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RACE 3

RACE

Risk Factor Driven Upstream Therapy in Early Persistent Atrial Fibrillation

The Routine versus Aggressive upstream rhythm Control for prevention of Early persistent atrial fibrillation in heart failure study

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Declaration of interest

- Research contracts (Medtronic to the institute)

Financial support RACE 3

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Background

- Maintenance of sinus rhythm improves AF-related symptoms

- However, sinus rhythm maintenance is cumbersome due to atrial remodelling, caused by risk factors and diseases underlying AF, and AF itself

- Recognition of the consequences of atrial remodelling has led to the notion that early intervening may prevent progression of AF

- Risk factor driven upstream therapy refers to interventions that aim to modify the atrial substrate, and also has a favourable effect on risk factors and diseases underlying AF

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Hypothesis

Risk factor driven upstream therapy is superior to conventional therapy for maintenance of sinus rhythm in patients with early persistent AF and heart failure

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Trial design

- Prospective, randomised, open label, superiority trial
- Investigator-initiated
- Multicenter: 14 sites in The Netherlands and 3 in United Kingdom
- Enrolment between 2009 and 2015
- 1 year follow-up

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Inclusion criteria

- Early symptomatic persistent AF
  - Total persistent AF duration >7 days and <6 months, a history of ≤1 ECV
  - Total AF history <5 years
- Early HF
  - Total history <1 year
  - One of the following:
    - HFpEF: LVEF ≥45%, NYHA II-III, and echo and NT-proBNP criteria
    - HFrEF: LVEF <45% and NYHA I–III
- Optimal documentation and treatment of underlying heart diseases
- Age ≥ 40 years

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Exclusion criteria

- Paroxysmal or transient or asymptomatic AF
- Use of anti-arrhythmic drugs
- Left atrial size >50 mm
- LVEF <25%
- NYHA IV
- Use of mineralocorticoid receptor antagonists
- Unstable cardiovascular conditions
- Inability to perform cardiovascular rehabilitation program

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Randomisation

- Patients were randomised to
  - Risk factor driven upstream therapy
  - Conventional therapy

- Randomisation was stratified for LVEF ≥45% and <45%

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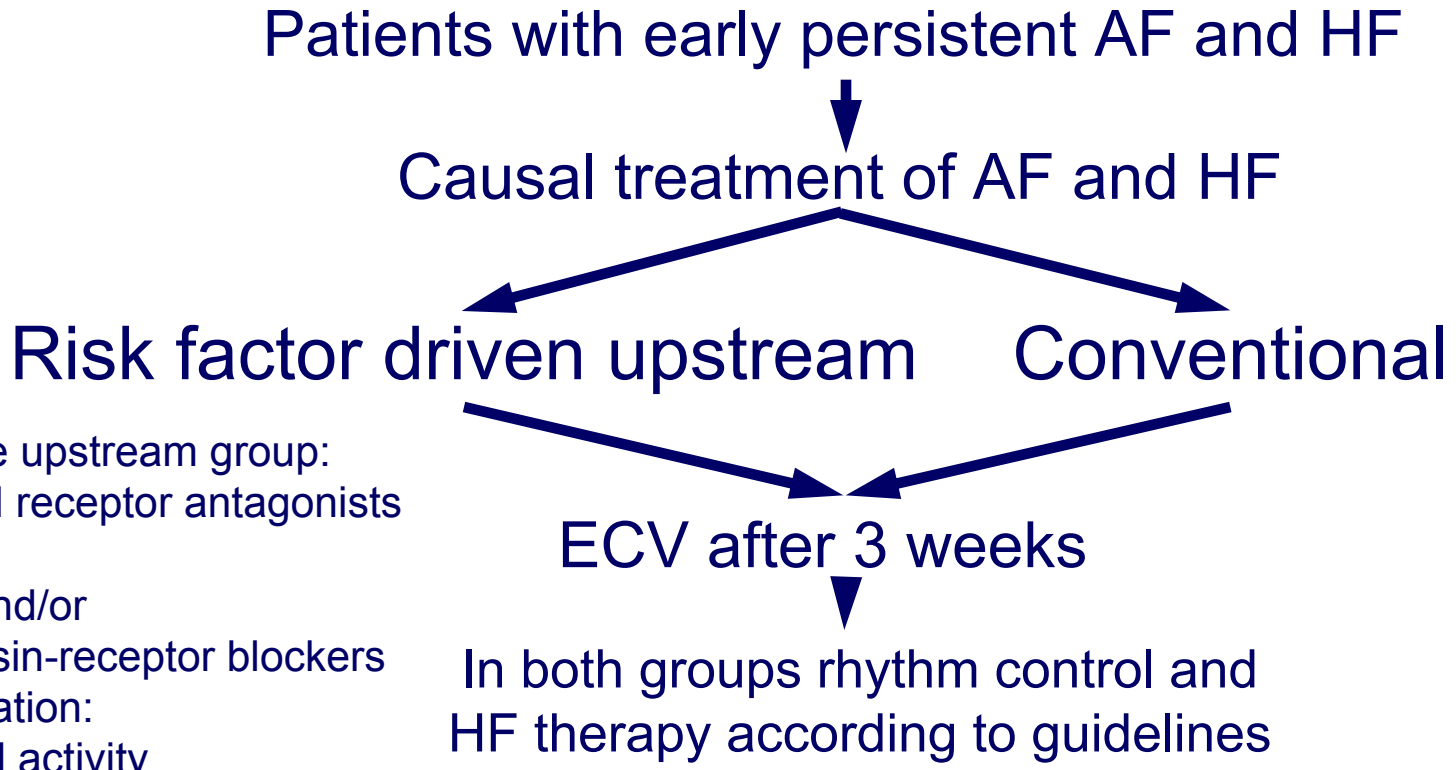
Flowchart



On top of that in the upstream group:

1. Mineralocorticoid receptor antagonists
2. Statins
3. ACE-inhibitors and/or
   angiotensin-receptor blockers
4. Cardiac rehabilitation:
   - physical activity
   - dietary restrictions
   - counselling

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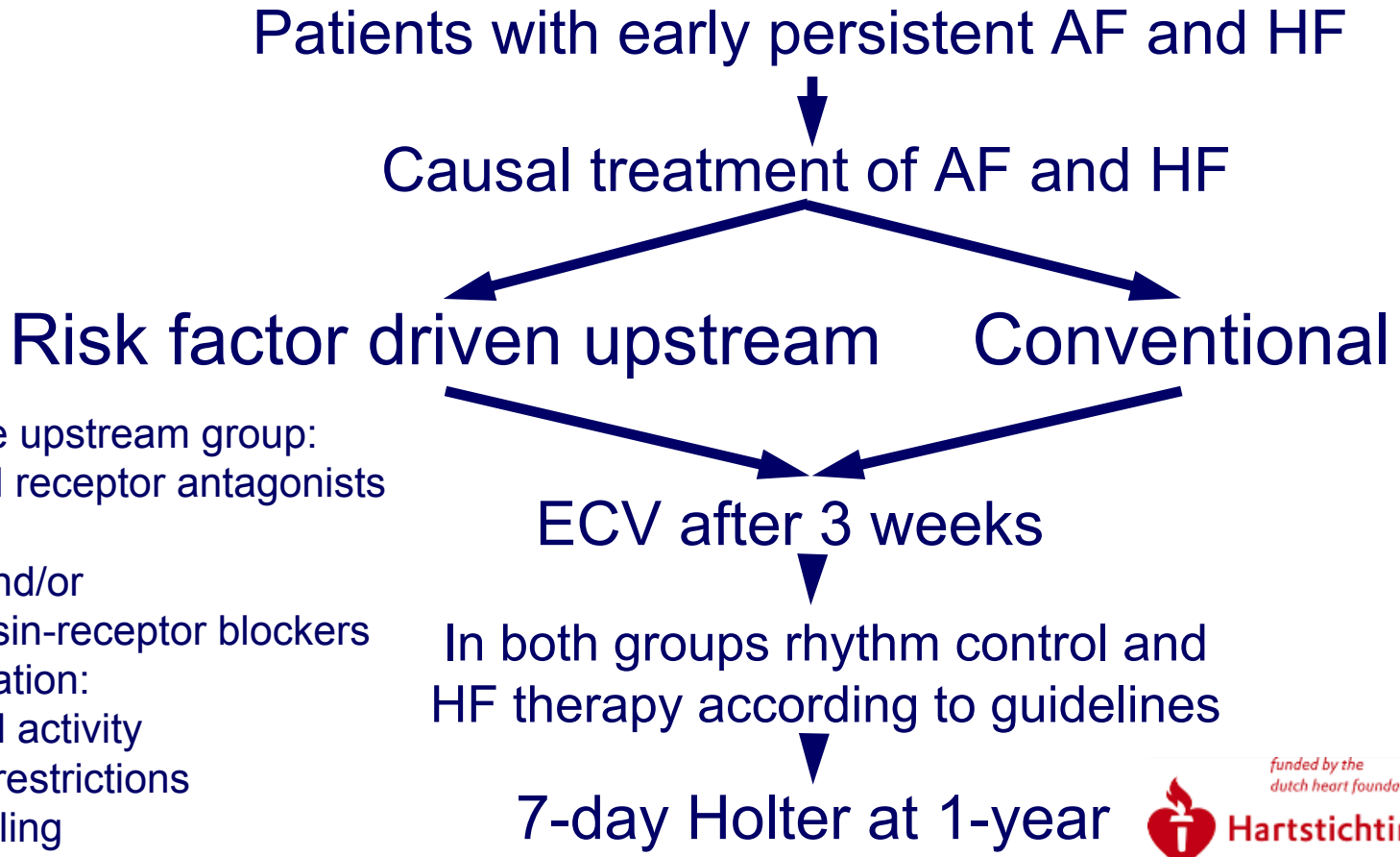
Flowchart



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Risk factor driven upstream therapy

- MRAs, ACE-Is and ARBs were dosed aiming to the highest tolerated dose
- Blood pressure target was < 120/80 mmHg
- Statins were prescribed at the recommended dosages

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Cardiac rehabilitation program

- Physical activity and exercise maintenance:
  - Supervised training started directly after inclusion, before ECV
  - 9 to 11 weeks 2-3 times per week
  - 6-weekly counseling to stimulate performing sports, 5 times per week ≥30min

- Dietary restrictions and drug adherence:
  - Counselling started 1 week after inclusion, then every 6 weeks
  - Restriction of sodium intake (<7.5 g salt/day)
  - Calorie reduction in case of BMI ≥27 kg/m^2
  - Fluid restriction depending on the severity of HF
  - Compliance to drug therapy

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Primary endpoint

Presence of sinus rhythm, defined as sinus rhythm during at least 6/7th of assessable time, at the 7-day Holter* at 1-year

*All 7-day Holters were analysed by central core lab blinded for randomised therapy

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Statistical analysis

- The statistical approach was testing for superiority, statistical hypotheses:
  H_o: Odds ratio ($Odds_{upstream}/Odds_{conventional}$) ≤ 1 (non-superiority)
  H_1: Odds ratio ($Odds_{upstream}/Odds_{conventional}$) > 1 (superiority)

- The null-hypothesis of no treatment benefit is rejected if the lower 95% confidence limit exceeded 1, which is equivalent to one-sided testing at an alpha level of 0.05

- 5 patients were excluded, because they did not fulfil the inclusion criteria

- Subgroup analyses are conducted to evaluate treatment interactions within pre-specified subgroups

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Patient characteristics

	Upstream	Conventional
	n=119	n=126
Age (years)	64±9	65±9
Male sex	79%	79%
Total history of AF (months)	3 (2-7)	3 (2-5)
Total persistent AF (months)	2 (1-4)	2 (1-4)
Duration of HF (months)	2 (1-4)	2 (1-4)
LVEF <45%	29%	29%
NT-proBNP (pg/ml)	1057 (694-1636)	1039 (717-1755)

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Patient characteristics

	Upstream	Conventional
	n=119	n=126
Hypertension	55%	62%
Diabetes	8%	13%
Coronary artery disease	16%	11%
Valve disease	9%	8%
Body mass index (kg/m^2)	29 (26-31)	28 (25-31)
CHA_2DS_2-VASc score	2 (1-3)	2 (1-3)

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Treatment at 1-year follow-up

	Upstream	Conventional
	n=119	n=126
MRA	85%	4%*
Statin	93%	48%*
ACE-I and/or ARB	87%	76%
Cardiac rehabilitation	92%	-
Maintaining ≥ 3 therapies	87%	-
Maintaining all 4 therapies	58%	-

* P<0.001

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Rhythm control during follow-up

	Upstream	Conventional
	n=119	n=126
Patients with repeat-ECVs	56%	51%
Patients with AADs	45%	43%
Patients with amiodaron	22%	25%
Patients with atrial ablations	4%	2%

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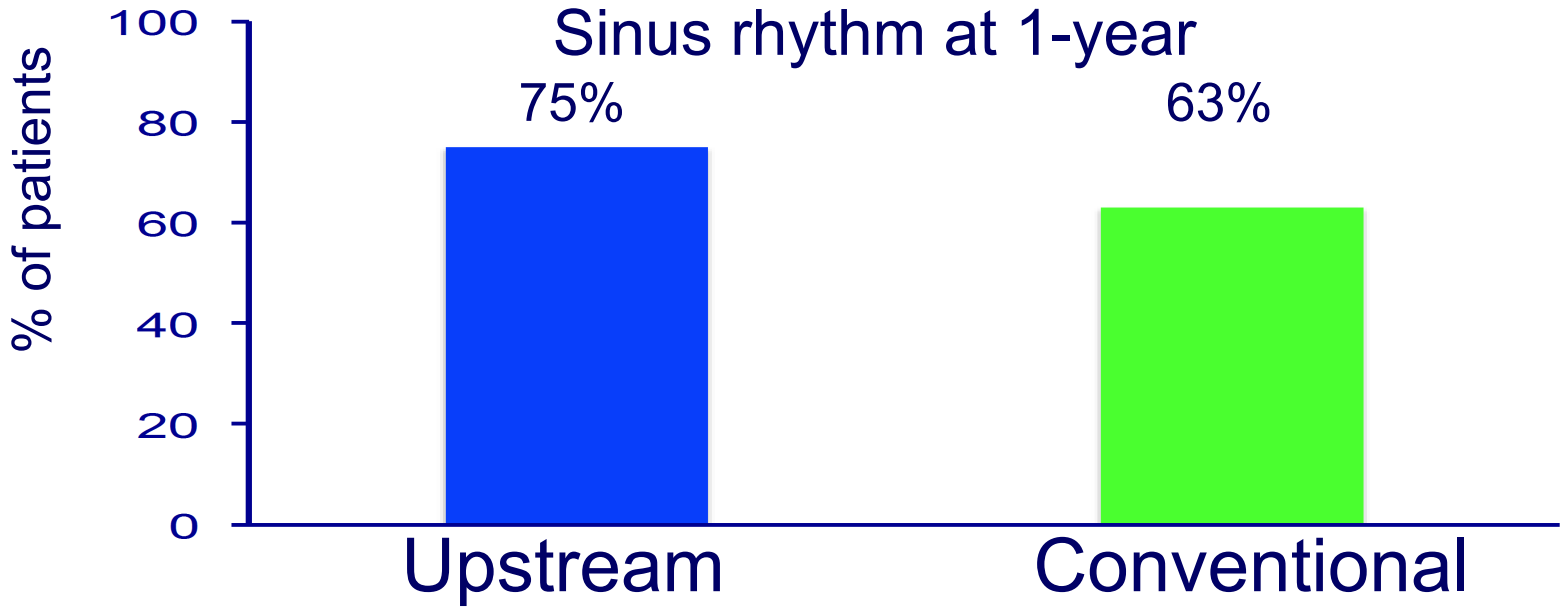
Primary endpoint



Odds ratio	1.765
Lower 95% confidence limit	1.115

Superiority hypothesis is proven p=0.021

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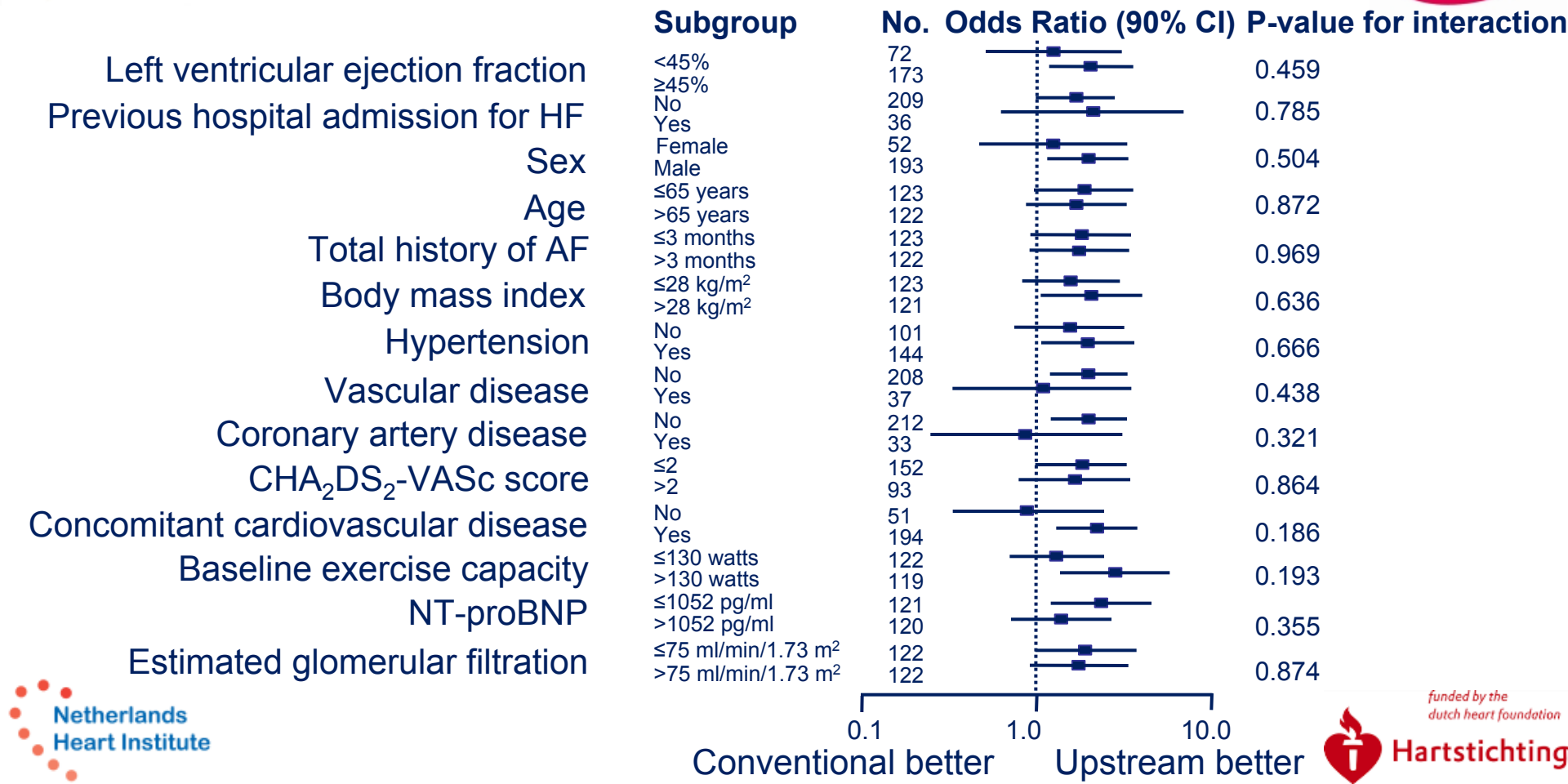
Primary endpoint in subgroups



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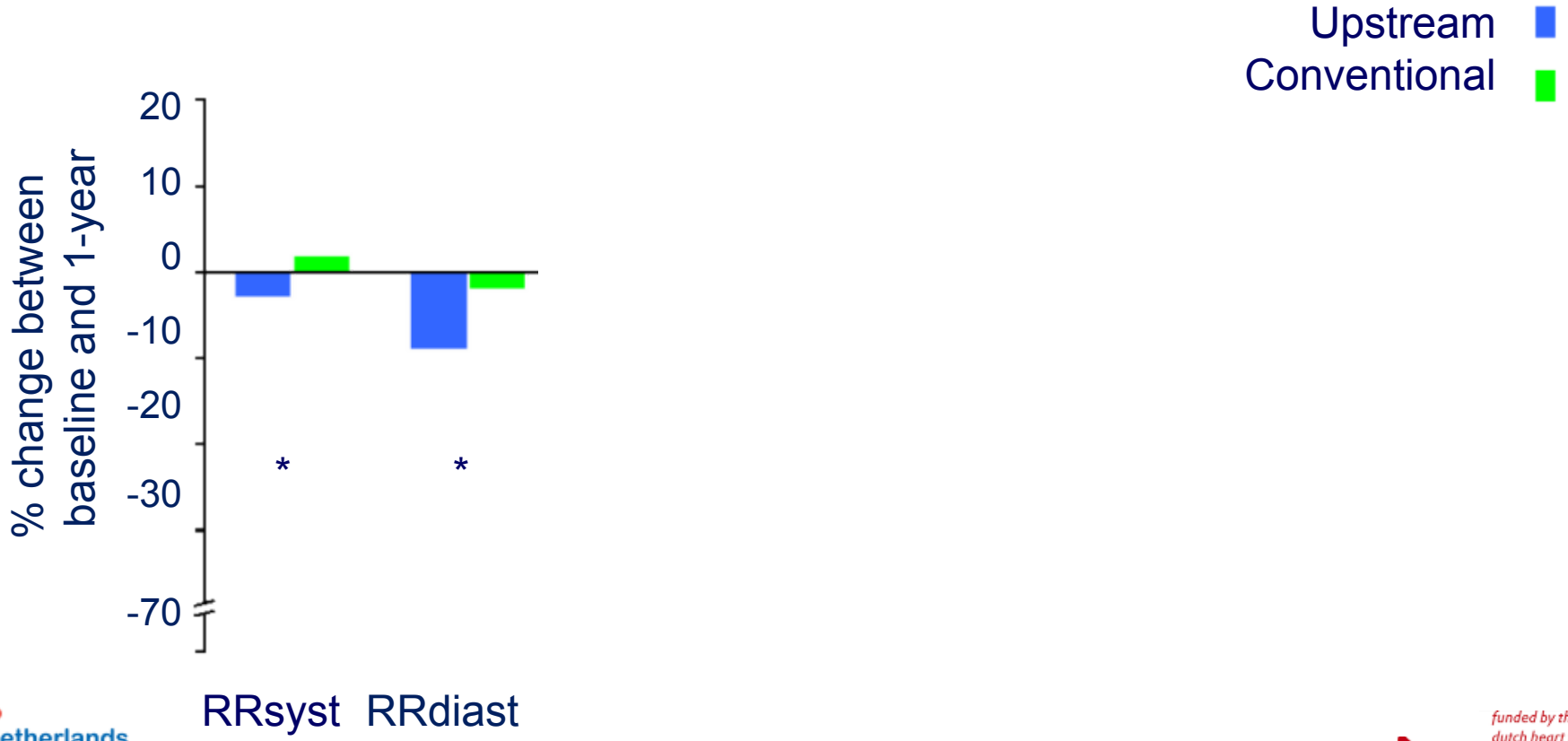
Changes in secondary endpoints



* P<0.05 upstream versus conventional group

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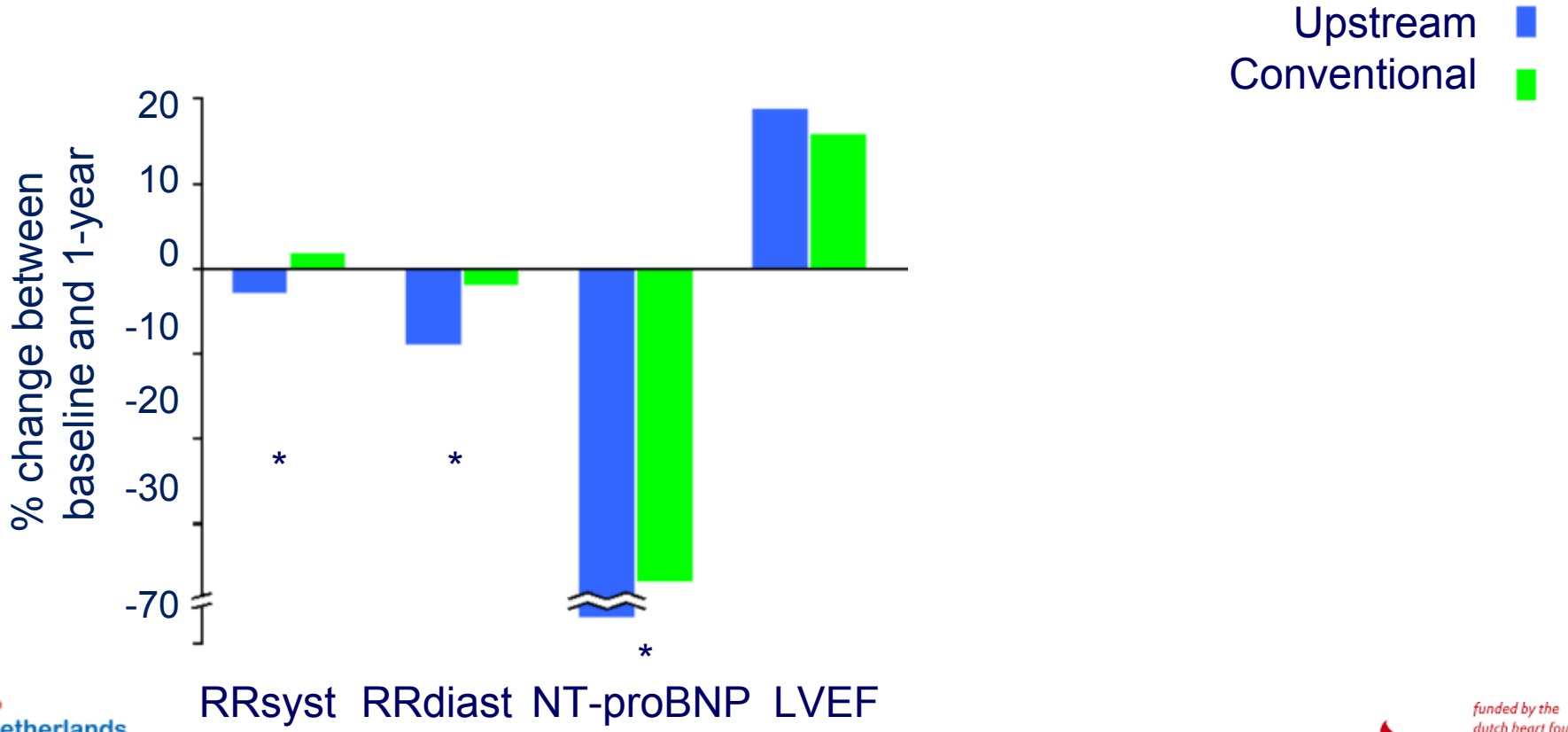
Changes in secondary endpoints



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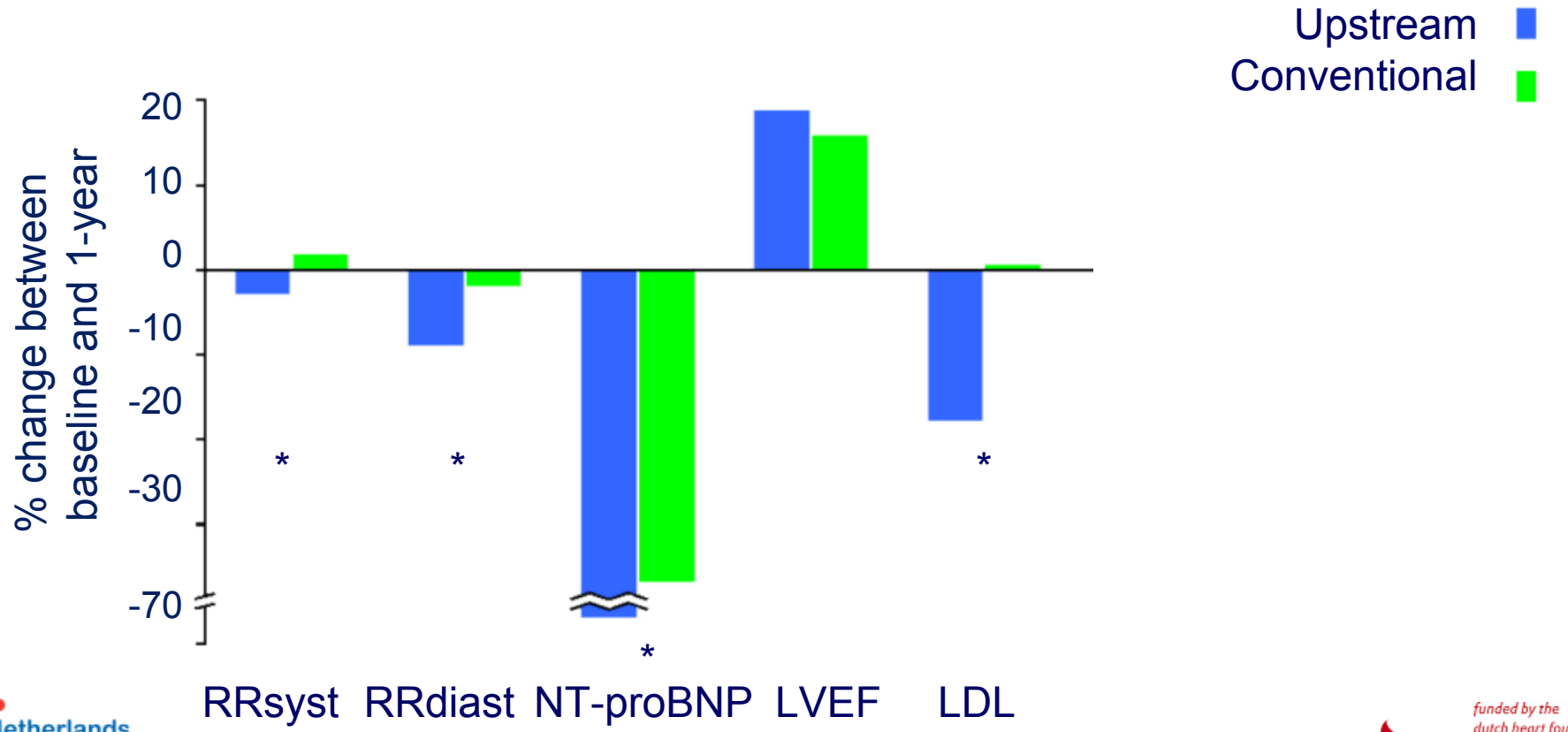
Changes in secondary endpoints



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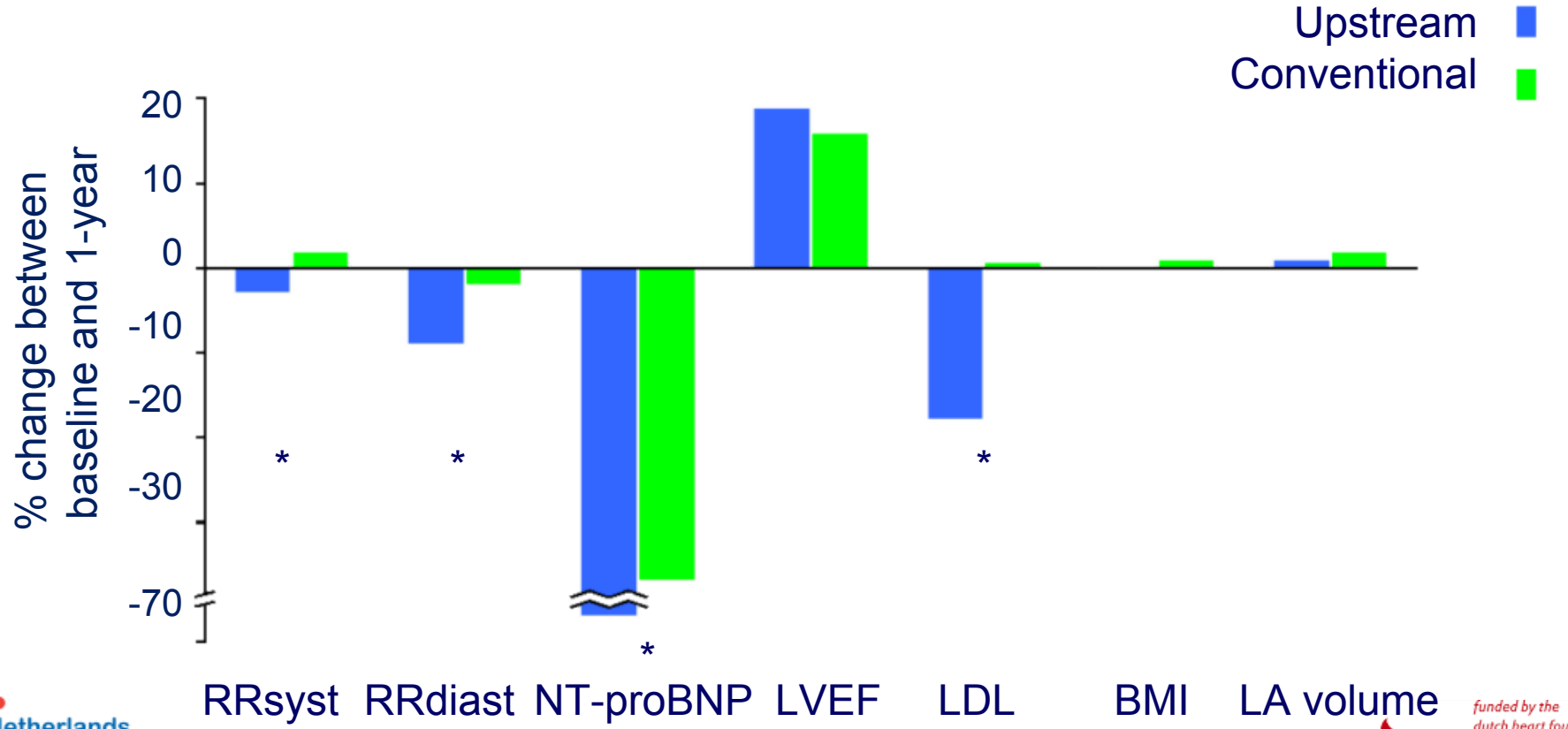
Changes in secondary endpoints



* P<0.05 upstream versus conventional group

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Secondary endpoints

	Upstream	Conventional
	n=119	n=126
Composite CV morbidity/mortality*	16%	17%
Individual components		
All-cause mortality	0%	2%
Hospital admission for HF	0%	2%
Hospital admission for AF	7%	10%
Hospital admission for other CV reasons	13%	7%

*All endpoints adjudicated by review committee, blinded for randomized therapy

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Safety endpoints

	Upstream	Conventional
	n=119	n=126
MRA adverse event	31%	-
Discontinuation	6%	-
Statin adverse event	17%	3%
Discontinuation	3%	1%
ACE-I and/or ARB adverse event	12%	6%
Discontinuation	1%	-

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Conclusion

The RACE 3 study demonstrates that risk factor driven upstream therapy, including treatment of risk factors and change of lifestyle, is effective and feasible to improve maintenance of sinus rhythm in patients with early persistent AF and HF

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Clinical implication

The effect of upstream therapy on reduction of risk factors and cardiovascular diseases, instead of atrial remodeling, was favourable

Therefore, our study may contribute to the shift to focus on risk factor modification to improve AF outcomes

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