

Dronedarone in the real world - how safe it is?



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MY CONFLICTS OF INTEREST ARE

Grants and/or lecturing fees from:
Bayer, Boehringer Ingelheim,
Bristol Myers Squibb,
Pfizer, Sanofi, St Jude Medical



Two studies stopped for safety reasons

2008

ANDROMEDA

(heart failure)

n=627

8.1% vs 3.8% died
(p=0.03)

2011

PALLAS

(permanent AF)

n=3,236

4.7% vs 2.4% died
(p=0.049)



U.S. Food and Drug Administration

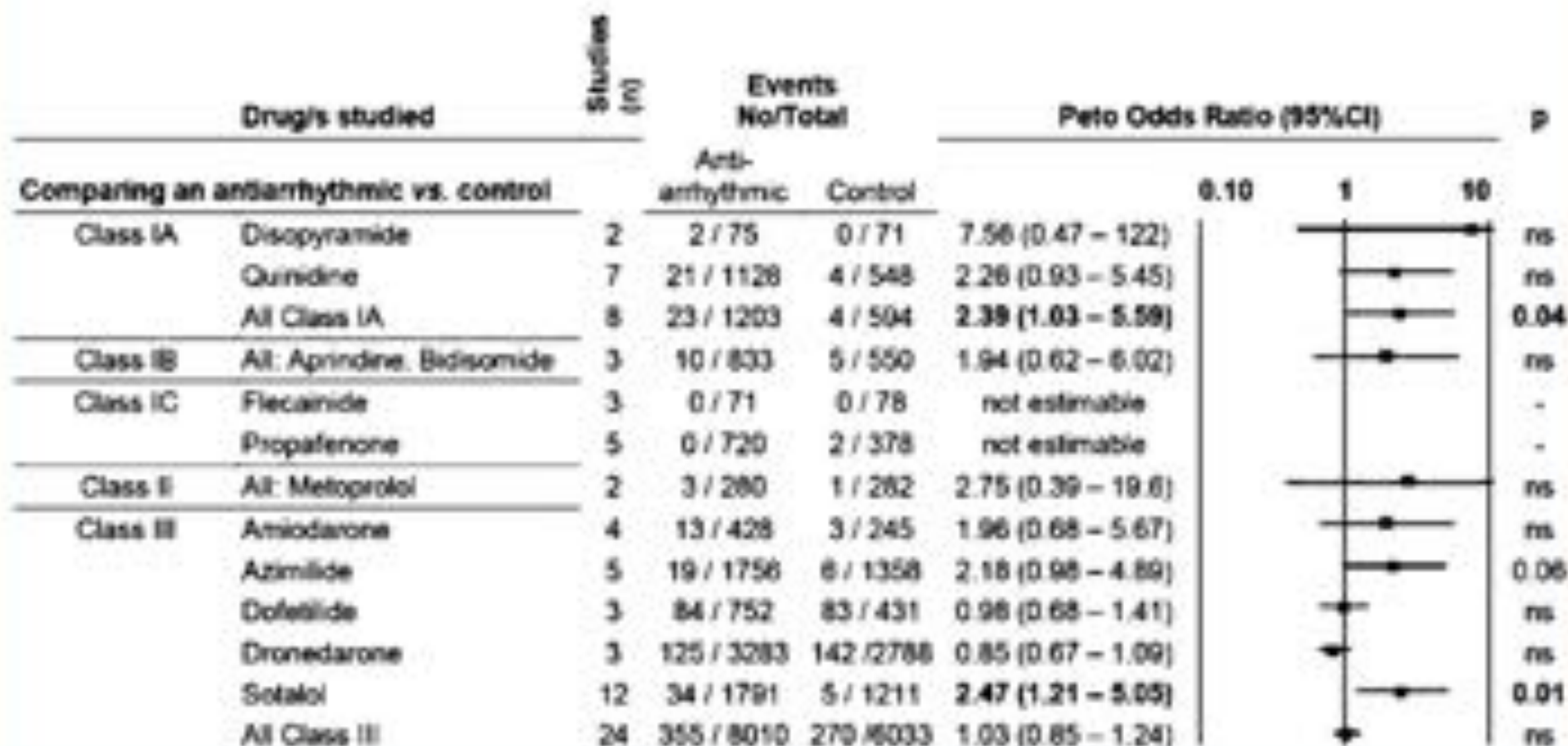
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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Antiarrhythmic drugs are problematic

Figure: Overall mortality





Dronedarone was introduced in Sweden
May 24, 2010

A registry study of the first 3 years

Friberg. Safety of Dronedarone in Routine Clinical Care, JACC 2014;63:2376

Linkage by civic registration number

CCYYMMDD-XXX

All residents irrespective of citizenship

Used in all health care contacts
and for all drug purchases



The Patient-register

all hospital and hospital affiliated open care
since 1987

not primary care



The Cause of Death register



The Drug register

all prescribed and dispensed drugs
in Sweden since 2005

not over-the-counter medication
and drugs used in hospitals

All patients with
AF
in the Patient register
2010-2012

n=174,995



**Dronedaronone
(ever)**

n=4,856

**No dronedaronone
(never)**

n=170,139

128 died

(annual mortality 1.3%)



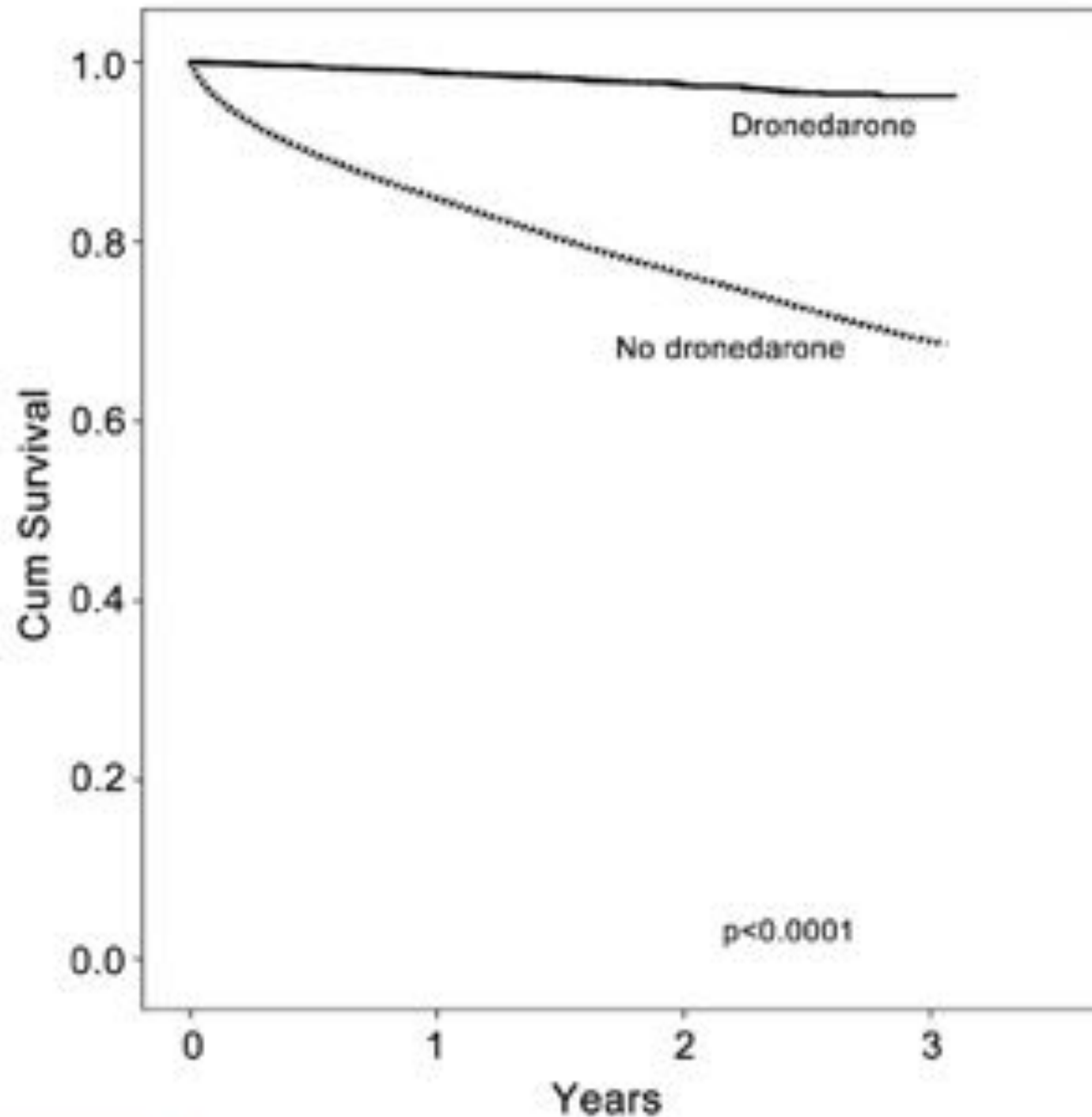


Figure 1

Unadjusted Mortality in Patients Exposed to Dronedarone

Unadjusted mortality in 4,856 patients with atrial fibrillation exposed to dronedarone compared with 170,139 patients with atrial fibrillation not exposed to dronedarone. Cum = cumulative.

Annual mortality (ITT)

Dronedarone 1,3%

No dronedarone 14,0%

128 died

(annual mortality 1.3%)



66 had stopped

taking dronedarone

(medication only lasting 25% of the time at risk)

Dronedarone-patients were

much younger and healthier



	Dronedarone (n=4,856)	No Dronedarone (n=170,139)
<i>Age</i>	66	76
<i>CHA₂DS₂-VASc</i>	2.5	3.8
<i>HAS-BLED</i>	1.9	2.6

Like comparing apples and oranges

	HR	95% CI
Univariate	0.10	0.08-0.12
Adjusted for age and sex	0.24	0.20-0.29
Multivariable adjustment	0.29	0.25-0.35



Propensity score matching



To make groups as similar as possible
with regard to background factors

Propensity score matching



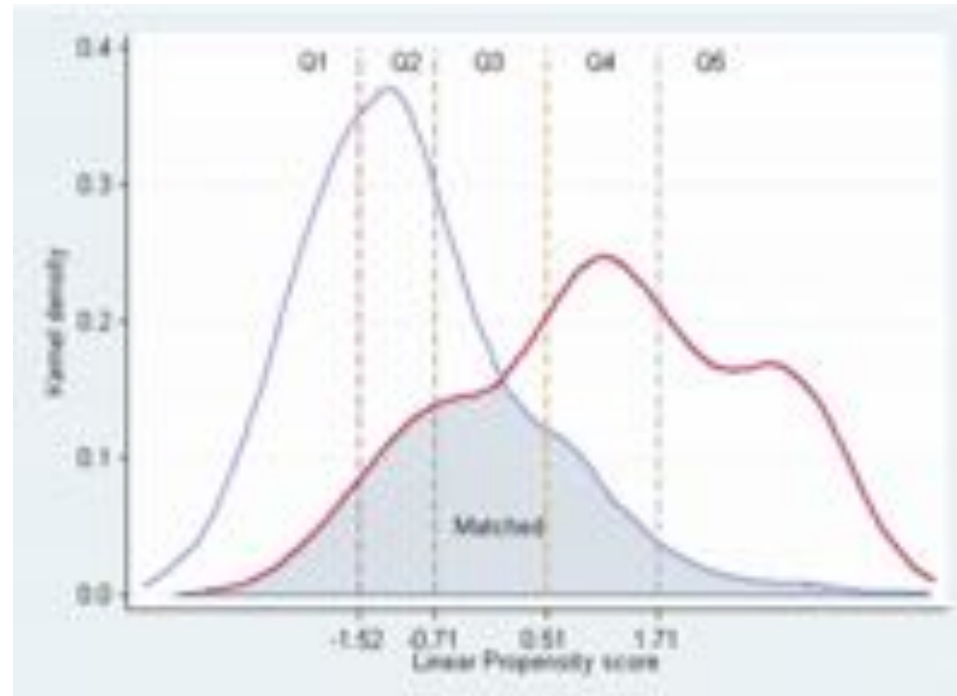
Step 1.

Multivariate logistic regression

Dependent variable: to get dronedarone

Independent variables: everything that may affect decisions about prescriptions

Propensity score matching



Step 2.

Match treated and untreated patients with similar scores pairwise

Exclude patients who does not find a match

Like comparing apples and ...apples



	Dronedarone (n=4,856)	No Dronedarone (n=4,856)
<i>Age</i>	<i>65.5</i>	<i>65.1</i>
<i>CHA₂DS₂-VASc</i>	<i>2.48</i>	<i>2.52</i>
<i>HAS-BLED</i>	<i>1.86</i>	<i>1.84</i>

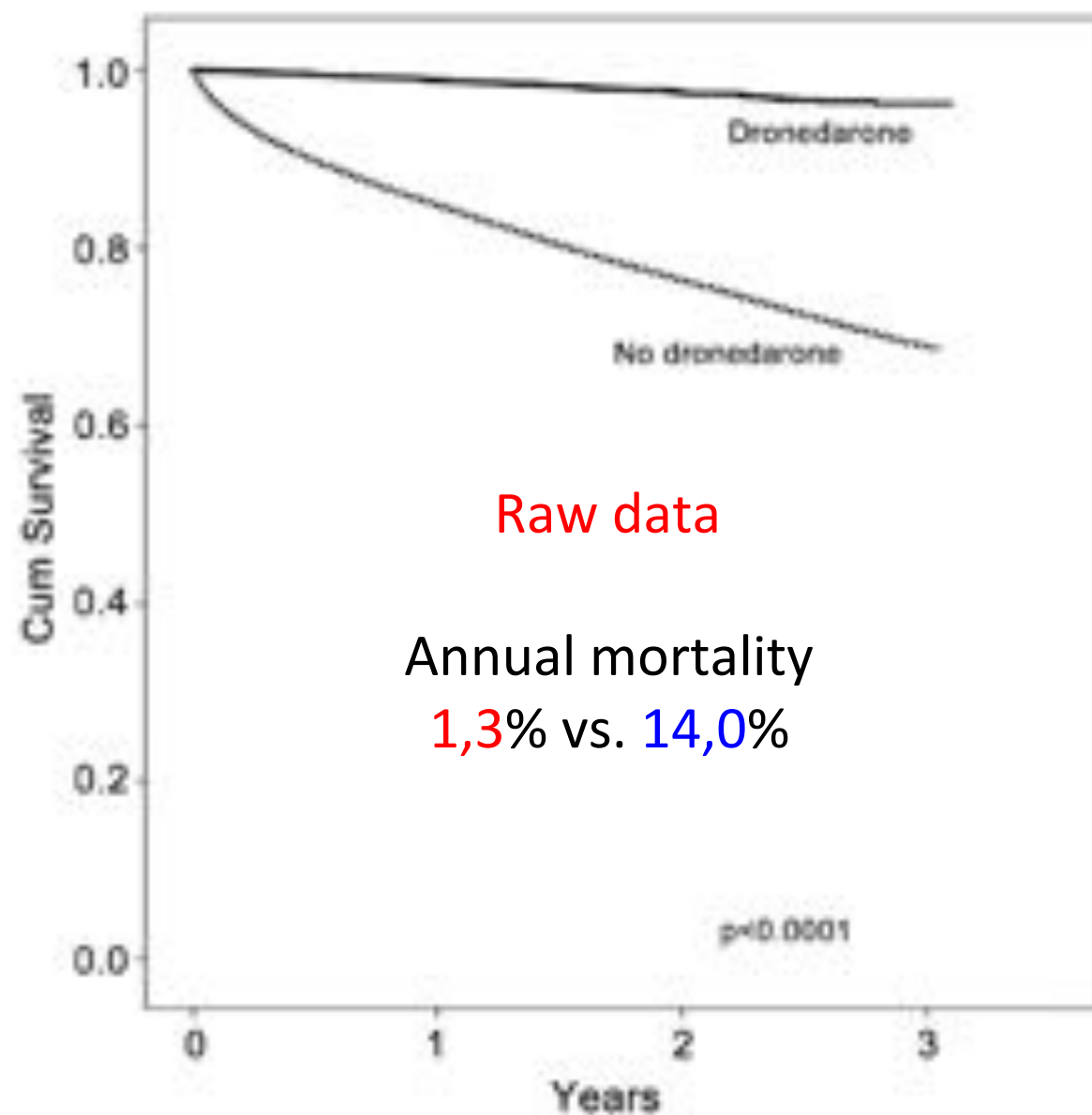


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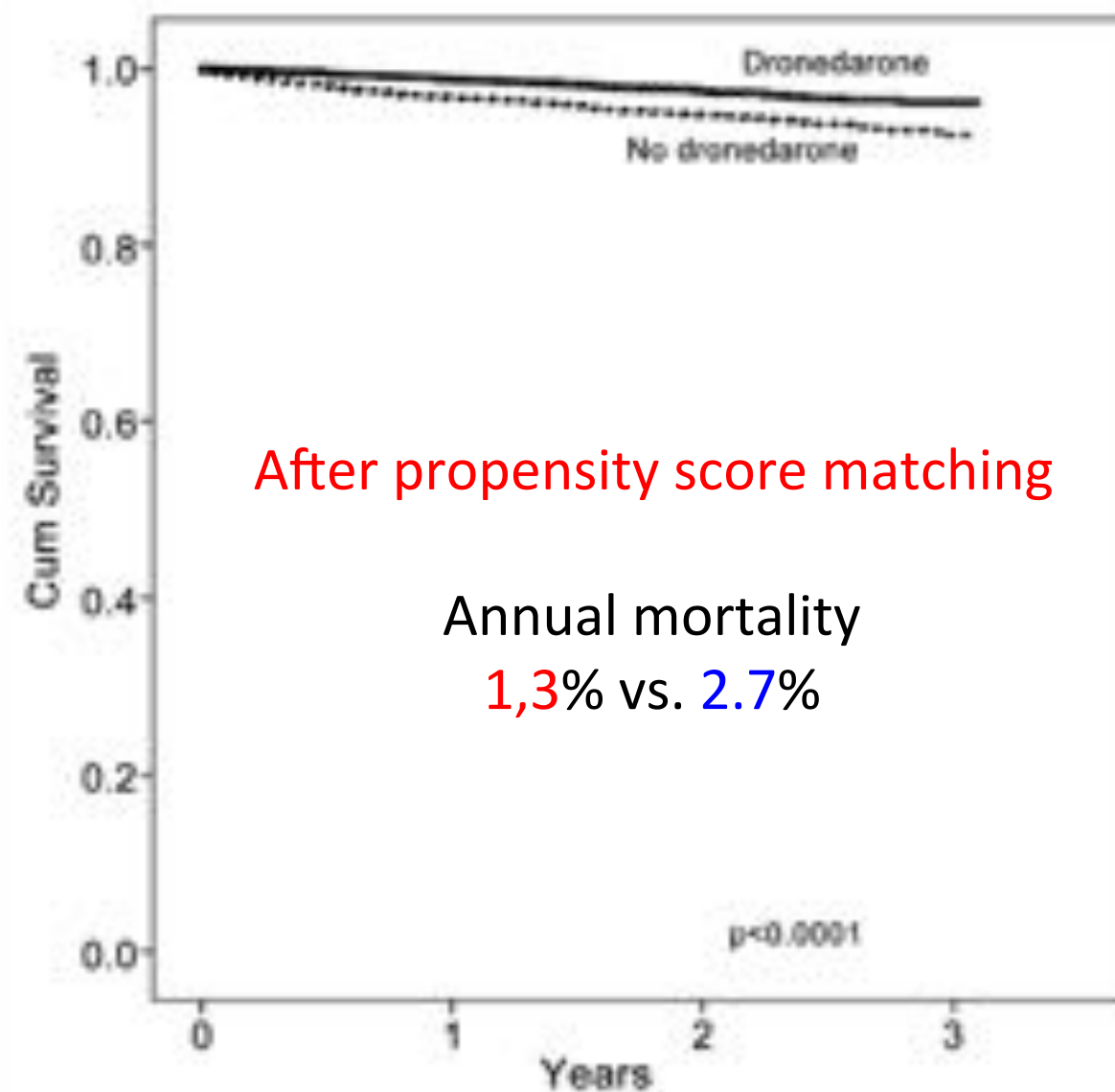


Figure 2

Unadjusted Mortality After Pairwise Matching for Propensity to Receive Dronedarone

Patients with atrial fibrillation exposed to dronedarone ($n = 4,856$) compared with patients with atrial fibrillation not exposed to dronedarone ($n = 4,856$). Cum = cumulative.

$$\text{SMR} = \frac{\text{observed number of deaths}}{\text{expected number of deaths}}$$

The expected number of deaths

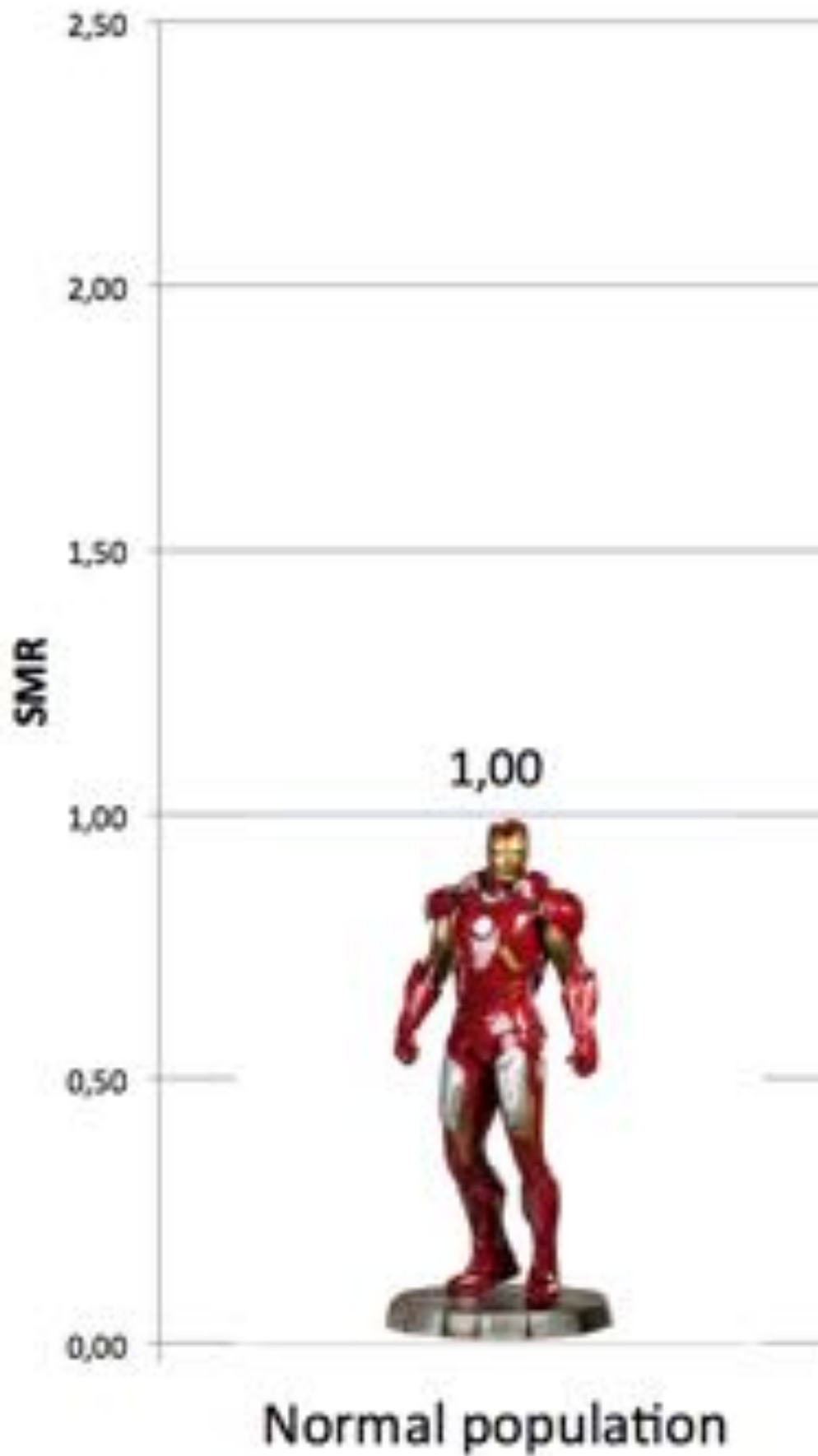
<http://www.scb.se/sv/Hitta-statistik/Statistik-efter-amne/Befolkning/Befolkningens-sammansattning/Befolkningsstatistik/25788/25795/>

Ålder	Dödsrisken ‰	
	Män	Kvinnor
45	1,44	1,09
46	1,77	1,15
47	1,88	1,28
48	2,13	1,31
49	2,50	1,53
50	2,71	1,84
51	2,98	1,95
52	3,08	2,14
53	3,72	2,57
54	4,06	2,57
55	4,32	2,98
56	4,94	3,07
57	5,21	3,45
58	5,98	3,77
59	6,51	4,00
60	7,05	4,78
61	7,78	4,98
62	8,71	5,51
63	9,34	6,06

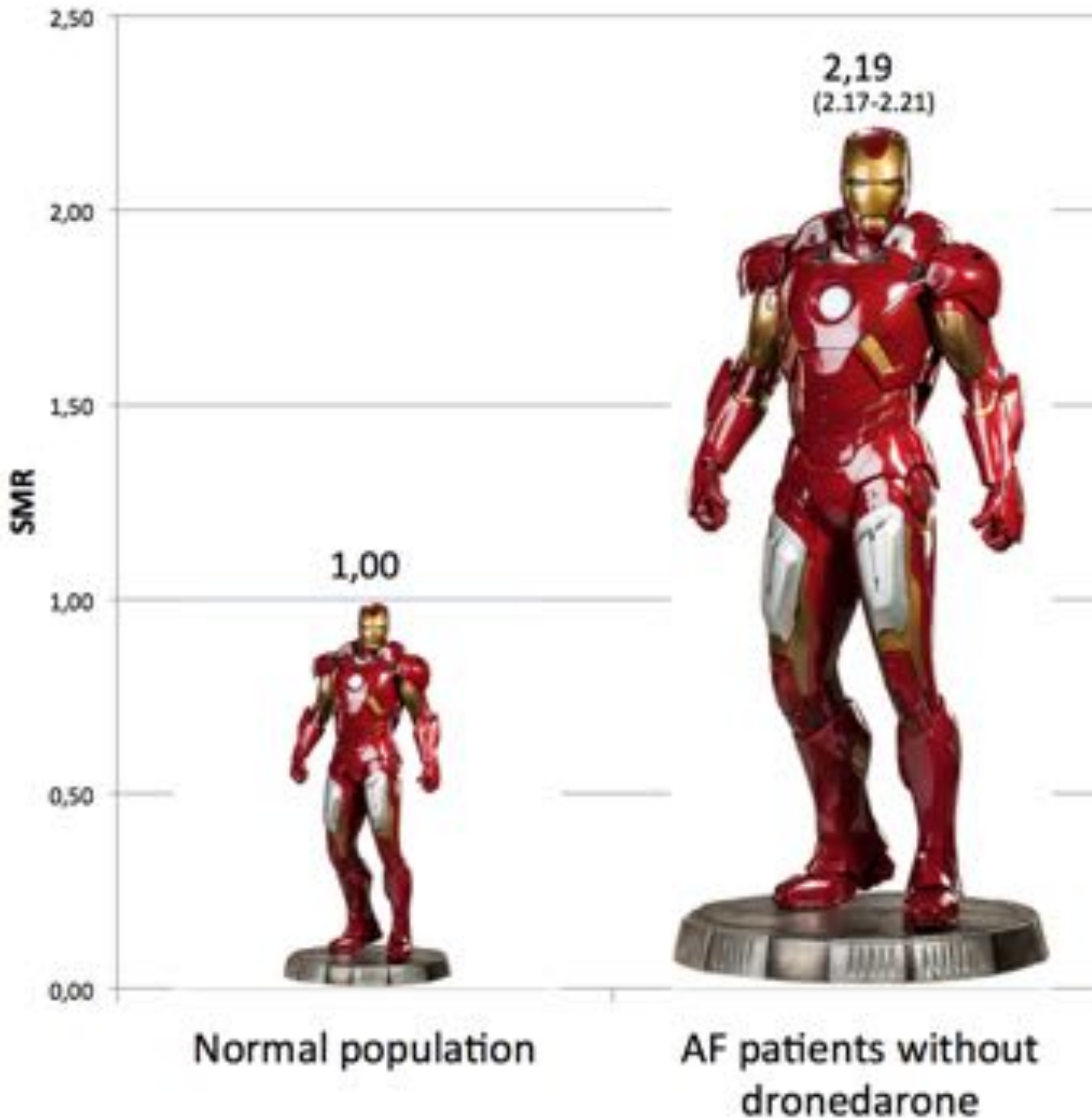


Statistiska centralbyrån
Statistics Sweden

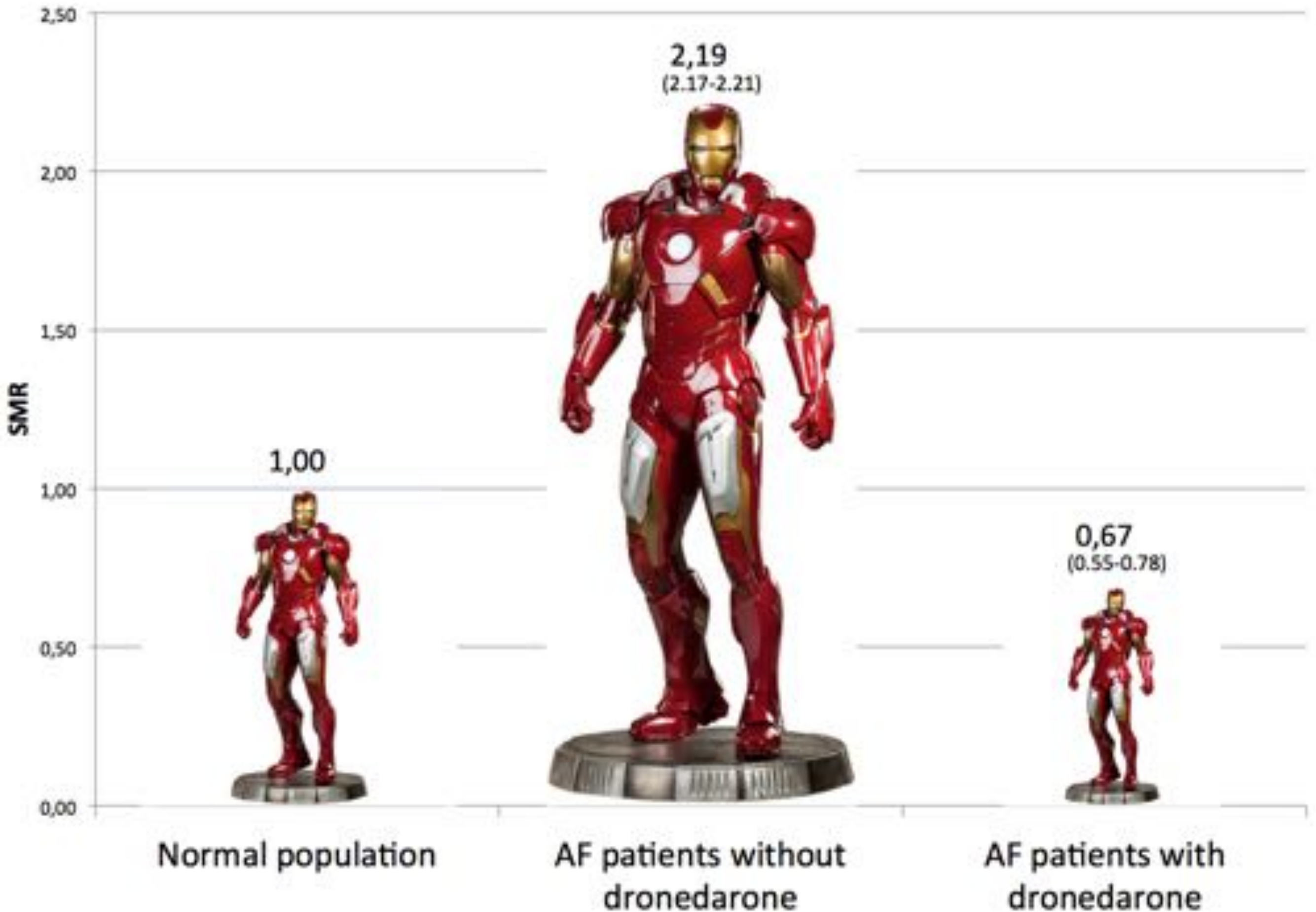
Standardized Mortality Ratio



Standardized Mortality Ratio



Standardized Mortality Ratio





one can adjust for what's in the registries
everything's not in the registries

The Cause of Death Register

	<i>ever dronedarone</i>	<i>never dronedarone</i>
<i>Cancer</i>	<i>38%</i>	<i>24%</i>
<i>Myocardial infarction</i>	<i>15%</i>	<i>9%</i>
<i>Heart failure</i>	<i>24%</i>	<i>43%</i>
<i>Stroke (ischaemic)</i>	<i>10%</i>	<i>9%</i>
<i>Sudden or unwitnessed death</i>	<i>1% (1)</i>	<i>1%</i>
<i>Liver disease</i>	<i>- (0)</i>	<i>1%</i>
<i>Other</i>	<i>13%</i>	<i>9%</i>

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66 year male
hypertension + IHD

One purchase of 100 tablets

Died 2 years later
– treatment 8% of time

Two later purchases
of Amiodarone and Bisoprolol

what about

heart failure patients

who got dronedarone although the shouldn't?

50 out of 1,707 died (annual mortality 2,9%)

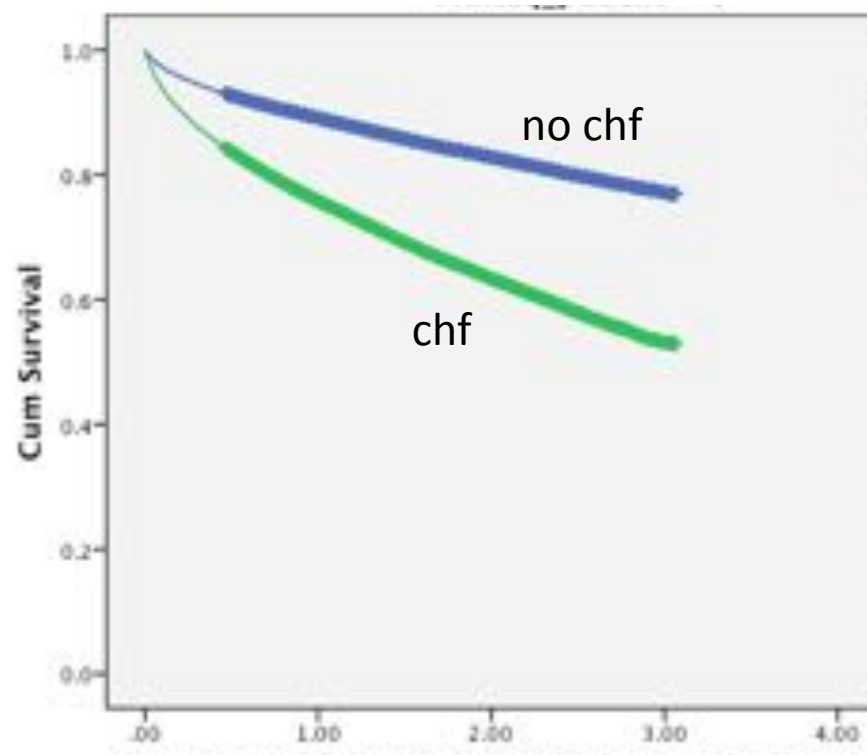
39 of them were no longer taking dronedarone

what about

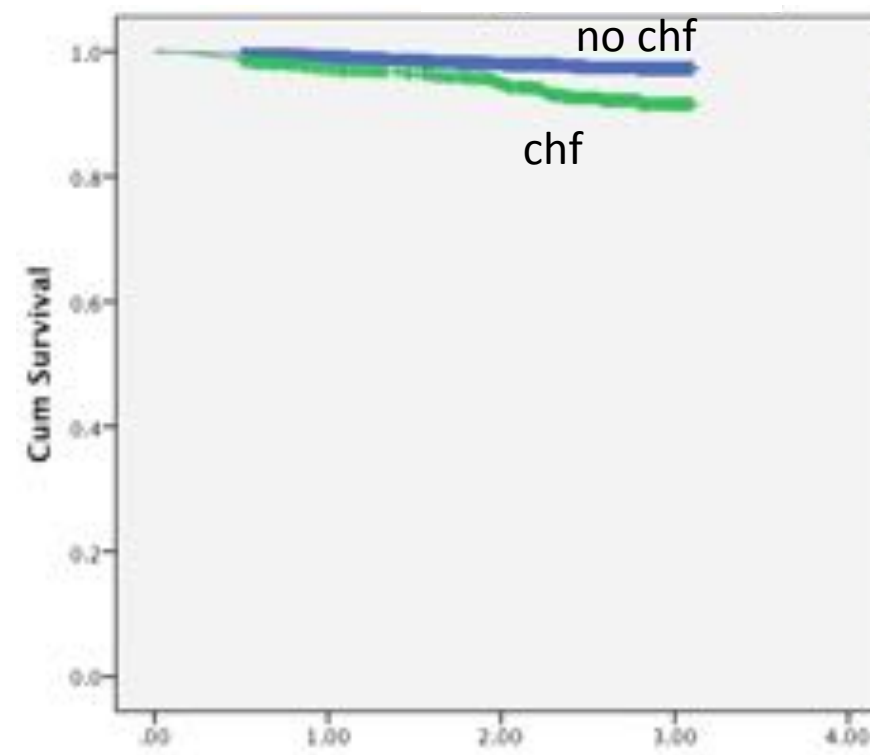
heart failure patients

who got dronedarone although the shouldn't?

Never dronedarone



Ever dronedarone



Annual mortality:
ever dronedarone 2,9 %
never dronedarone 23,9 %

what about
liver side effects?



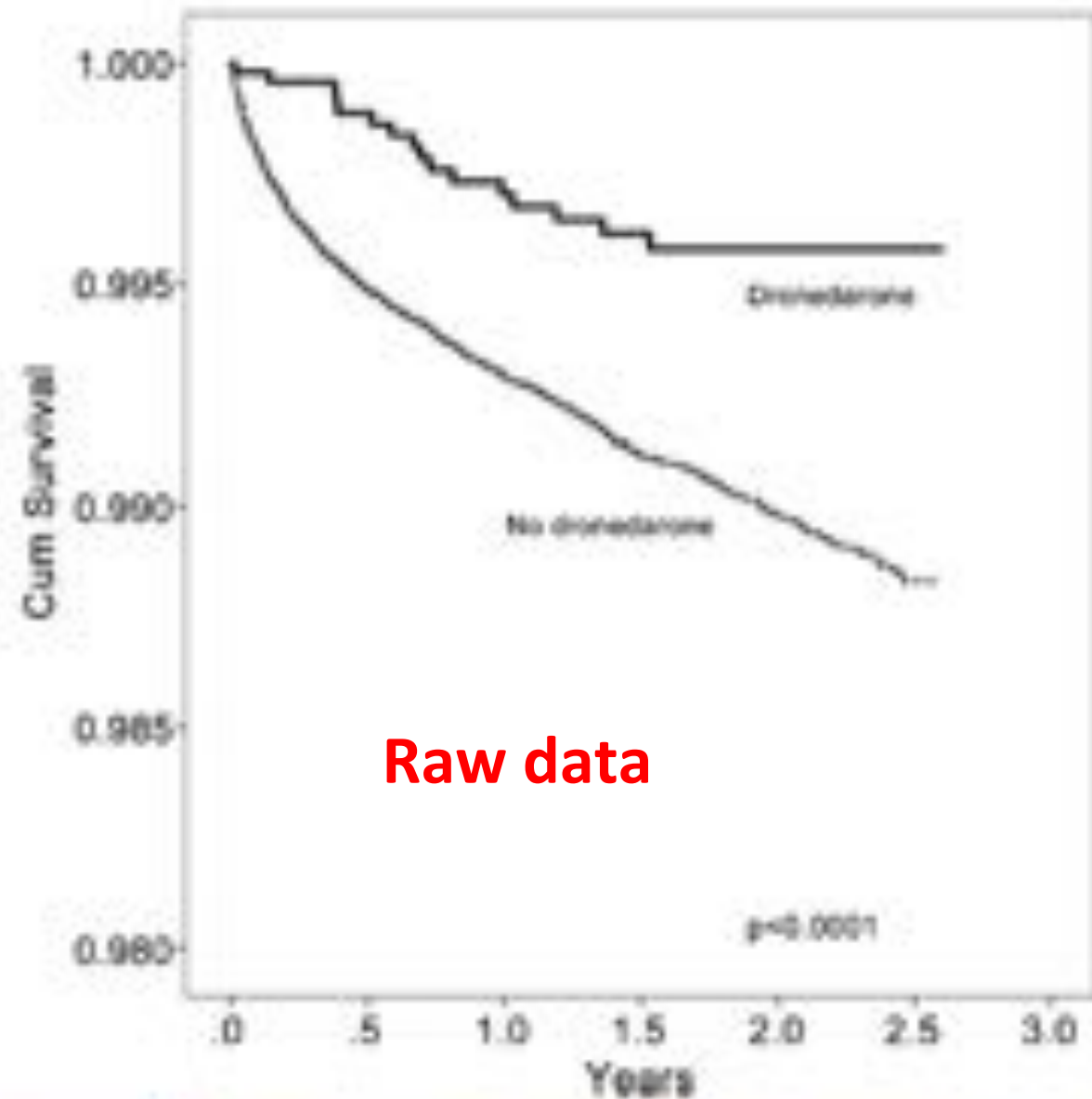
what about
liver side effects?



16 patients (0,22%) without previously known liver disease got a liver diagnosis (ICD-10 K70-77)

11 had stopped taking dronedarone before the diagnosis was made

New diagnosis of liver disease (ITT)

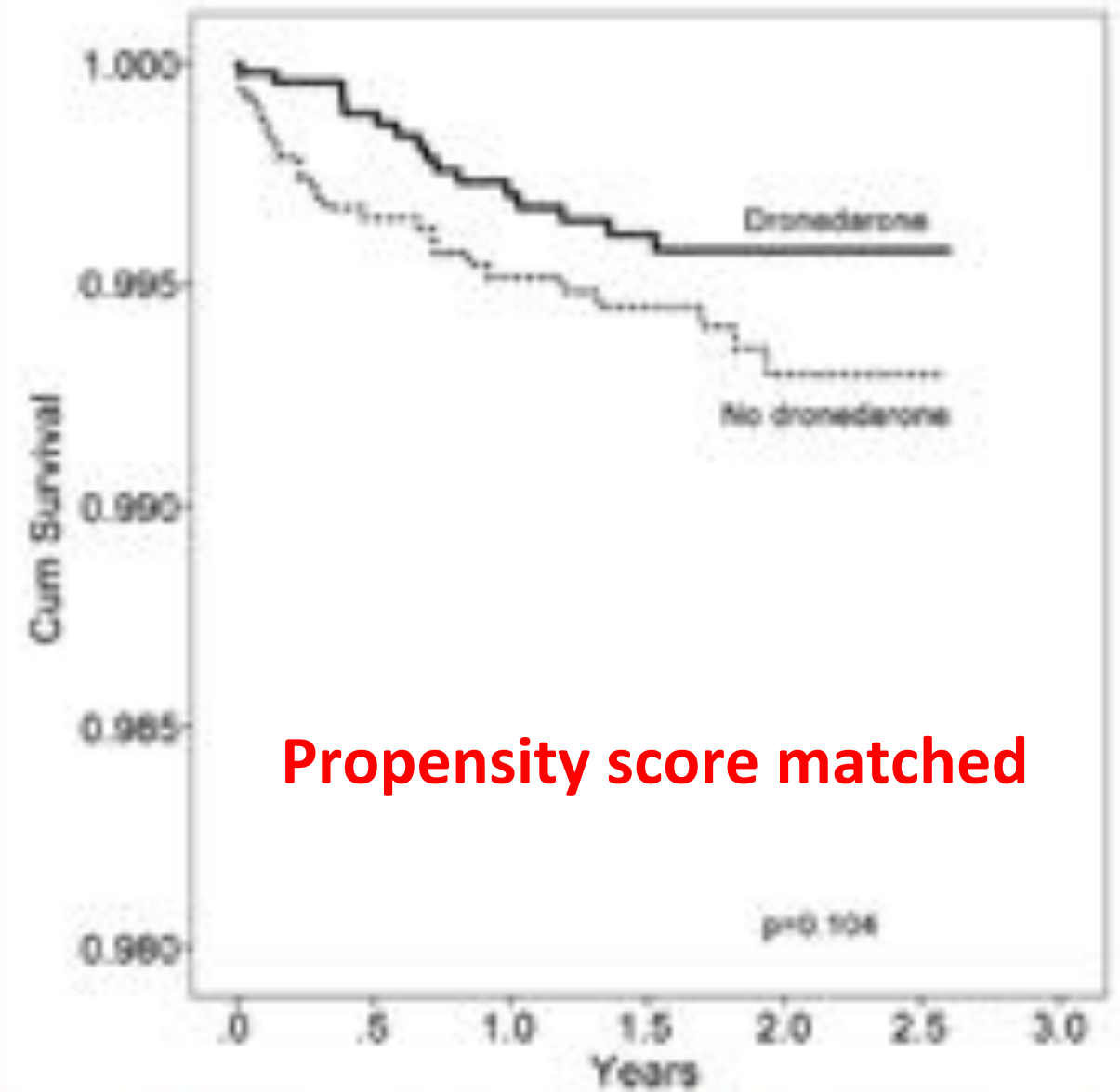


Raw data

Figure 4

Unadjusted Incidence of Liver Disease in Patients Exposed to Dronedaron

Unadjusted incidence of liver disease in 4,856 patients with atrial fibrillation exposed to dronedarone compared with 170,139 patients with atrial fibrillation not exposed to dronedarone. Note abbreviation of scale. Cum = cumulative.



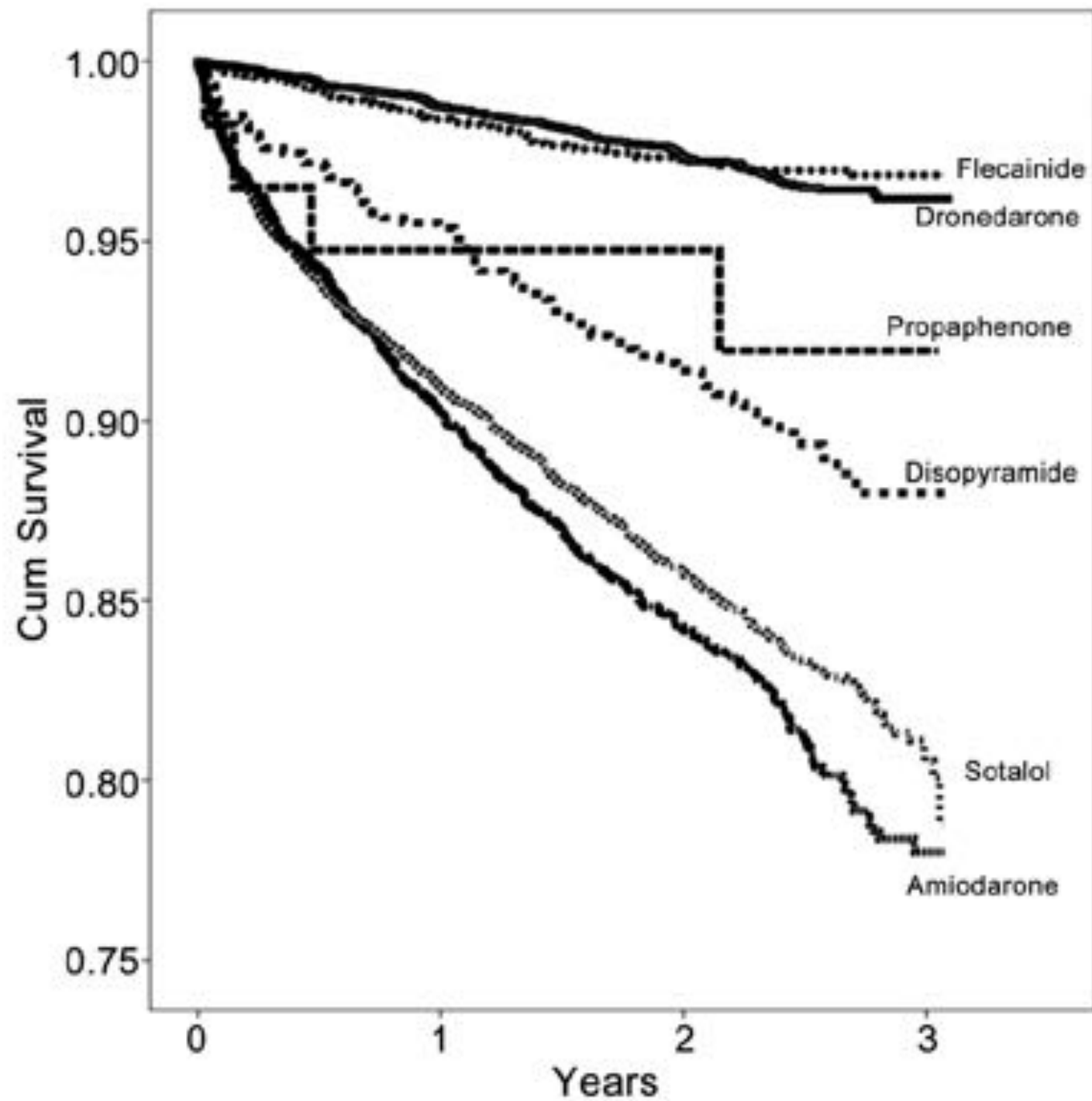
Propensity score matched

Figure 5

Unadjusted Incidence of Liver Disease After Pairwise Matching for Propensity to Receive Dronedaron

Comparison of 4,856 patients with atrial fibrillation exposed to dronedarone and 4,856 AF patients not exposed to dronedarone. Note abbreviation of scale. Cum = cumulative.

Mortality in relation to antiarrhythmic treatment at baseline



Conclusions:

- 1) Dronedarone patients in Sweden were much healthier than other AF patients**

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- 2) Ample room for confounding by indication**

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- 1) Dronedarone patients in Sweden were much healthier than other AF patients**
- 2) Ample room for confounding by indication**
- 3) Prescription of dronedarone to healthy patients (as in Sweden) appears to be safe.**



Thank you



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SAFETY

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