RAte Control Efficacy in Permanent Atrial Fibrillation

A Randomized Comparison of Lenient Rate Control versus Strict Rate Control Concerning Morbidity and Mortality

RACE II

funded by the Netherlands Heart Foundation

AFFIRM, RACE

Rate control is an acceptable alternative for treatment of persistent AF

and

may even be adopted as first choice therapy

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Background RACE II

The optimal level of heart rate control during atrial fibrillation is unknown

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Heart rate control - guidelines

- Heart rate in rest 60 - 80 bpm
- Heart rate during moderate exercise

  90-115 bpm

Fuster et al. Guidelines Eur Heart J 2006

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Strict rate control ?

- Pro
  - lower incidence CHF
  - fewer strokes
  - better survival
  - fewer symptoms
  - improved quality of life
- Contra
  - irregular HR still present?
  - adverse effects drugs
  - pacemaker implants
  - higher costs
  - more difficult to achieve

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Hypothesis

Lenient rate control is not inferior to strict rate control in patients with permanent AF in terms of cardiovascular mortality and morbidity

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Inclusion criteria

- Age ≤ 80 years
- Permanent AF ≤ 12 months
- Heart rate > 80 bpm
- On oral anticoagulation

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Exclusion criteria

- Paroxysmal or transient AF
- Known contra-indications for strict or lenient RC (e.g. previous adverse effects on AAD)
- Unstable heart failure
- Cardiac surgery < 3 months
- Stroke
- Current or foreseen PM/ ICD/ CRT
- Inability to walk or bike

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Primary endpoint (composite)

- Cardiovascular mortality
- Hospitalization for heart failure
- Stroke, systemic emboli, major bleeding
- Syncope, sustained VT, cardiac arrest
- Life-threatening adverse effects of RC drugs
- Pacemaker implantation for bradycardia
- ICD implantation for ventricular arrhythmias

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Stroke

- Sudden onset of focal neurological deficit consistent with occlusion major cerebral artery
- Documented by CT or MR imaging
- Categorized as ischemic, hemorrhagic or indeterminate

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Major bleeding

- Requiring hospitalization with reduction of hemoglobin level of at least 20 mg/L
- Requiring transfusion of at least 2 units
- Symptomatic bleeding in critical area or organ
- Fatal

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Severe adverse effects RC drugs

- Digitalis intoxication
- Conduction disturbances necessitating hospitalization

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Statistical Analysis

Non-inferiority boundary is 10% absolute difference

Statistical hypotheses

H_o: $R_{RC} - R_{ECV} \geq 10\%$ (inferiority)

H_1: $R_{RC} - R_{ECV} < 10\%$ (non-inferiority)

The null hypothesis of inferiority will be rejected when the upper limit of the 2-sided 90% confidence interval of the risk difference does not exceed 10%.

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Treatment

- Patients were randomized to
  - Lenient rate control
  - Strict rate control

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Treatment

- Patients were treated with negative dromotropic drugs (i.e. beta-blockers, non-dihydropyridine calcium-channel blockers and digoxin, alone or in combination)
- Dosages of drugs were increased or drugs combined until the heart rate target was achieved

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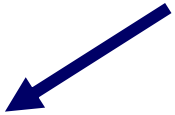
Permanent AF > 80 bpm



lenient

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Permanent AF > 80 bpm

lenient

HR < 110 bpm
(12 lead ECG)

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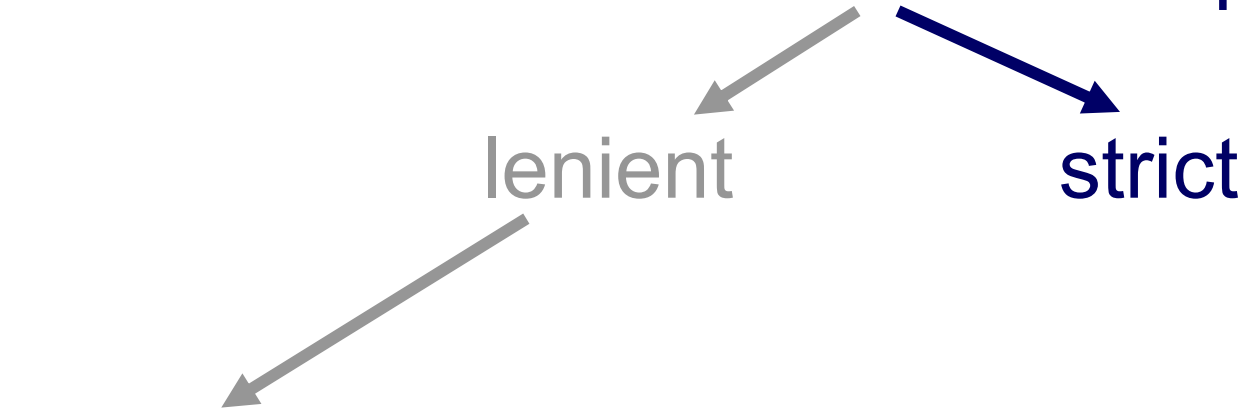

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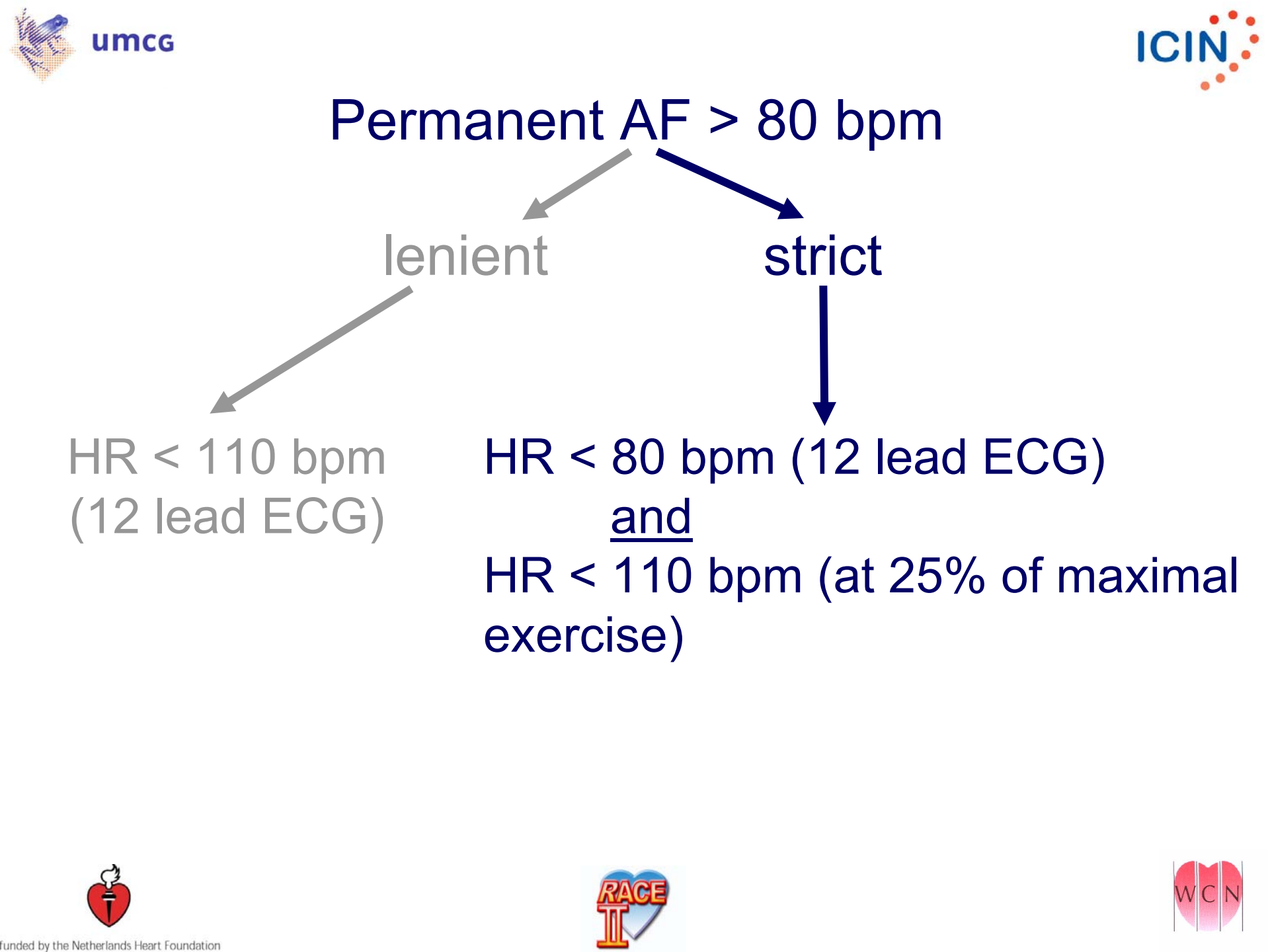

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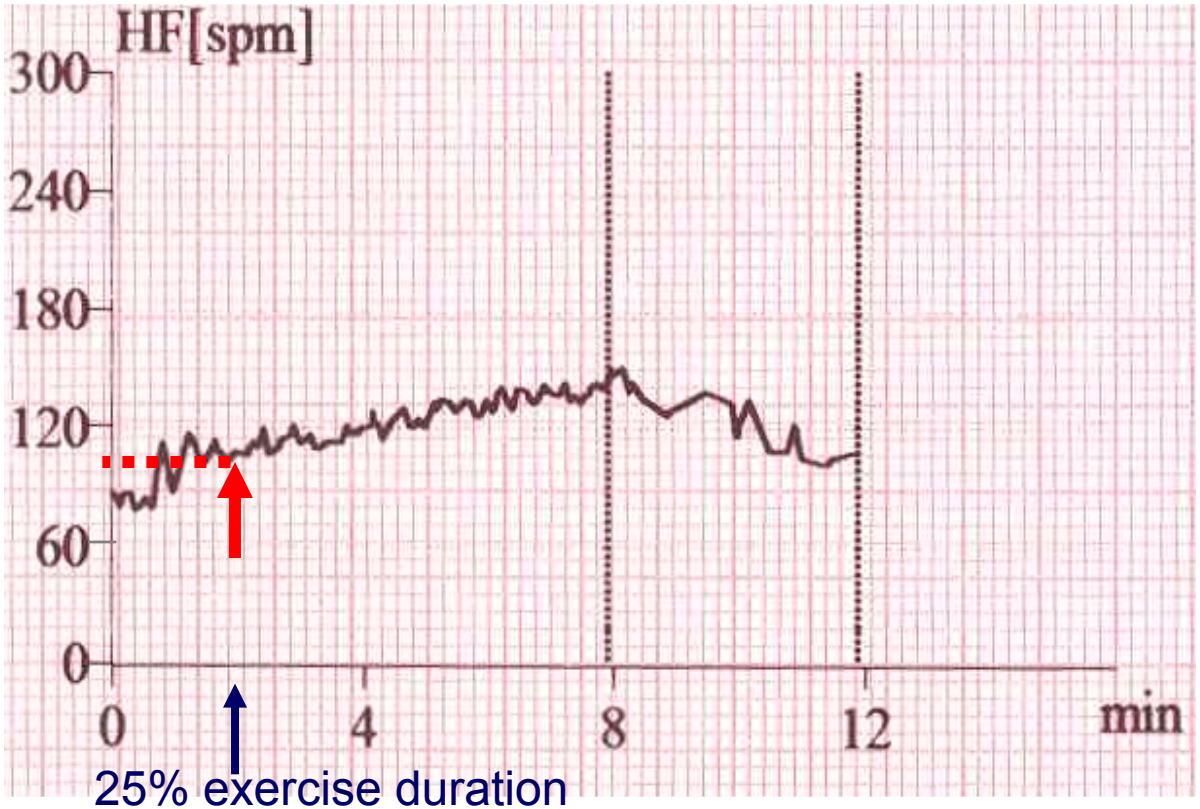

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Permanent AF > 80 bpm

lenient

HR < 110 bpm
(12 lead ECG)

strict

HR < 80 bpm (12 lead ECG)

and

HR < 110 bpm (at 25% of maximal exercise)

After achieving rate control target:

Holter for safety

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Baseline characteristics

	Lenient control n= 311	Strict control n=303
Age	69±8	67±9 years
Male	66%	65%
Duration AF		
Total duration	16 (6-54)	20 (6-64) months
Permanent AF	3 (1-6)	2 (1-5) months

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Baseline characteristics

	Lenient control n= 311	Strict control n=303
Hypertension	64%	58%
CAD	22%	15%
Valve disease	21%	20%
COPD	12%	14%
Diabetes mellitus	12%	11%
Lone AF	2%	2%

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Baseline characteristics

	Lenient control n= 311	Strict control n=303
$CHADS_2$ score	1.4±1.0	1.4±1.2
0-1	57%	64%
2	30%	22%
3-6	13%	14%

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Baseline characteristics

	Lenient control n= 311	Strict control n=303
Echocardiograpy (mm)		
Left atrial size	46±6	46±7
LV end-diastolic size	51±7	51±8
LV end-systolic size	36±8	36±9
LV ejection fraction	52±11	52±12

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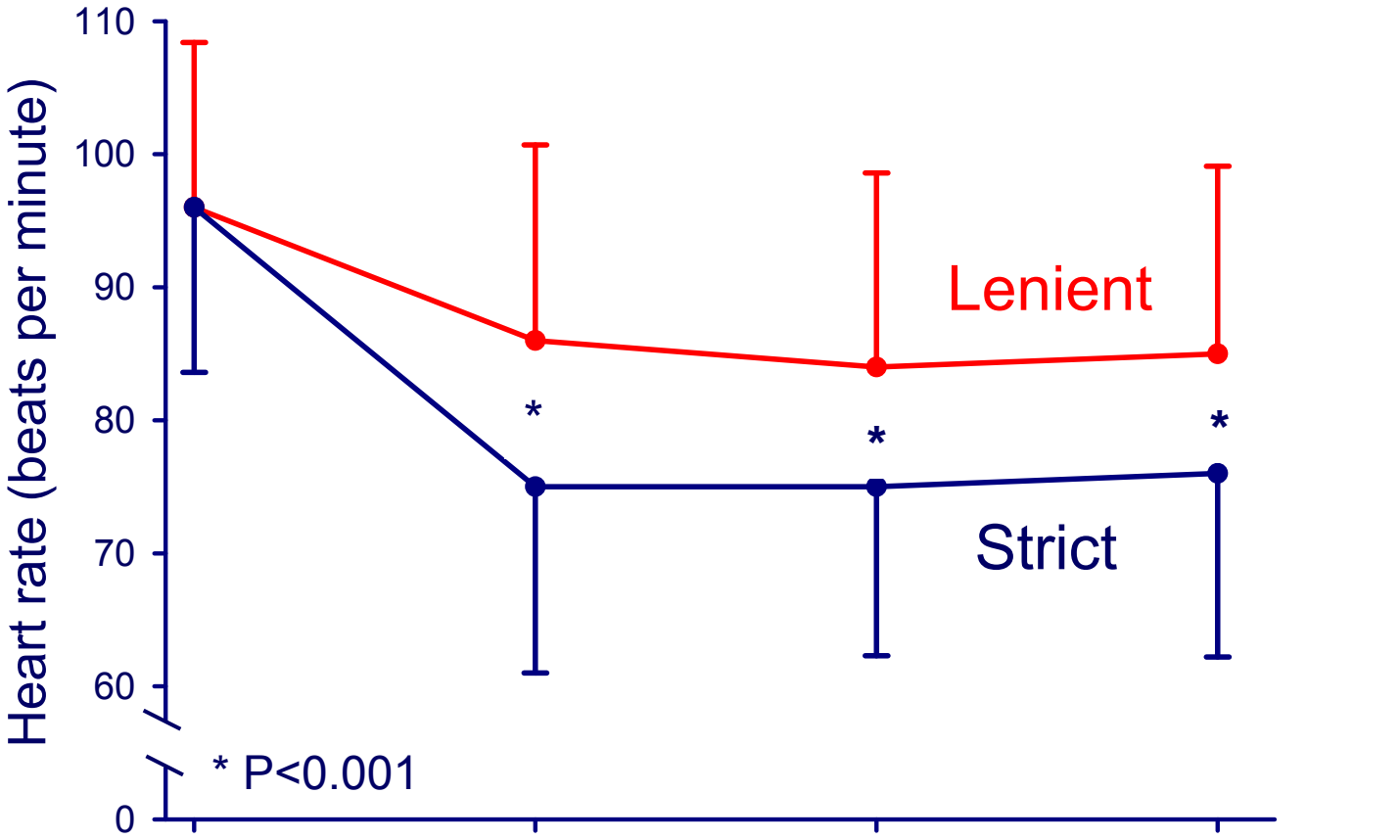
Heart rate during study



No. At Risk	0	12	24	36
Lenient	311	302	291	237
Strict	303	284	277	240

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Rate control targets at end of dose adjustment phase

	Lenient control n= 311	Strict control n=303
Rate control target	98%	67%*
Resting target	98%	75%
Exercise target	-	73%
Visits to achieve target	75	684*
Median	0 (0-0)	2 (1-3)

* P<0.001

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Primary outcome

Estimated cumulative incidence at 3 years

	Lenient control	Strict control
Endpoint	12.9%	14.9%
Risk difference	-2.0%	
90% CI	(-7.6%, 3.5%)	
Upper limit	10%	

P <0.001 for prespecified noninferiority margin

Rejection of inferiority hypothesis

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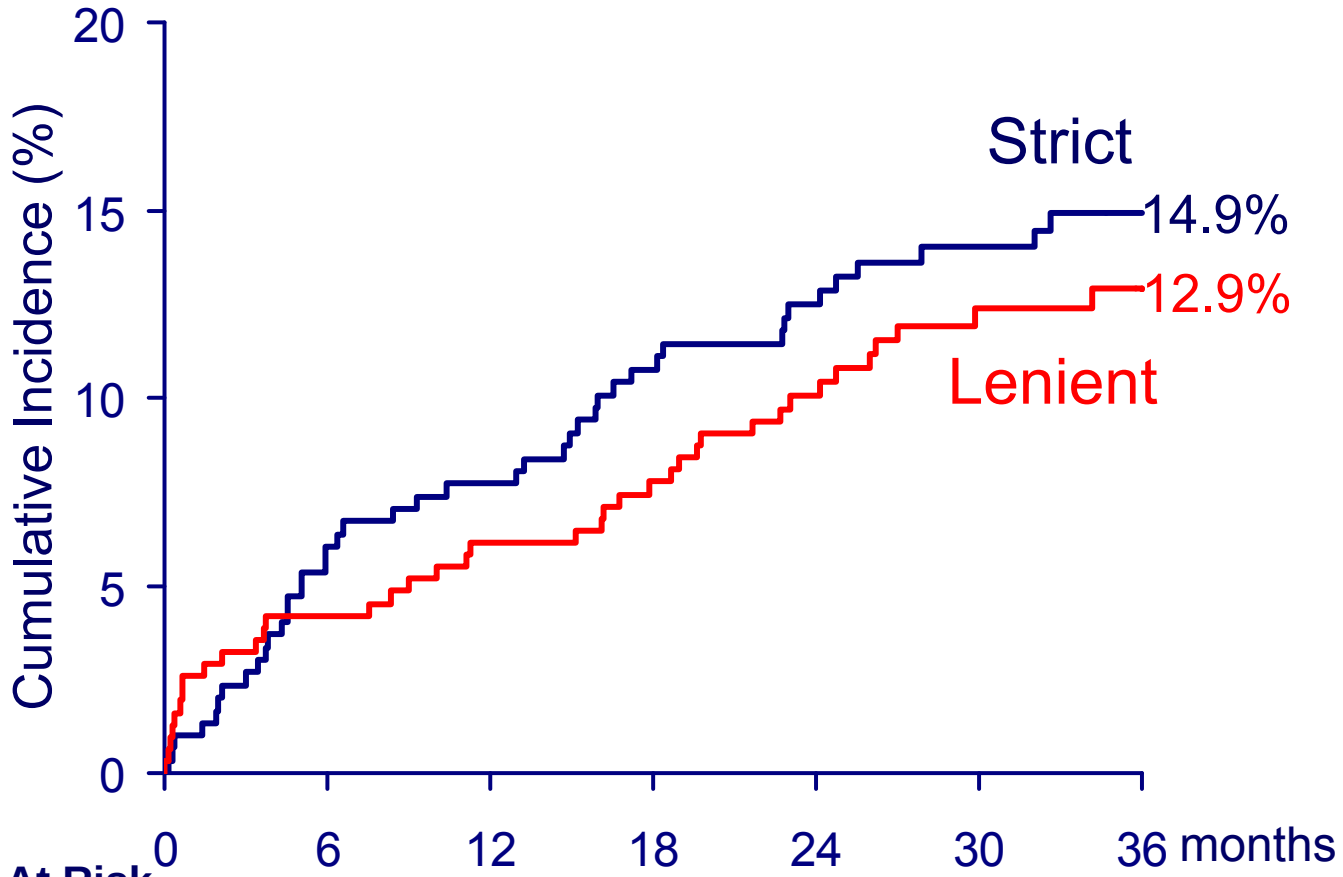
Cumulative incidence primary outcome



No. At Risk							
Strict	303	282	273	262	246	212	131
Lenient	311	298	290	285	255	218	138

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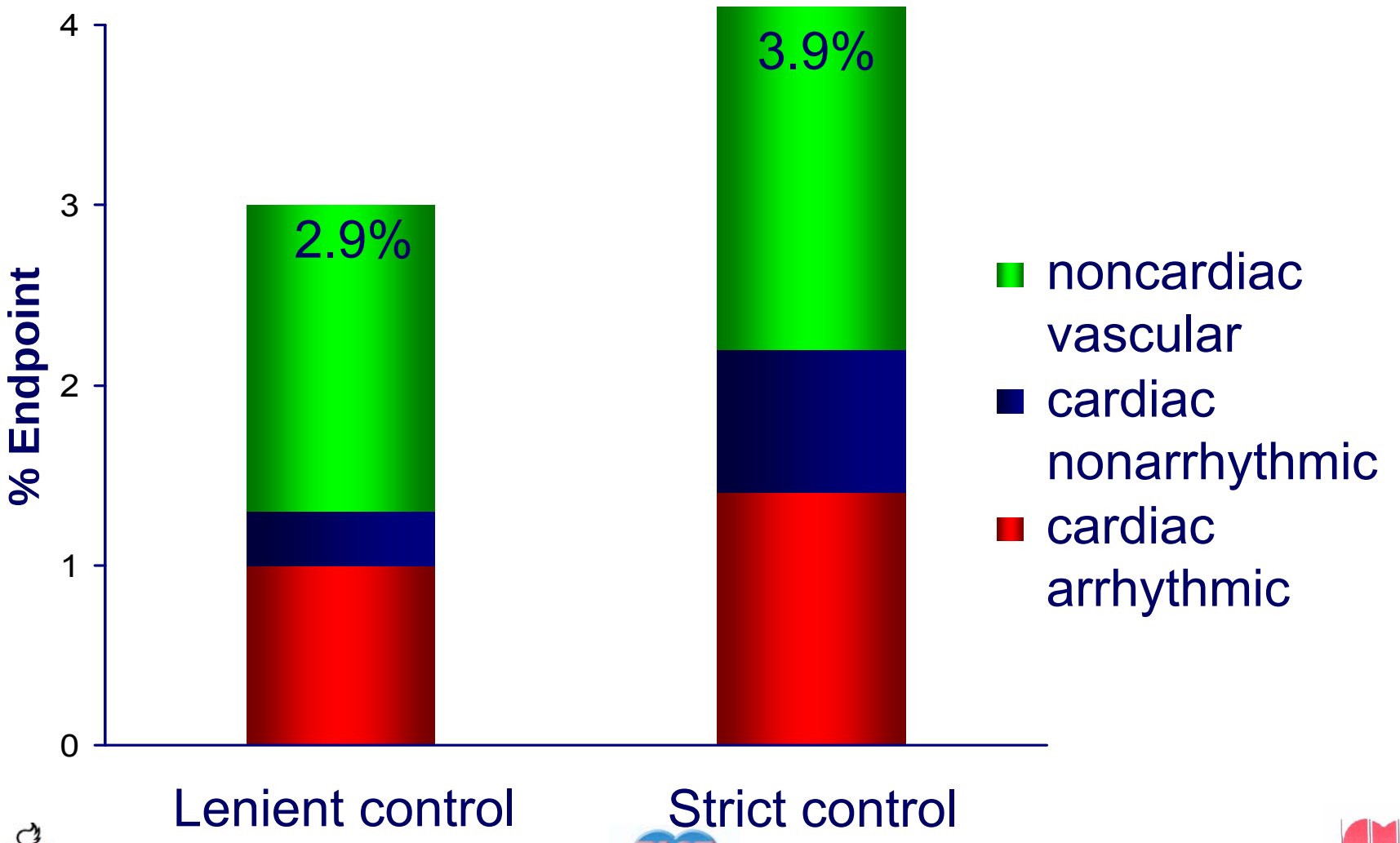
Causes of cardiovascular death



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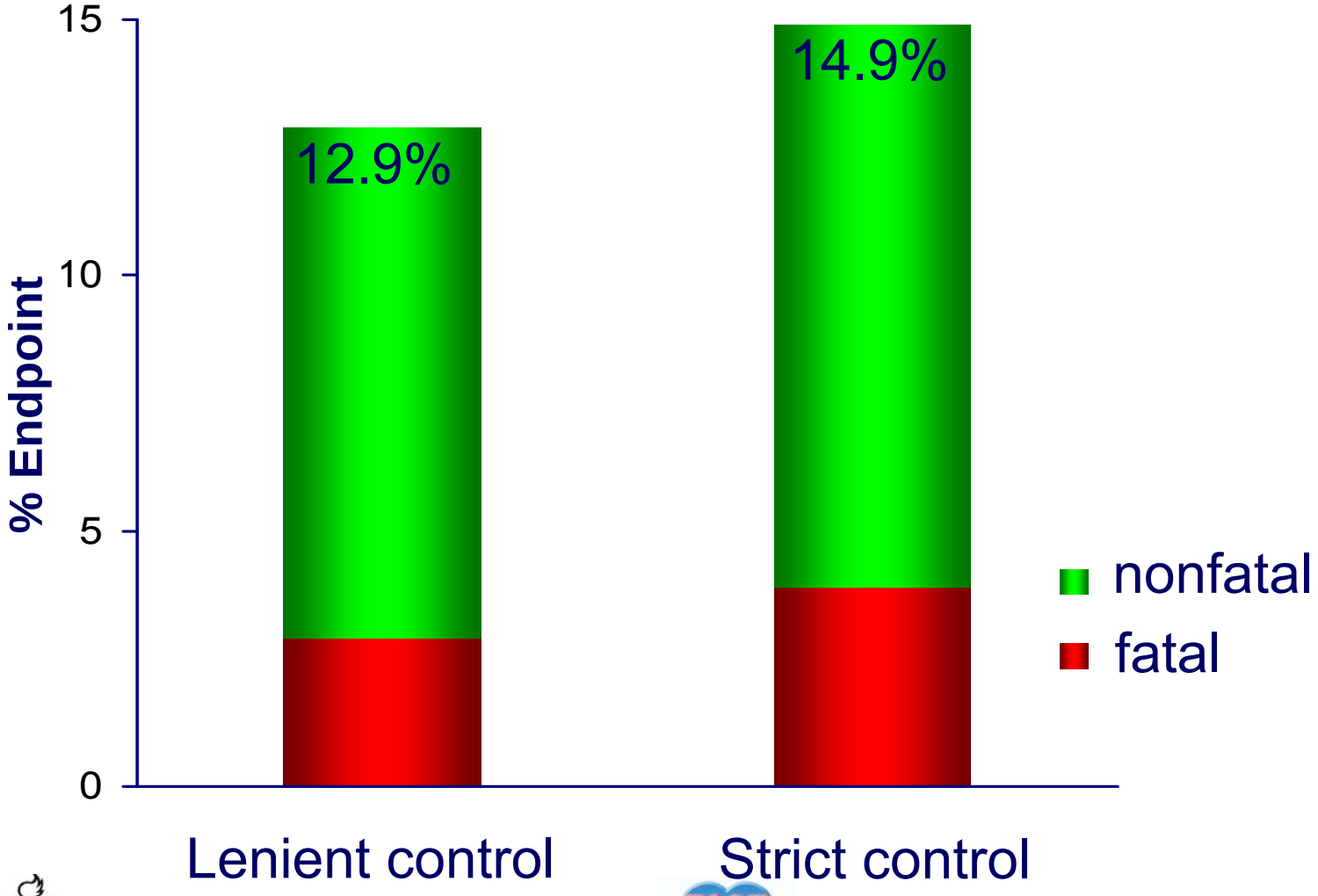
Nonfatal and fatal endpoints



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Components of primary outcome

	Lenient control n= 311	Strict control n=303
Primary outcome	12.9%	14.9%
CV mortality	2.9%	3.9%
Heart failure	3.8%	4.1%
Stroke	1.6%	3.9%
Bleeding	5.3%	4.5%
Adverse effects	1.1%	0.7%
Pacemaker	0.8%	1.4%
Syncope	1.0%	1.0%
ICD	0%	0.4%

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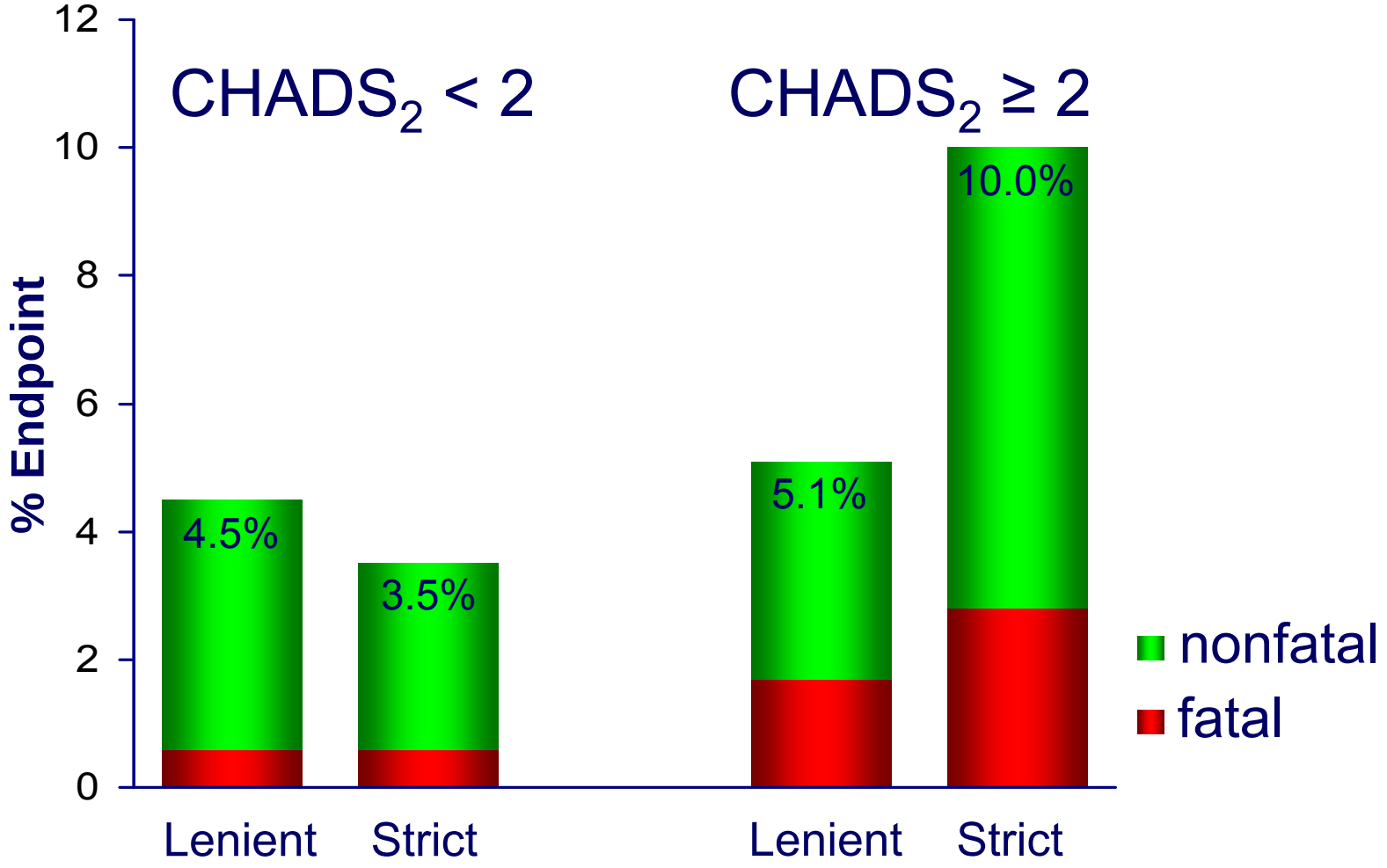
Nonfatal and fatal endpoints



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Symptoms

	Lenient control	Strict control
At baseline	56%	58%
Palpitations	20%	27%
Dyspnea	34%	37%
Fatigue	28%	32%
At end of study	46%	46%
Palpitations	11%	10%
Dyspnea	30%	30%
Fatigue	24%	23%

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Conclusion

- The RACE II study shows that lenient rate control is not inferior to strict rate control
- Lenient rate control is more convenient since fewer outpatient visits and examinations are needed

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Clinical implications

- Lenient rate control may be adopted as first choice rate control strategy in patients with permanent atrial fibrillation
- This applies for high and low risk patients with permanent atrial fibrillation

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