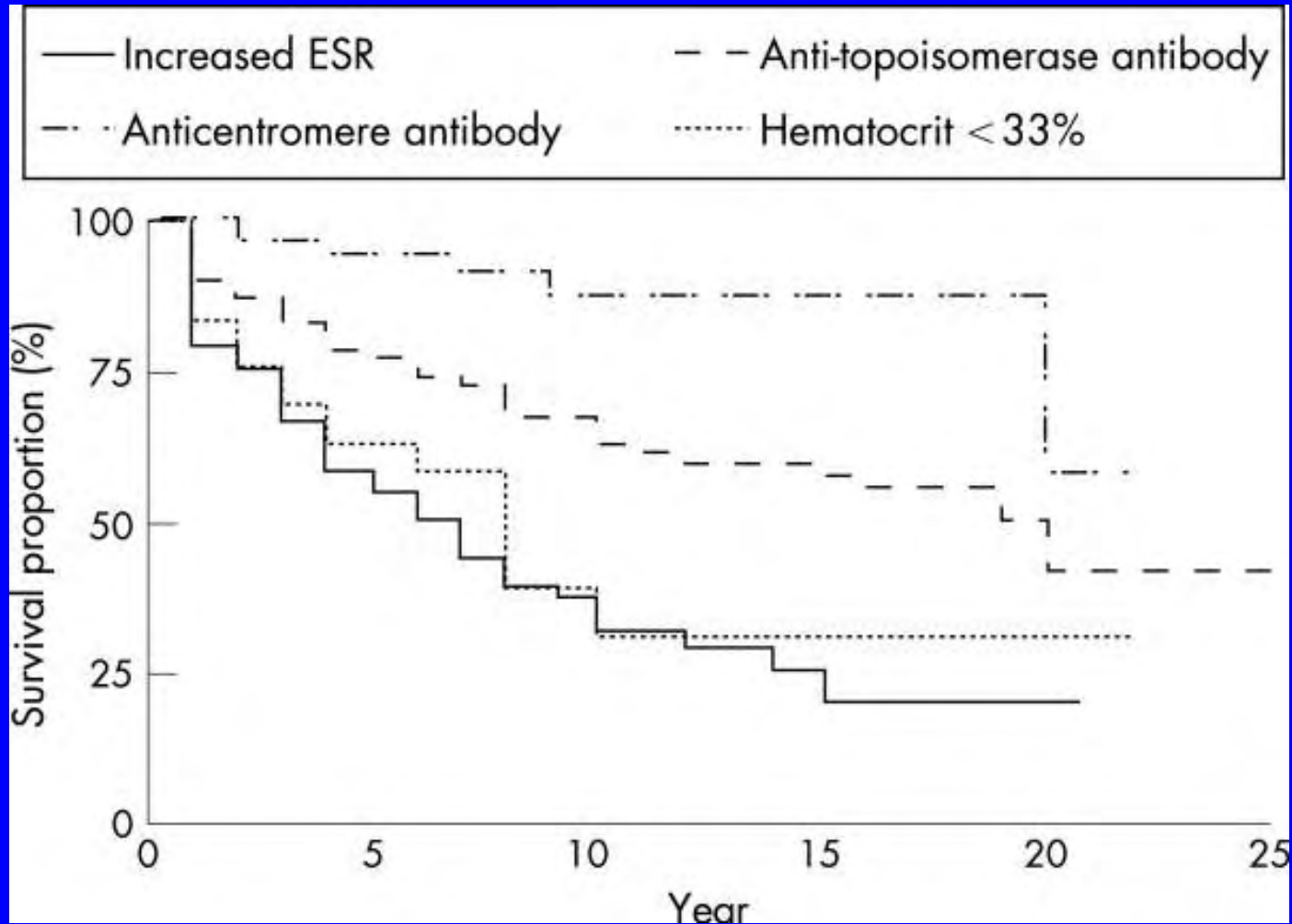
- **366 patients**
- **86% female, Age at disease onset 44 years**
- **72% limited**
- **Disease duration at time of diagnosis or time of 1<sup>st</sup> visit 12 years**
- **Duration of follow up 6 years**

# Hungarian Survival

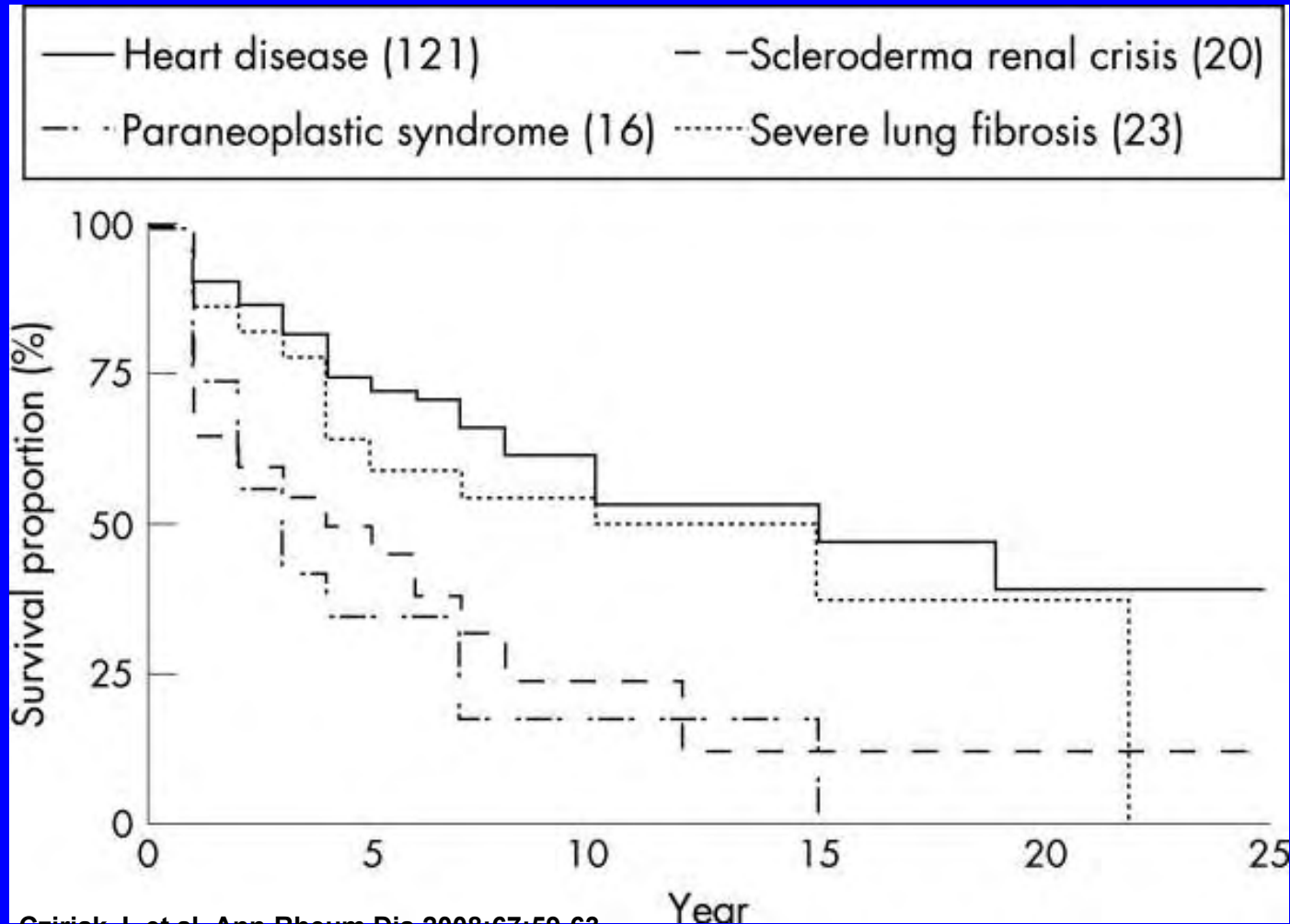
- Kaplan Meyer analysis followed using univariate analysis for 'bad' outcomes, followed by Cox proportional hazards modeling.
- Kaplan Meyer analysis appears to be from first visit.
- 18% were not included, missing data.
- Causes of death – 93 deaths, 86 from SSc (92%) but that includes cancer (paraneoplastic), ? Many of missing were deaths from natural causes?

# Survival in SSc Subsets



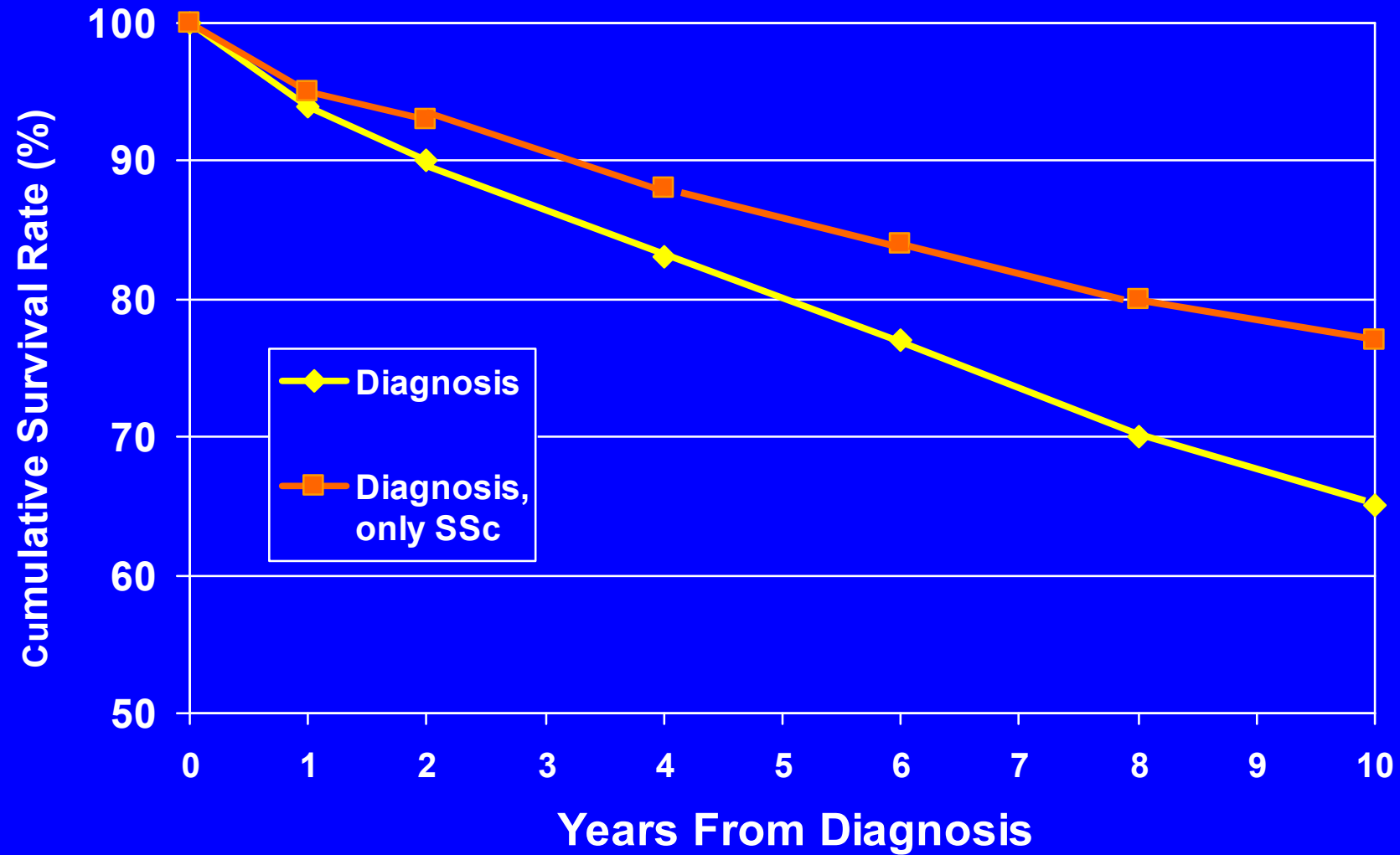


# Survival in scleroderma Organ Subsets

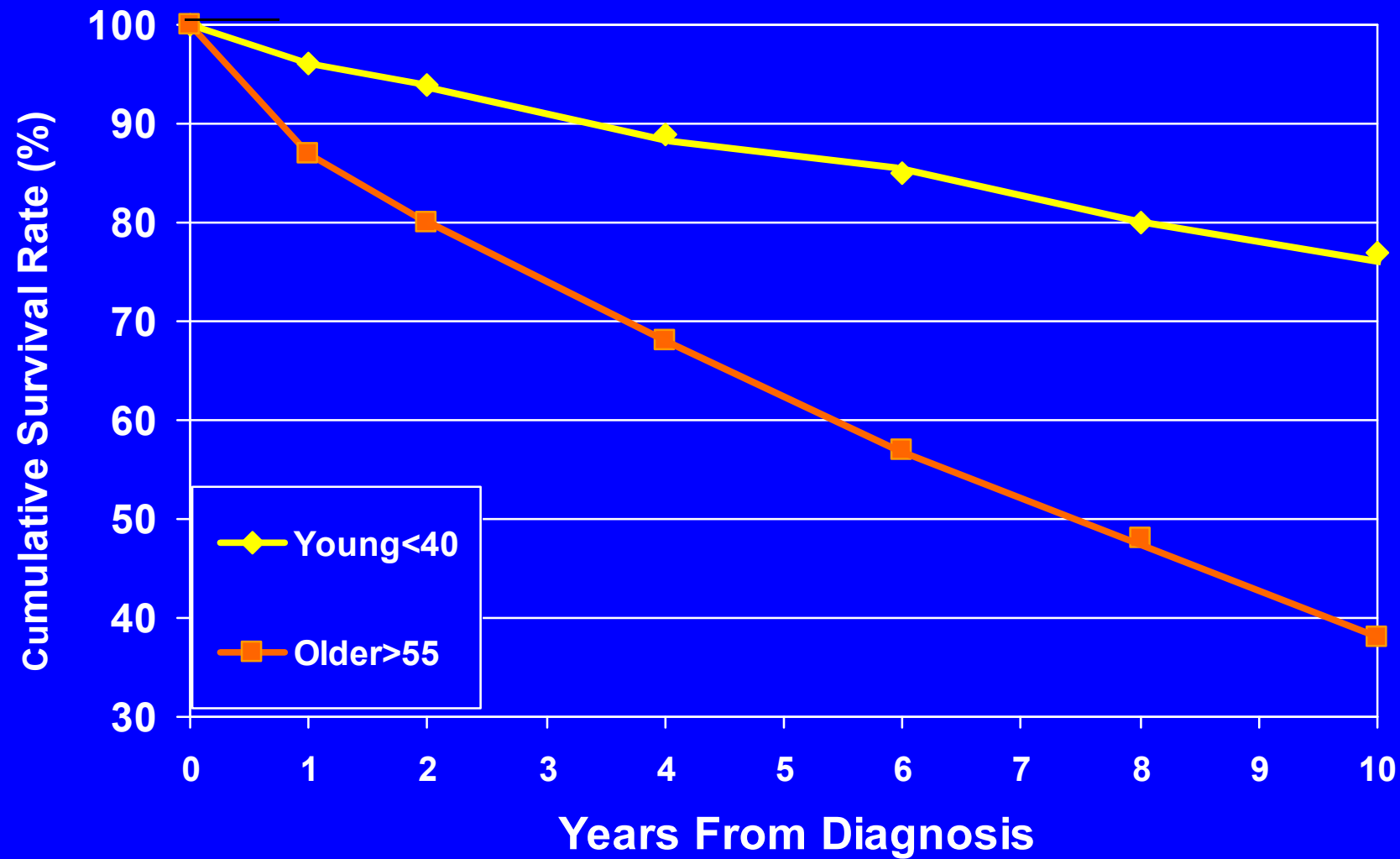


Czirjak, L et al. *Ann Rheum Dis* 2008;67:59-63

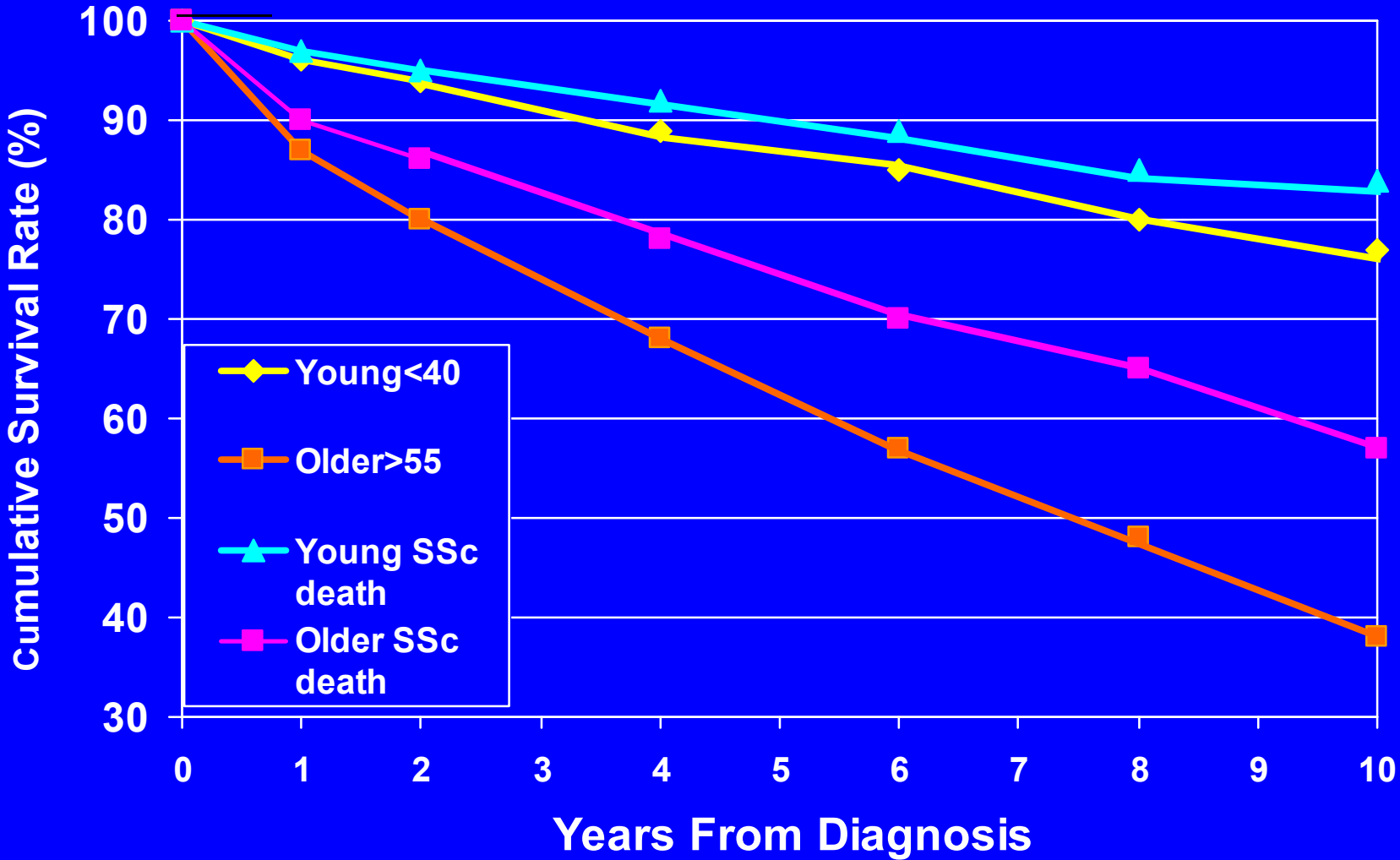
# Survival in SSc depending on Cause of Death



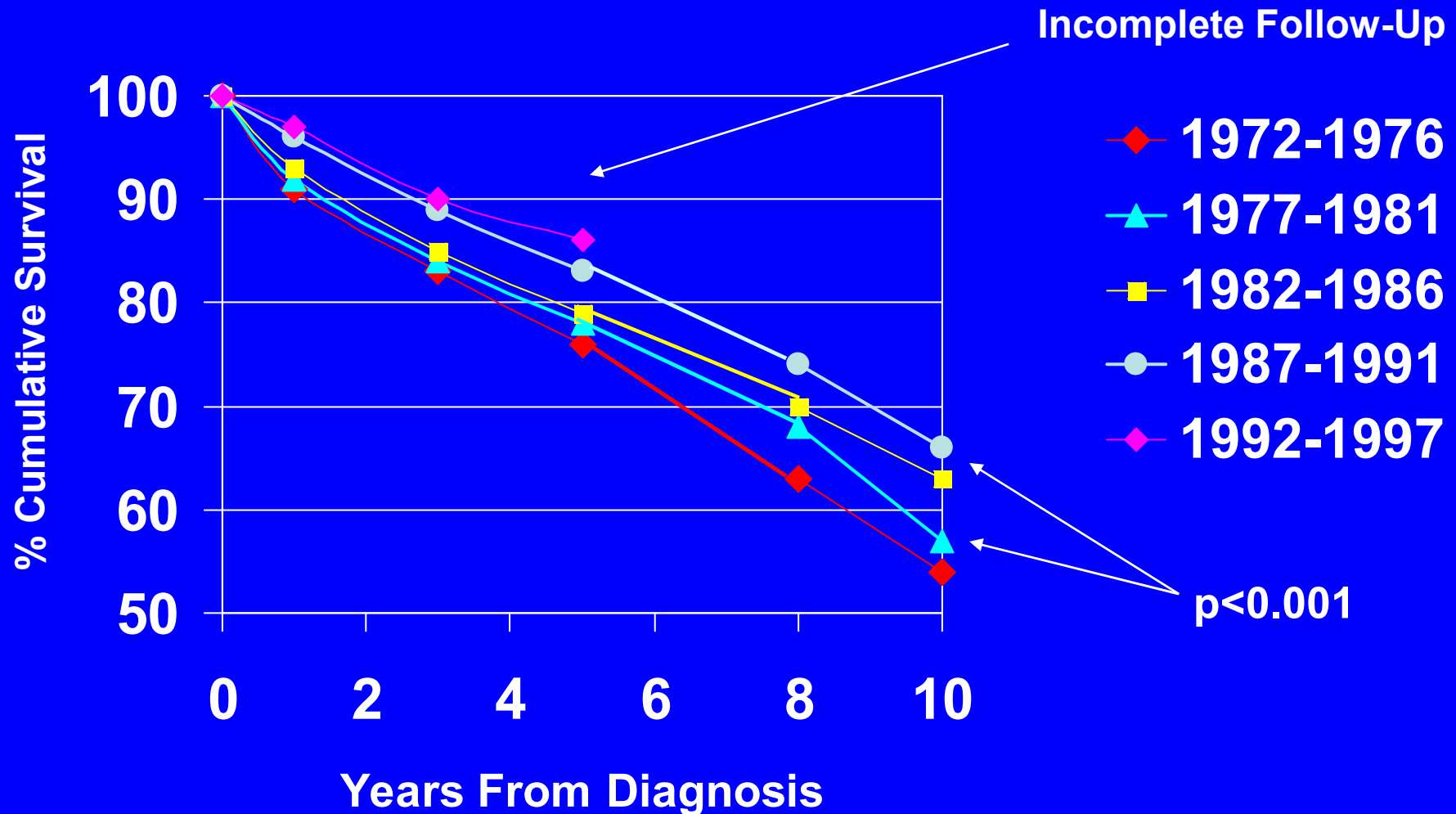
# Survival in Different Age Groups Subsets



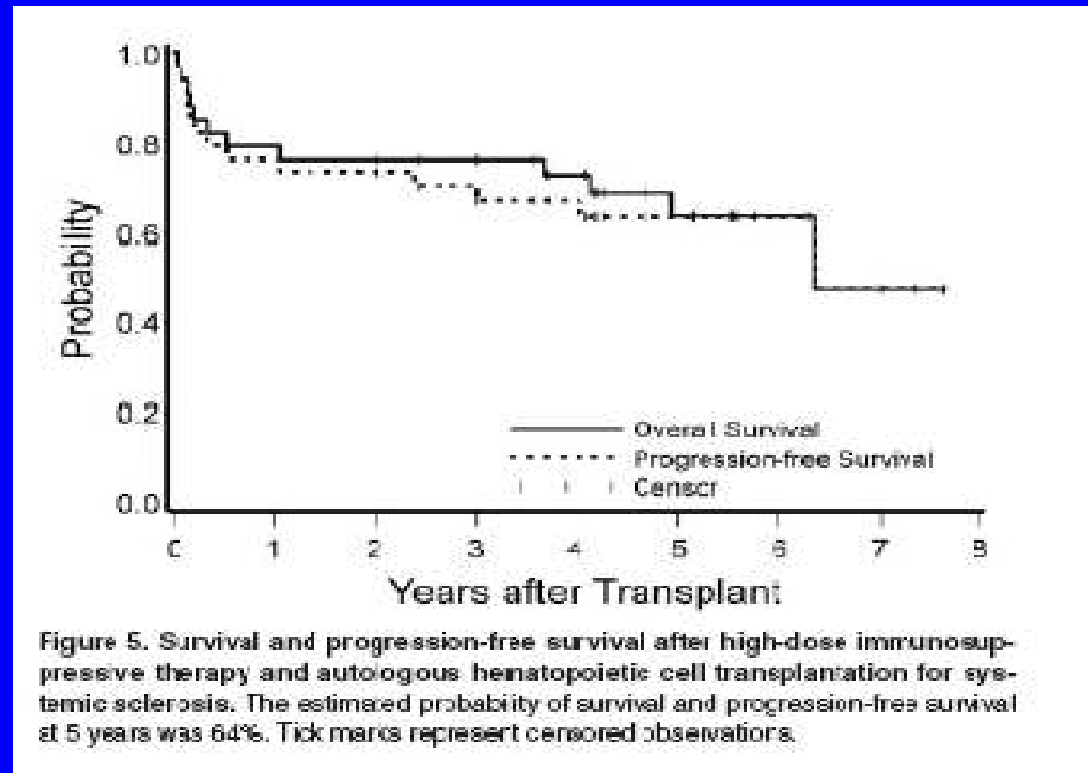
# Survival in Different Age Groups Subsets and only SSc Deaths



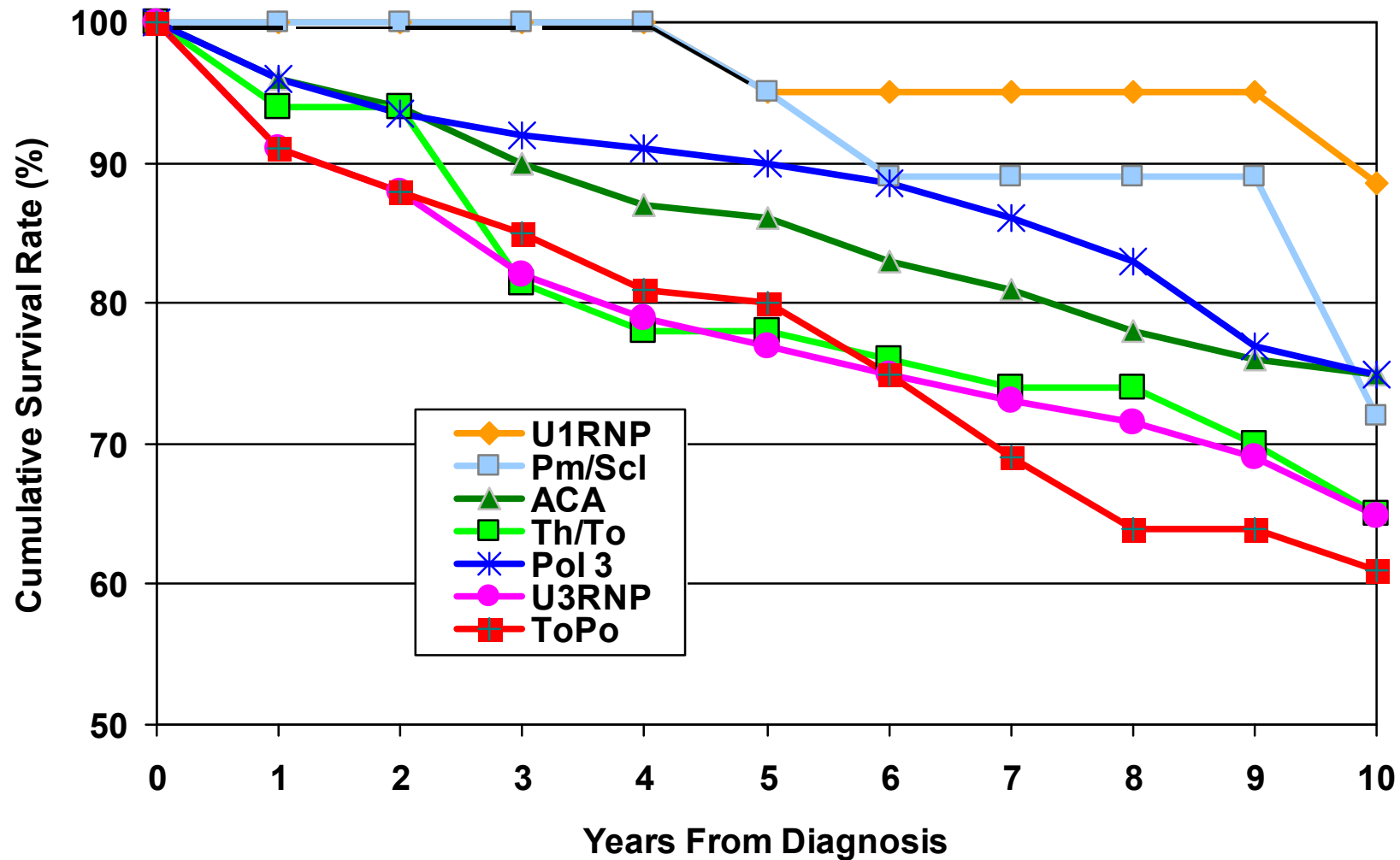
# Survival in Systemic Sclerosis over the last 30 years



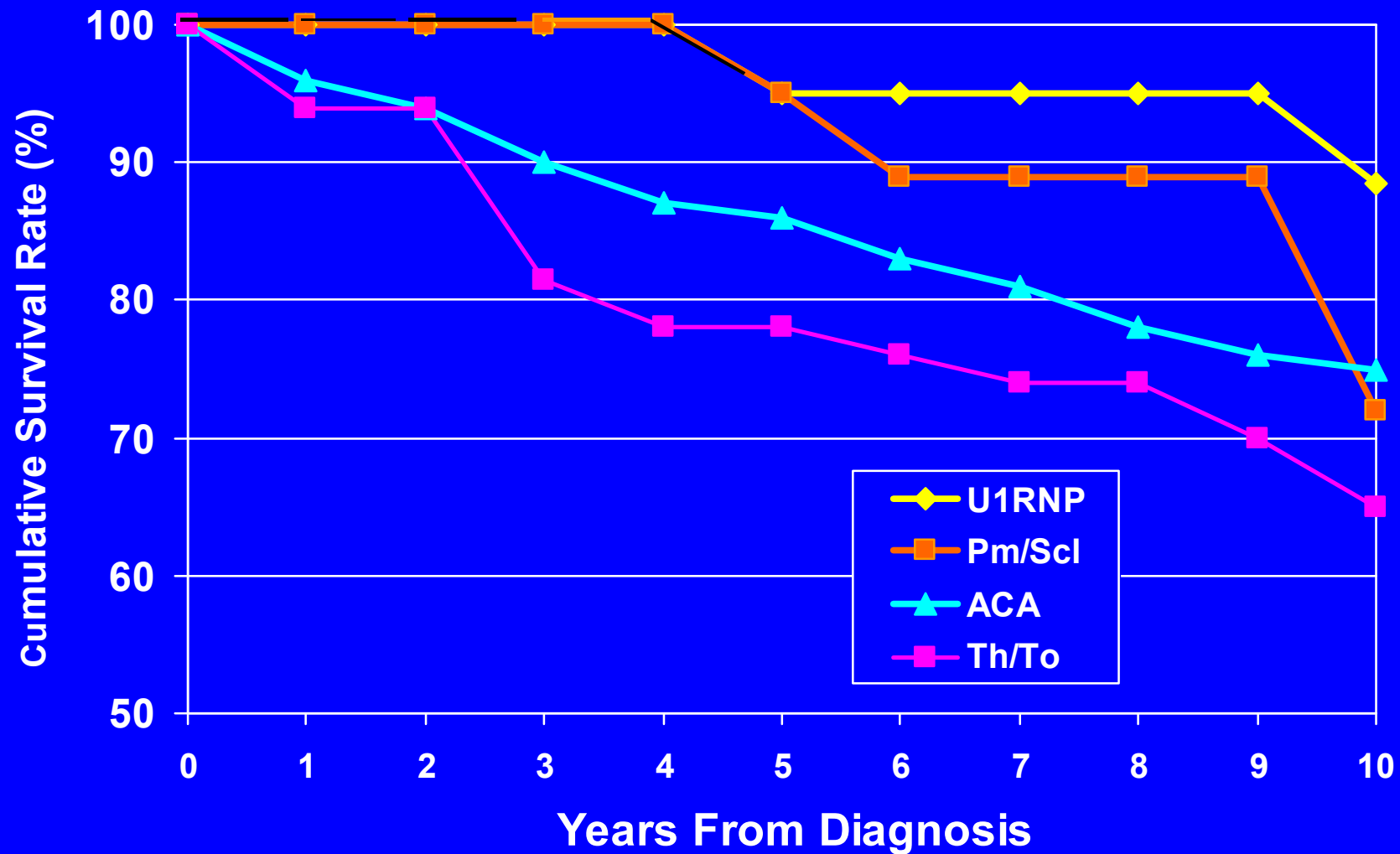
# Survival with Bone Marrow Transplant Study



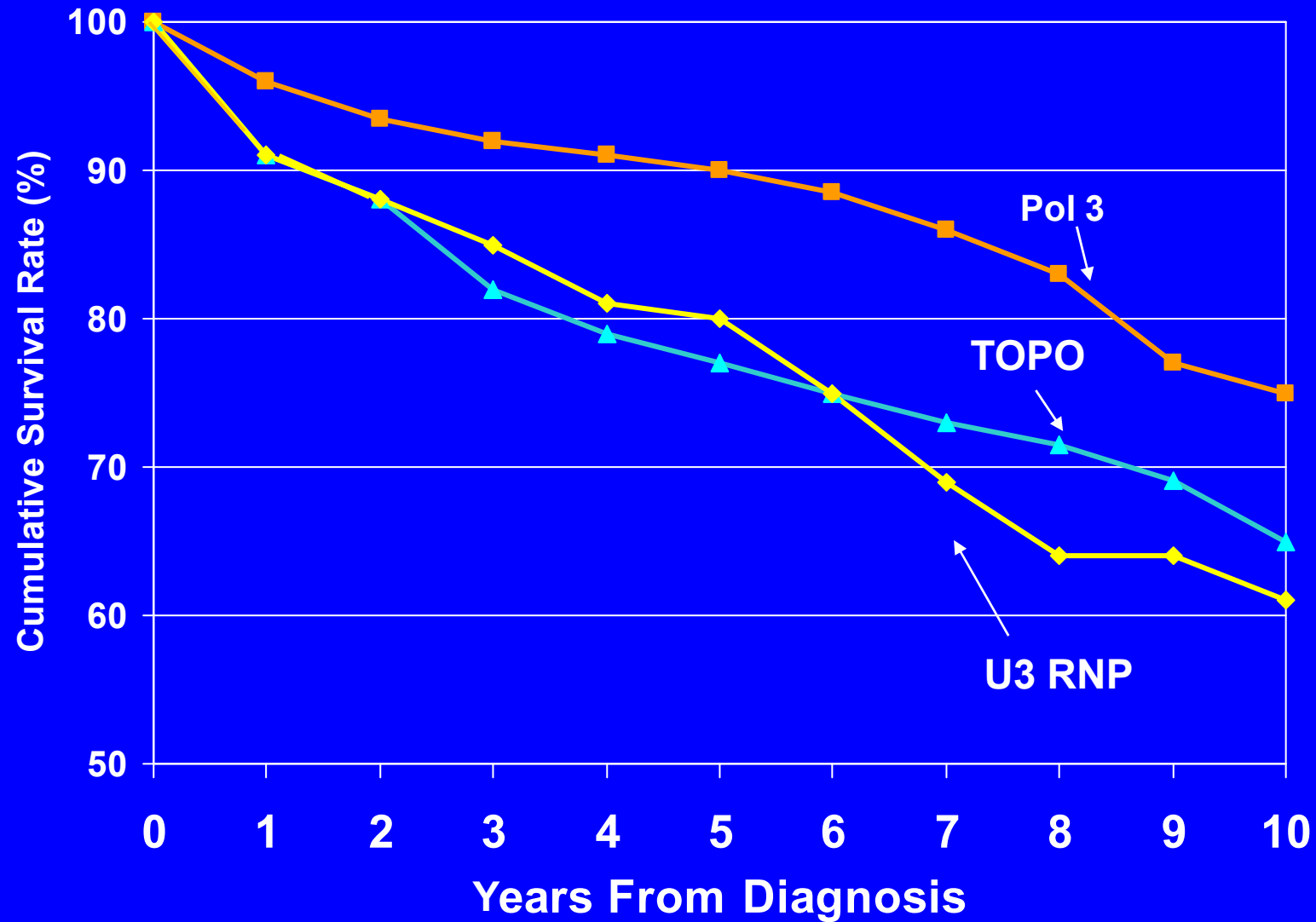
# Survival in Auto-antibody Subsets



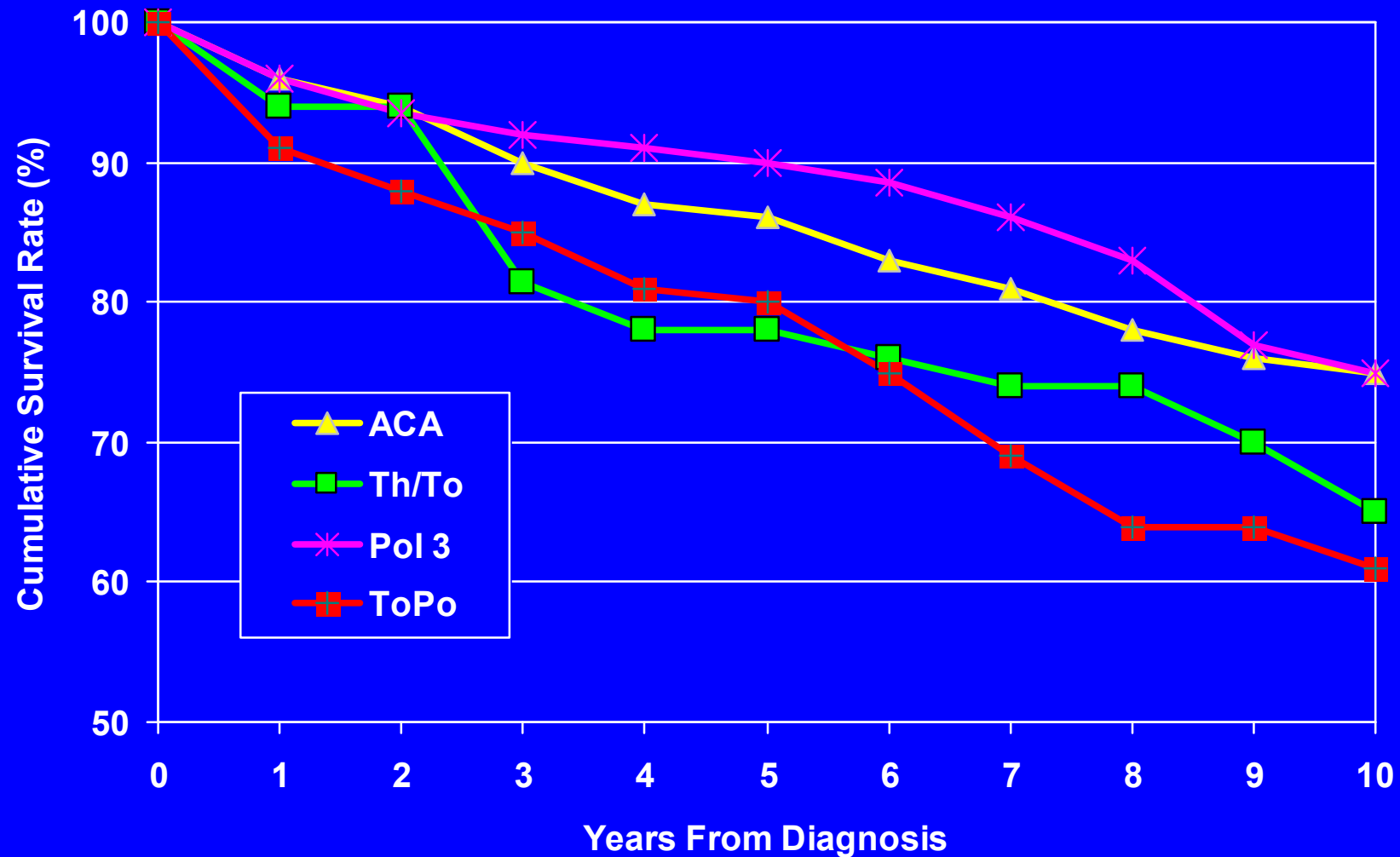
# Survival in Limited Scleroderma Subsets



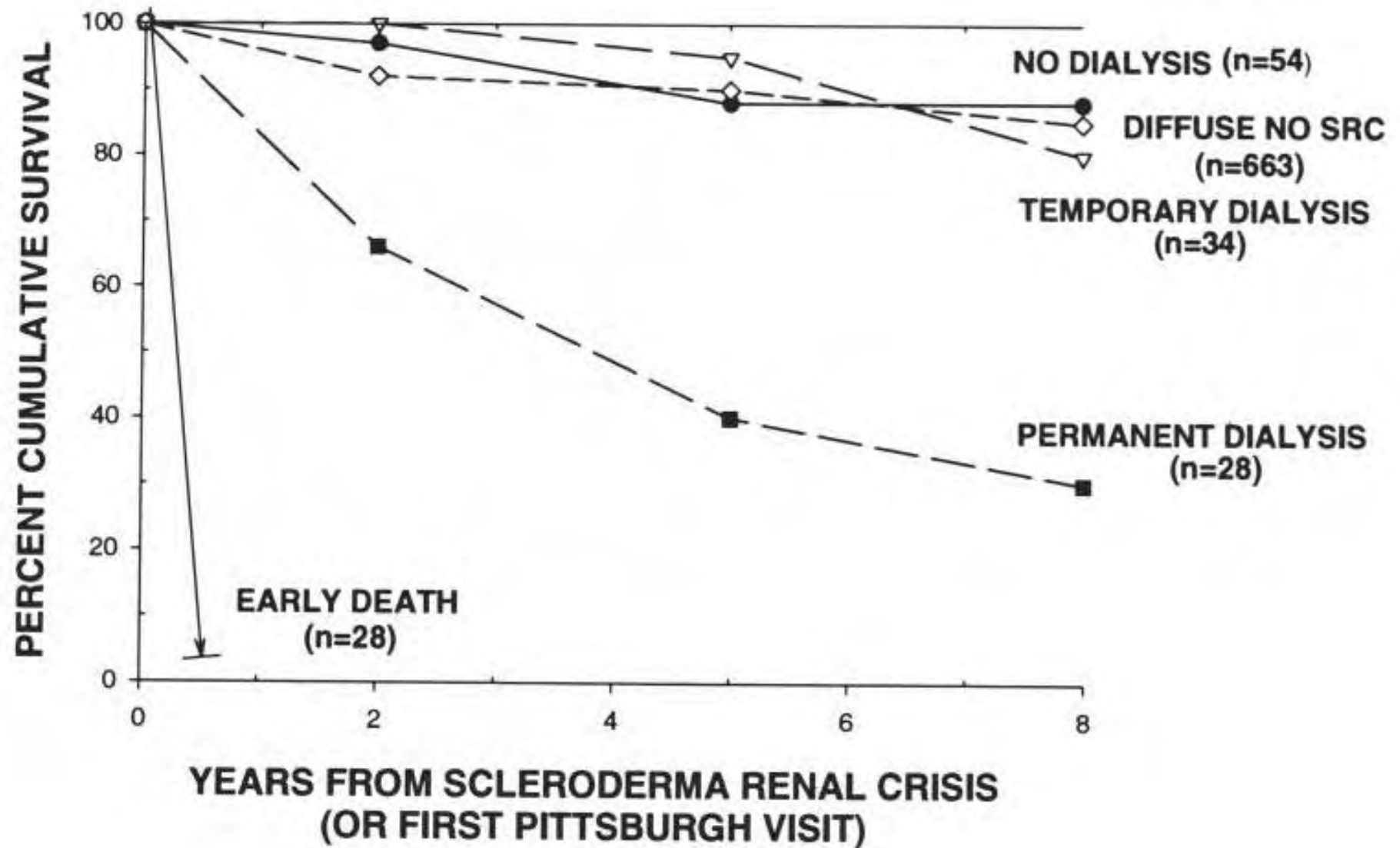
# Survival in Diffuse Scleroderma Subsets



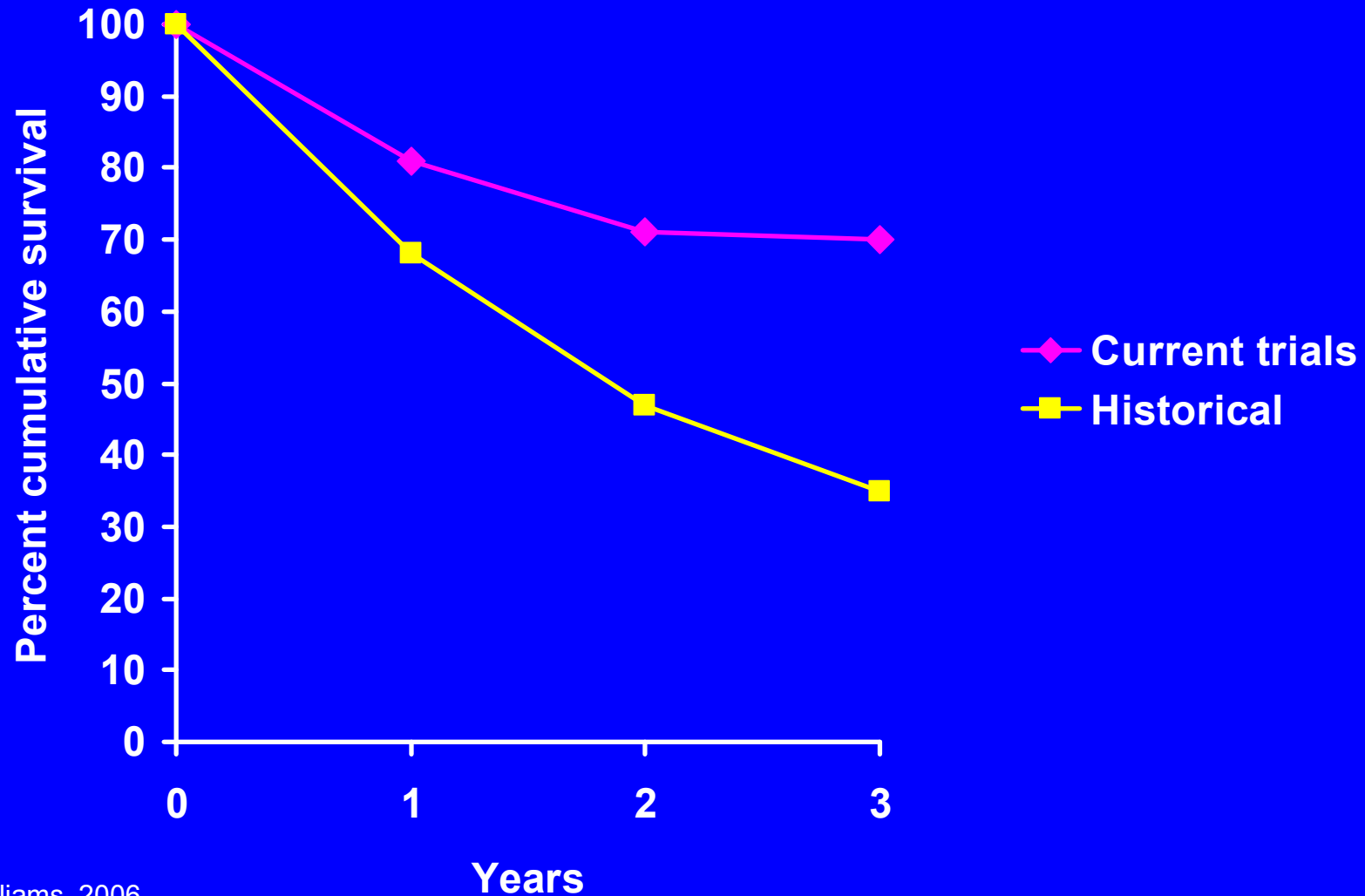
# Survival in Auto-antibody Subsets



# SURVIVAL AFTER SCLERODERMA RENAL CRISIS



# Survival of Scleroderma PAH



Williams, 2006

# Summary

- **Survival is improving**
- **Survival analysis are very important but they can be very difficult to do and interpret.**
- **Follow up is critical and every effort possible must be done to determine outcome of patient.**
- **Careful and systematic determination of causes of death are going to be important going forward.**