Atrial Shunt for HFpEF/HFmrEF: 5-Year Outcomes in the REDUCE LAP-HF II Trial

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TECHNOLOGY AND HEART FAILURE THERAPEUTICS

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All relevant financial relationships have been mitigated

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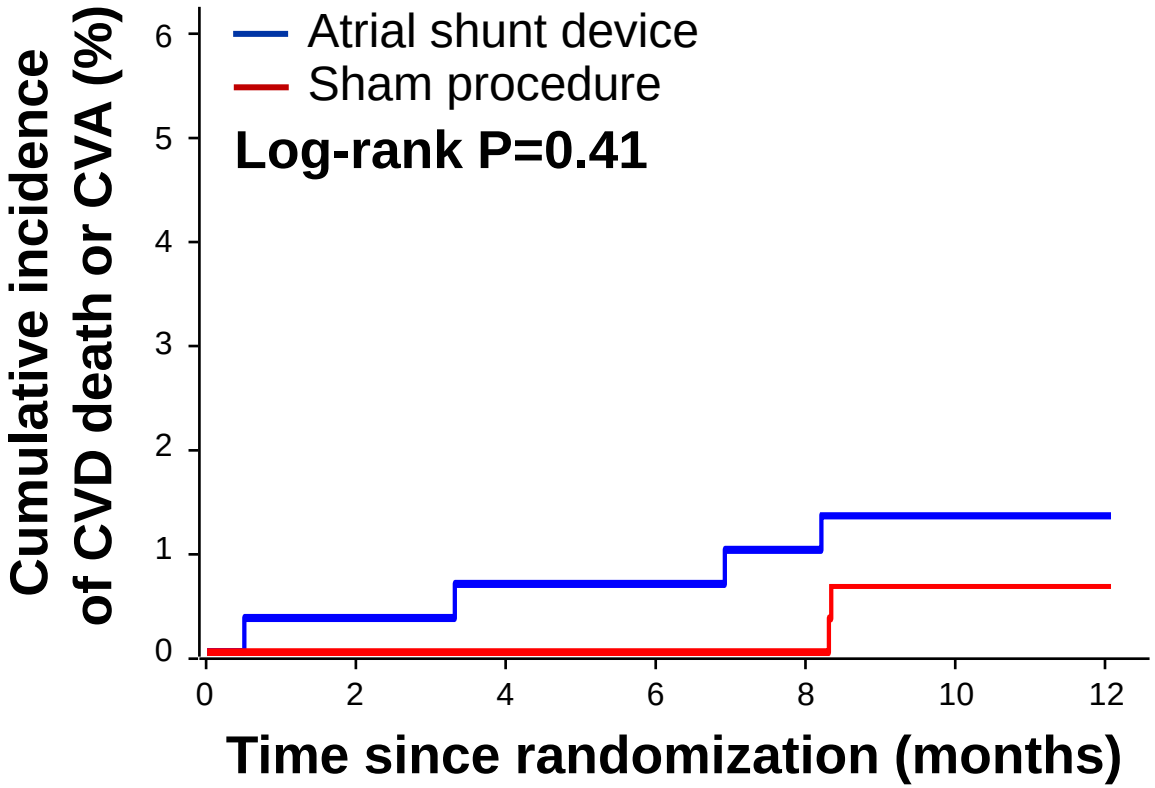
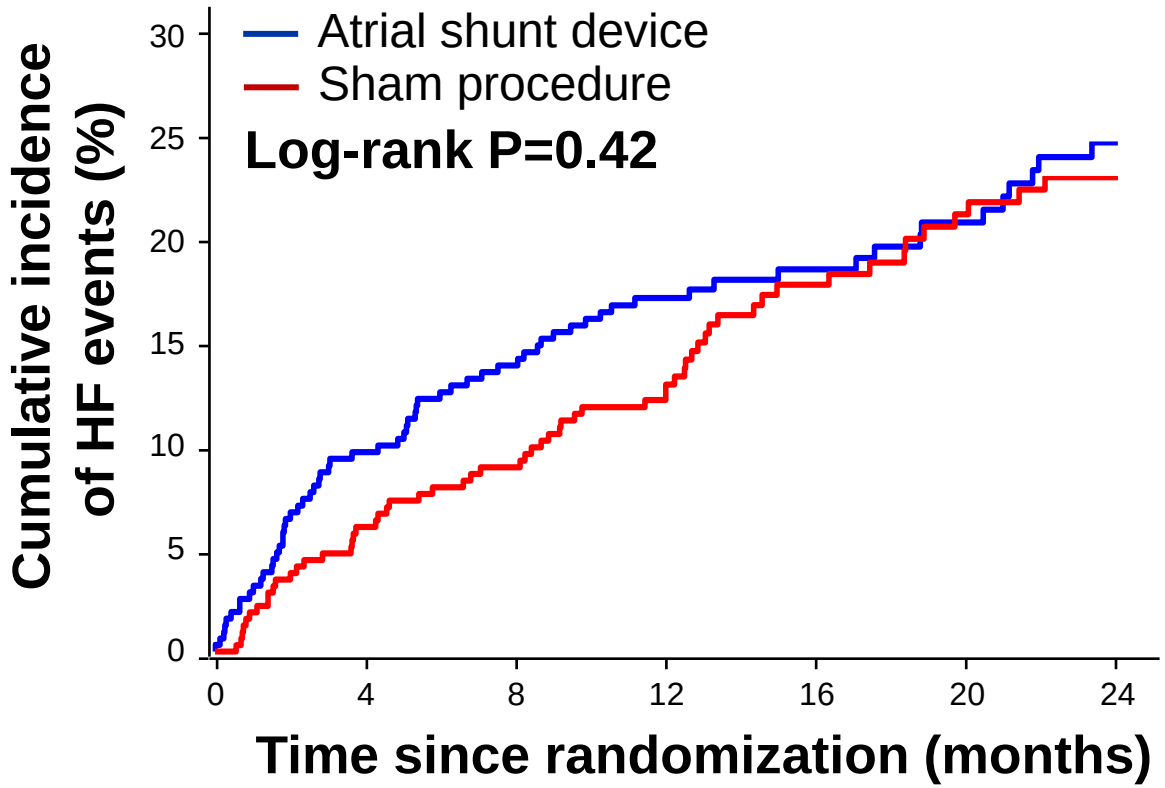
REDUCE LAP-HF II (n=626): Primary results





Win ratio: 1.0 (95% 0.8-1.2)
Finkelstein-Schoenfeld p-value=0.85

- 93% HFpEF, 7% HFmrEF
- Randomized 1:1 shunt vs. sham
- Exercise RHC in all
- Peak PCWP ≥25 mmHg

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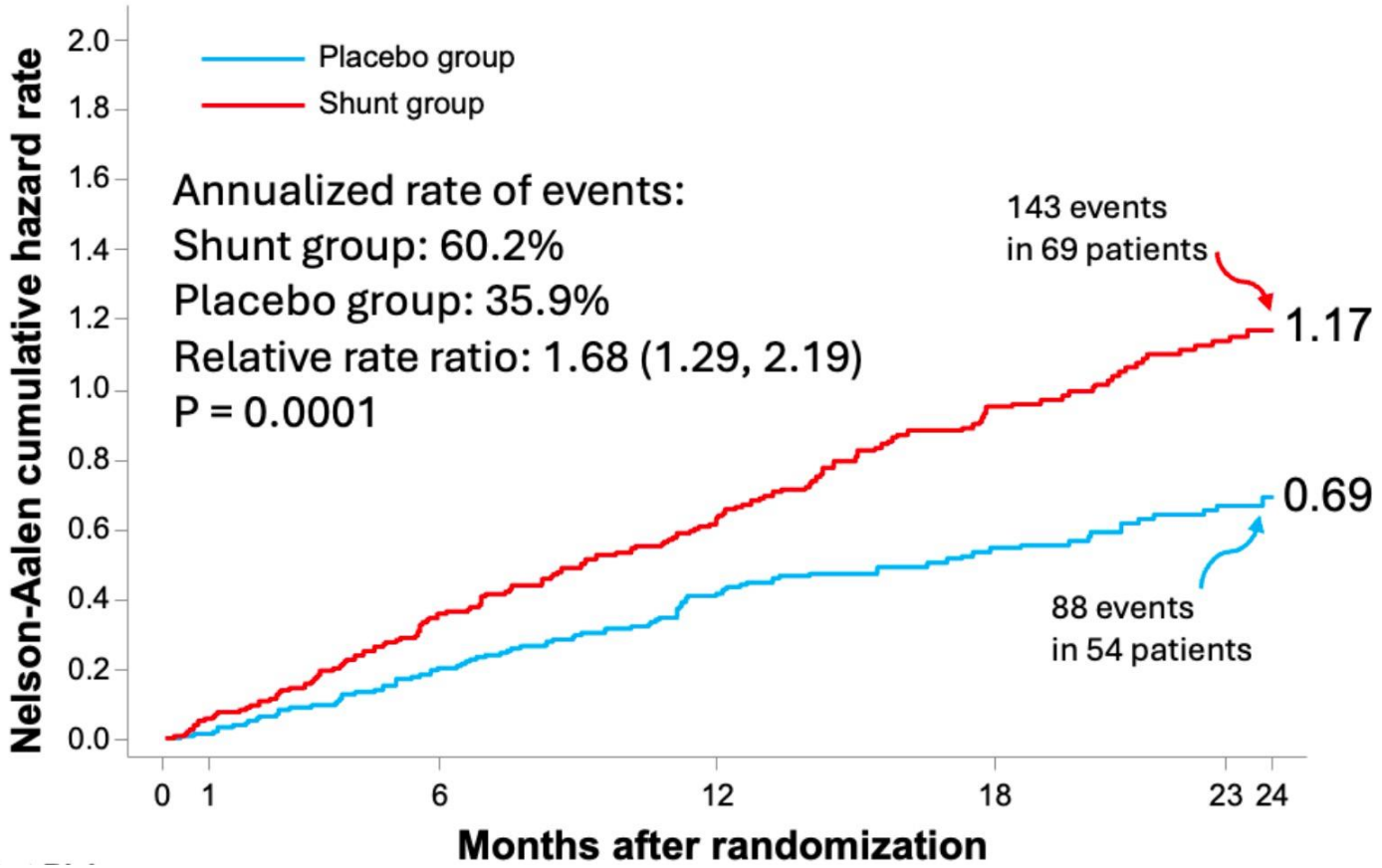
Shah SJ, et al. *Lancet* 2022

Are atrial shunts harmful in HFpEF?

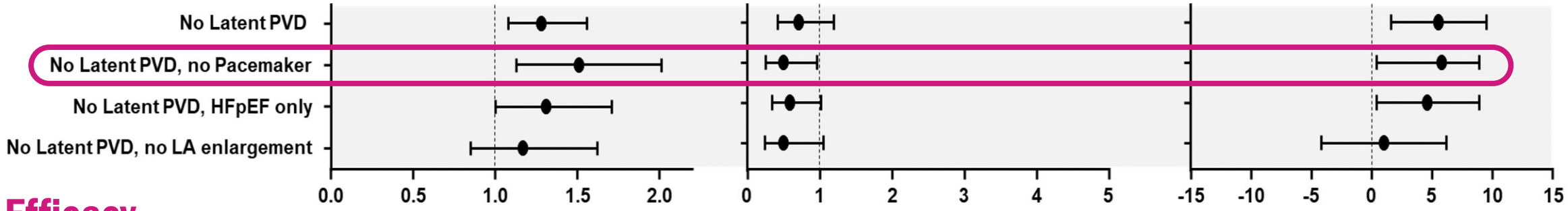
RELIEVE-HF HFpEF group (LVEF ≥40%)



Stone GW, et al. *Circulation* 2024

REDUCE LAP-HF II: Responder analyses

- **Pre-specified + post-hoc subgroup analyses:**
  - ⇢ Identified a potential **responder subgroup**
  - ⇢ 50% of randomized patients (n=313)
  - ⇢ Peak exercise PVR <1.74 WU + no pacemaker/ICD
  - ⇢ **After 12 months of follow-up: Beneficial treatment response**



Efficacy endpoints
(shunt vs. sham, responders)

↑Win ratio = 1.43 (p=0.009)

↓HF events (IRR 0.49, P=0.035)

↑KCCQ (+5.9 points; =0.01)

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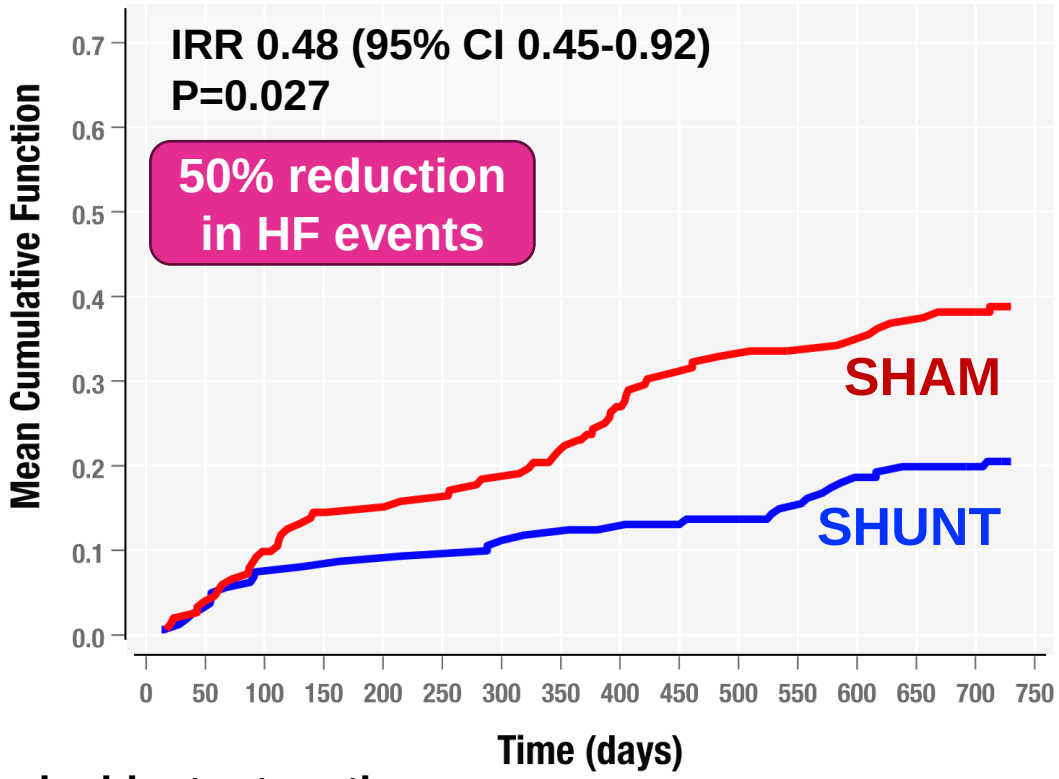
Borlaug BA…Shah SJ *Circulation* 2022

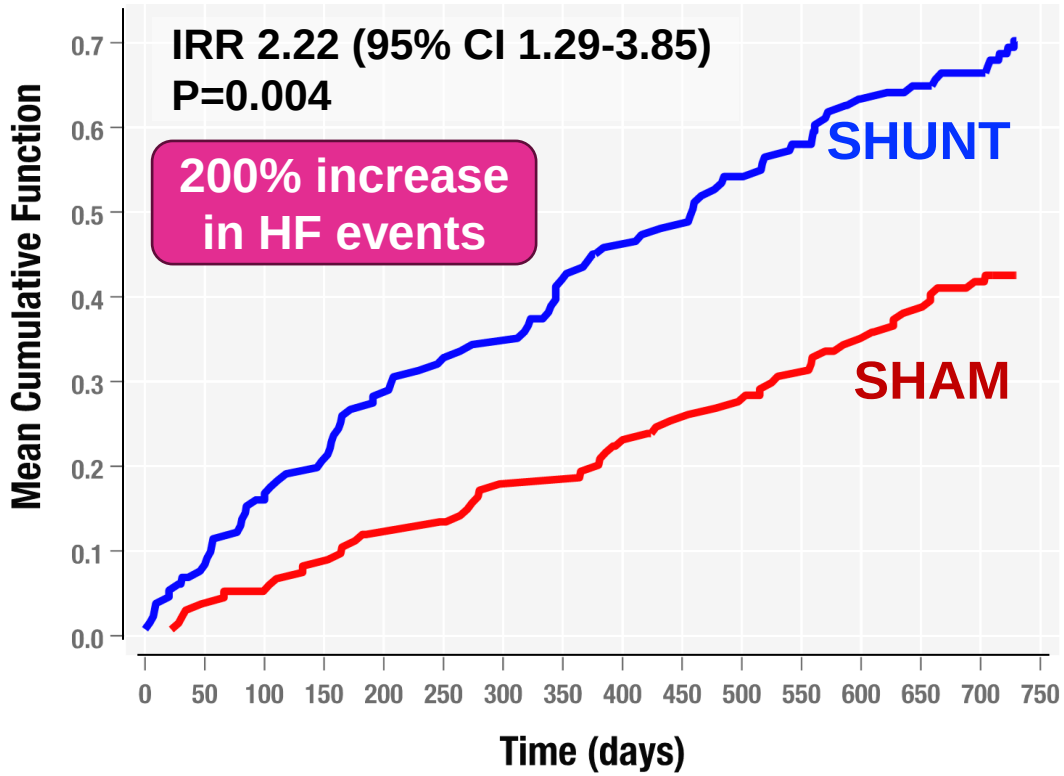
REDUCE LAP-HF II: Responder analyses

2-year HF event rate analysis: atrial shunt vs. sham

RESPONDERS (win ratio = 1.36)



NON-RESPONDERS (win ratio = 0.73)



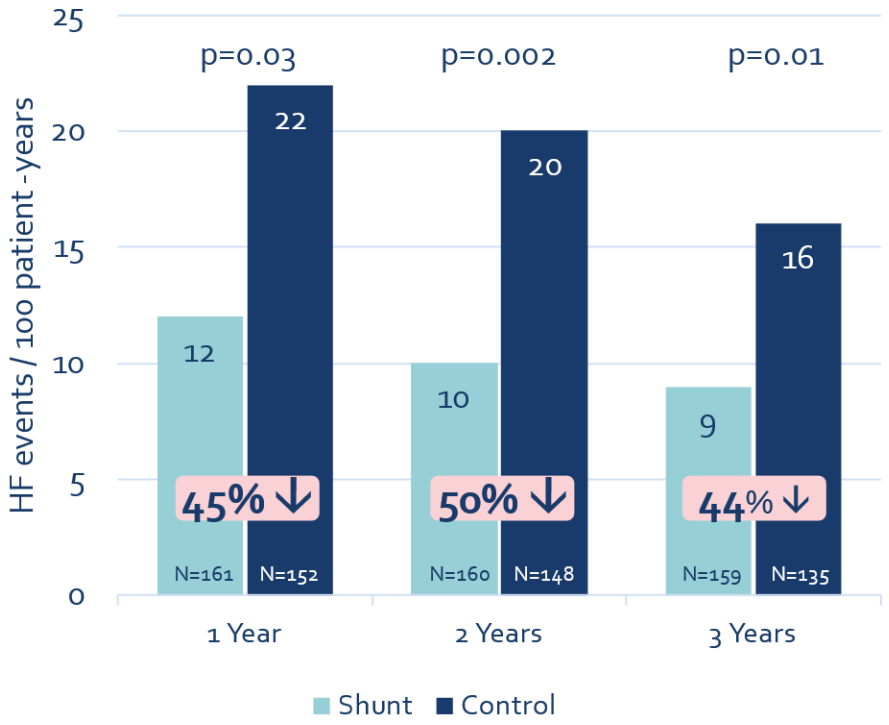
IRR = incident rate ratio

Borlaug BA…Shah SJ. *Circulation* 2022; Gustafsson F…Shah SJ. *JACC Heart Fail* 2024

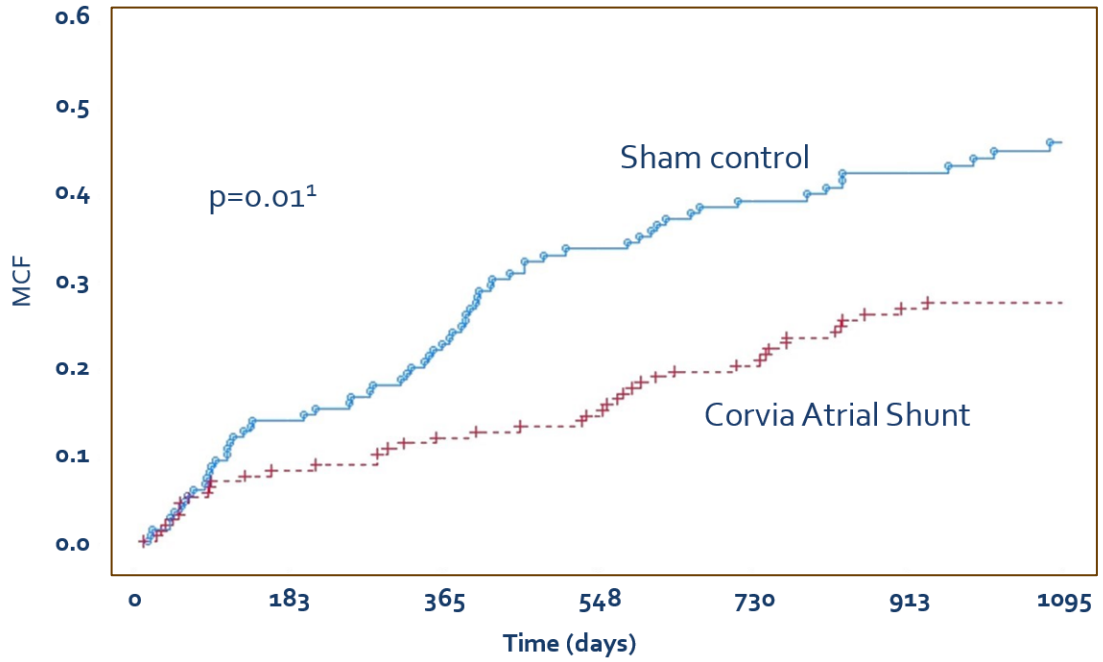
REDUCE LAP-HF II: Responder analyses

3-year results in the responder subgroup: atrial shunt vs. sham

Heart Failure Event Rate



Mean Cumulative Heart Failure Events



Treatment	161	160	160	159	155	150	133
Control	152	150	150	146	139	118	101

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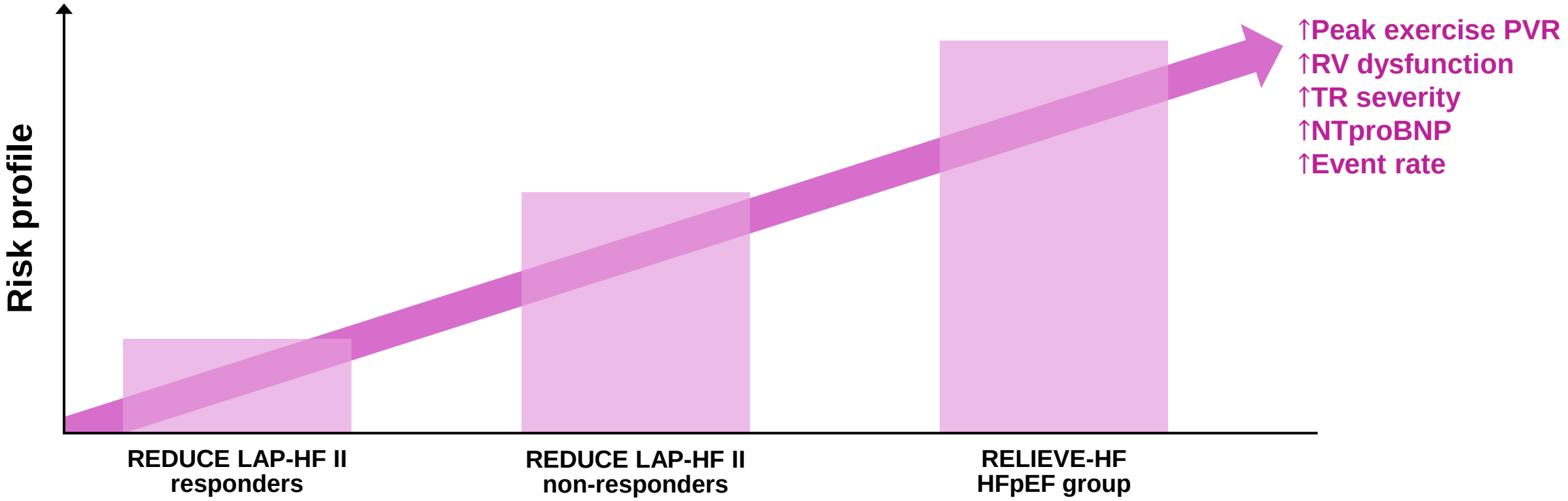
Litwin SE…Shah SJ. *Am Heart J* 2024

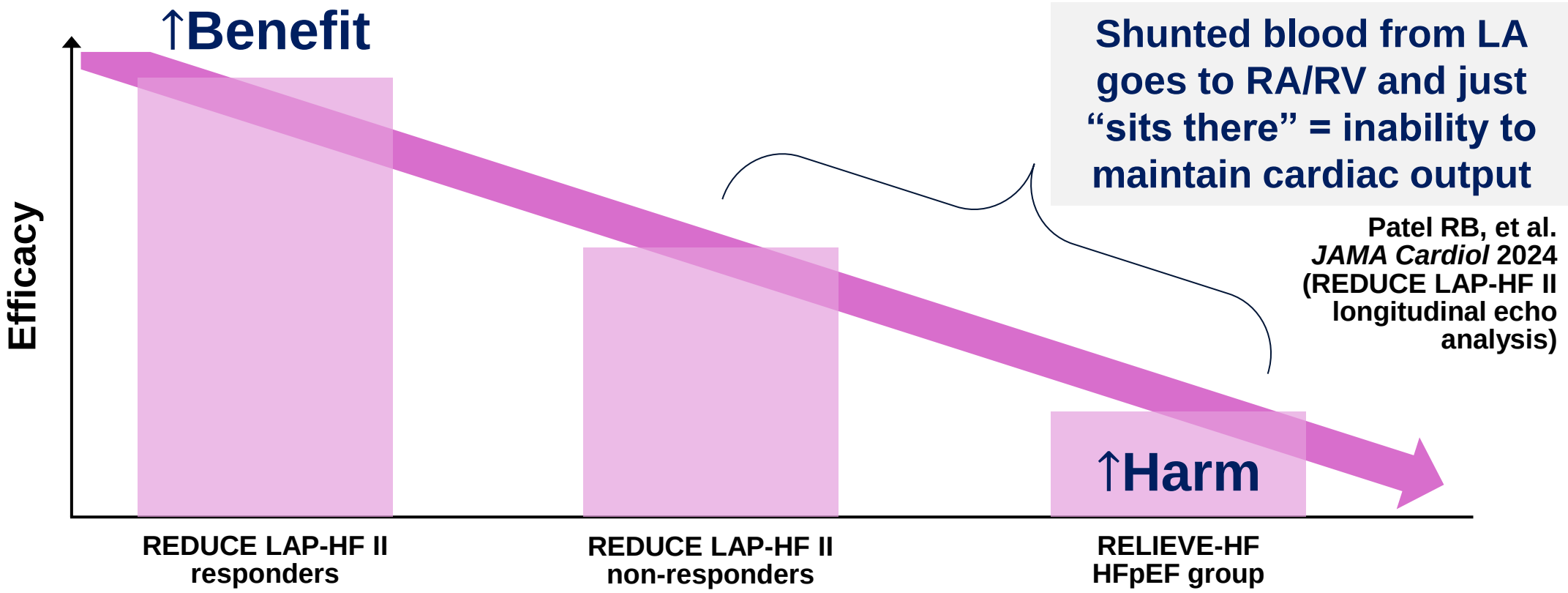
Efficacy and safety of atrial shunts in HFpEF

Depends on phenotype…



Efficacy and safety of atrial shunts in HFpEF

Depends on phenotype…



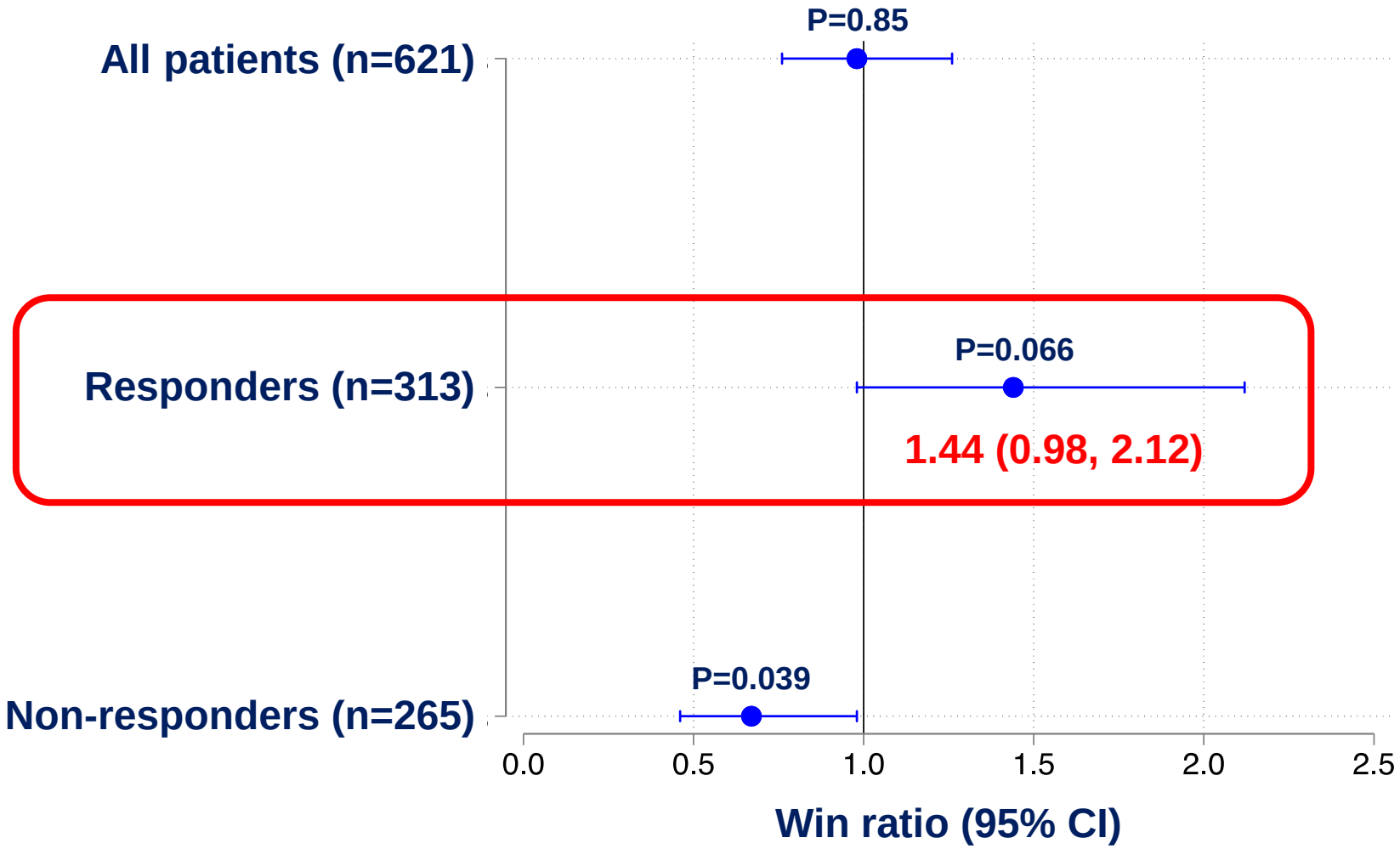
Shunted blood from LA goes to RA/RV and just "sits there" = inability to maintain cardiac output

Patel RB, et al. *JAMA Cardiol* 2024 (REDUCE LAP-HF II longitudinal echo analysis)

REDUCE LAP-HF II 5-year outcomes: Key questions

- Do patients with atrial shunt develop late HF events?
- Do the benefits in the responder group persist out to 5 years of follow-up?
- Is an atrial shunt a risk factor for embolic stroke?
- Do patients with an IASD in the responder group have attenuation of improvement of symptoms and QOL during long-term follow-up?

REDUCE LAP-HF II: 5-year primary results*



Win ratio:

- CV death or non-fatal ischemic stroke
- Total (first and recurrent) HF events
- Change in KCCQ-OSS

***5-year outcomes are still preliminary (89.7% complete)**

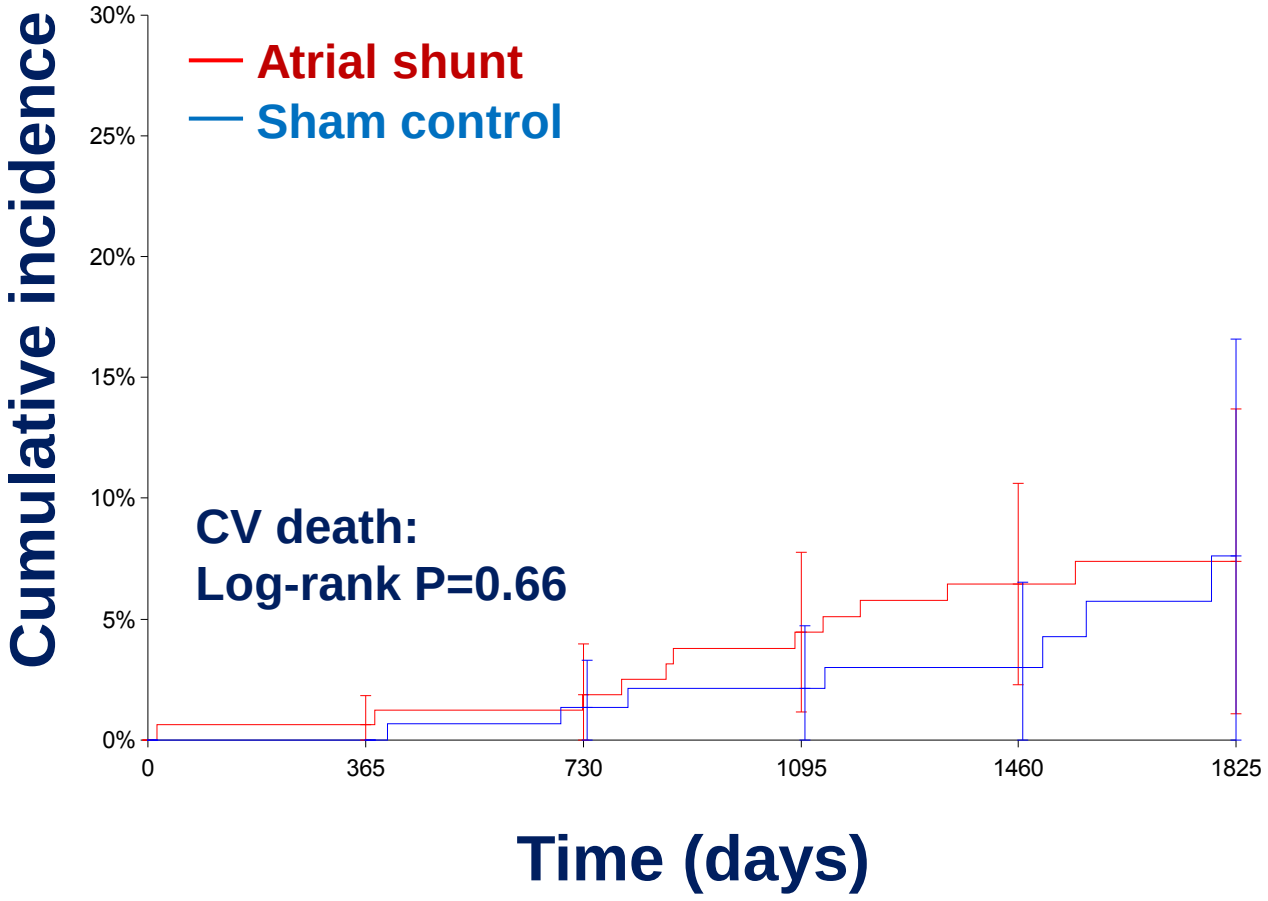
Components of the win ratio

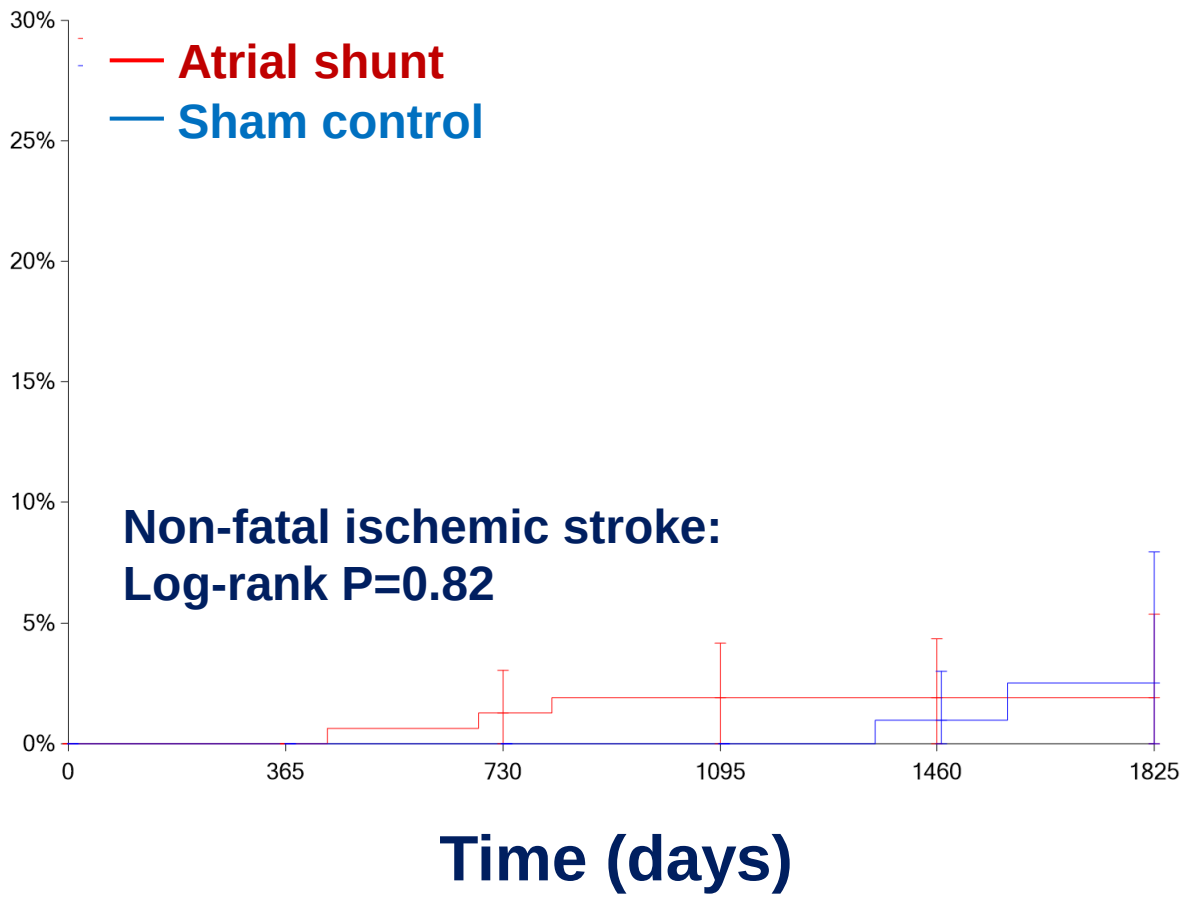
Outcome	All patients (n=621)		Responders (n=313)		Non-responders (n=265)	
	Atrial shunt	Sham control	Atrial shunt	Sham control	Atrial shunt	Sham control
CV death or non-fatal ischemic stroke (95% CI)	14.6 (8.2-20.9)	11.6 (4.4-18.8)	9.3 (2.3-16.3)	10.0 (0.0-20.0)	21.2 (9.2-33.2)	14.5 (2.9-26.2)
CV death (95% CI)	11.1 (5.5-16.8)	8.8 (2.3-15.2)	7.4 (1.1-13.7)	7.6 (0.0-16.6)	15.1 (4.8-25.5)	10.6 (0.4-20.9)
Non-fatal ischemic stroke (95% CI)	3.6 (0.0-7.2)	3.0 (0.0-7.1)	1.9 (0.0-5.4)	1.5 (0.0-7.9)	6.4 (0.0-14.2)	4.3 (0.0-11.4)
Total rate of HF events per 100 patient years	17	18	10	15	24	20
Delta KCCQ (median [IQR])	15.4 (0.8, 28.6)	11.5 (-9.6, 26.3)	19.4 (8.1, 36.7)	7.2 (-9.8, 19.7)	3.6 (-7.6, 23.2)	13.4 (-6.2, 25.5)

Responder group: Components of the win ratio

Outcome at 5 years	Responders (n=313)		P-value
	Atrial shunt	Sham control	
CV death or non-fatal ischemic stroke (95% CI)	9.3 (2.3-16.3)	10.0 (0.0-20.0)	0.61
CV death (95% CI)	7.4 (1.1-13.7)	7.6 (0.0-16.6)	0.66
Non-fatal ischemic stroke (95% CI)	1.9 (0.0-5.4)	1.5 (0.0-7.9)	0.82
Total rate of HF events per 100 patient years	10	15	0.014
Delta KCCQ (median [IQR])	19.4 (8.1, 36.7)	7.2 (-9.8, 19.7)	0.007
Win ratio	**1.44 (0.98, 2.12)**		**0.066**

Responder group: CV death and non-fatal stroke





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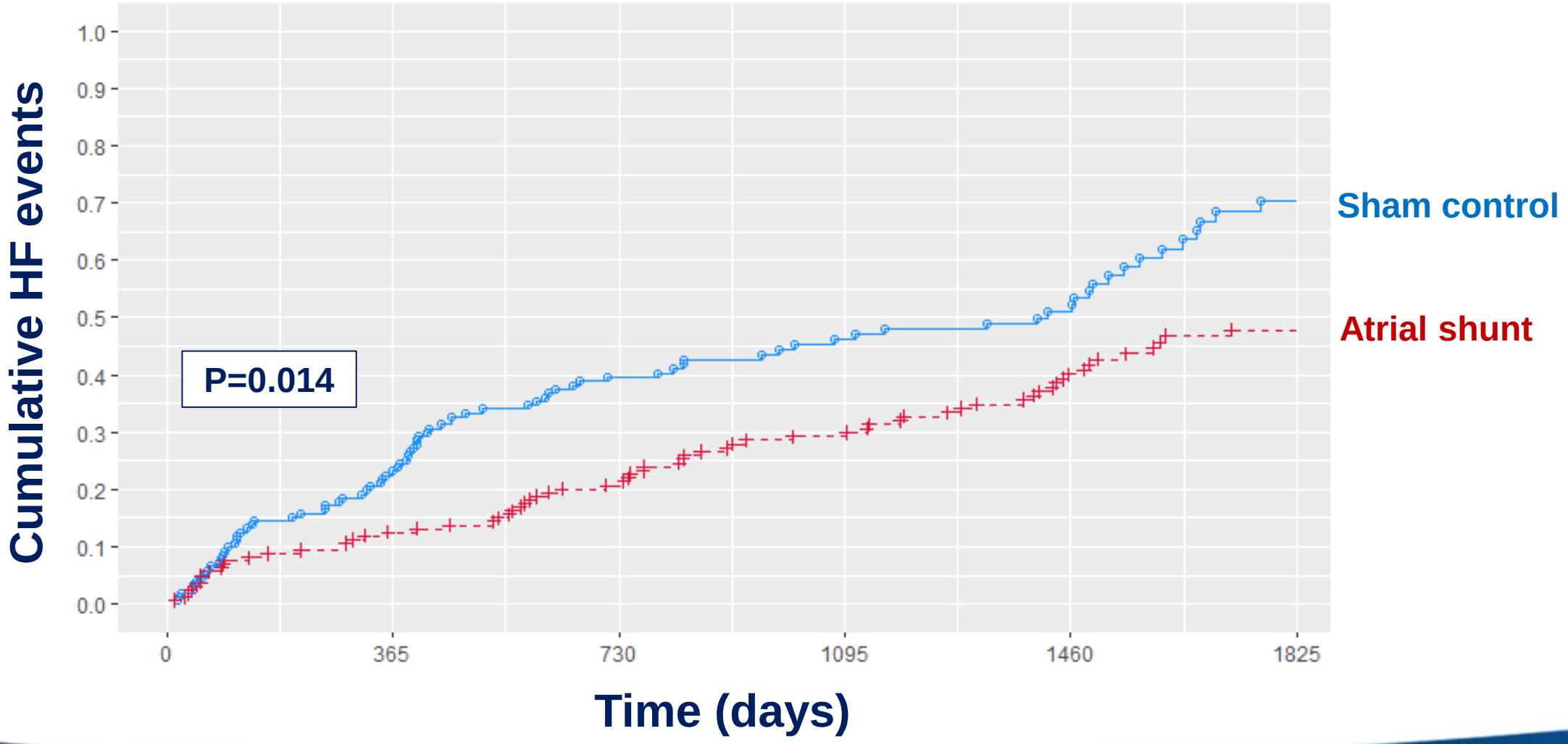
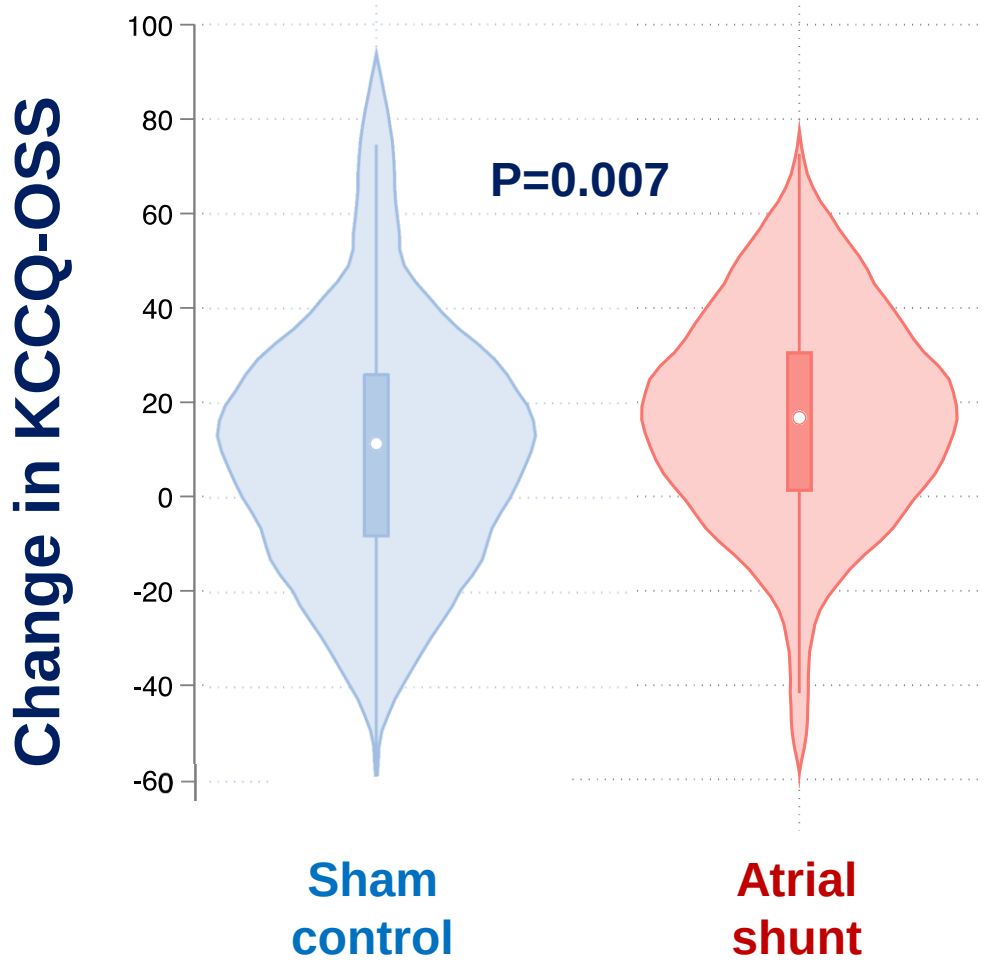
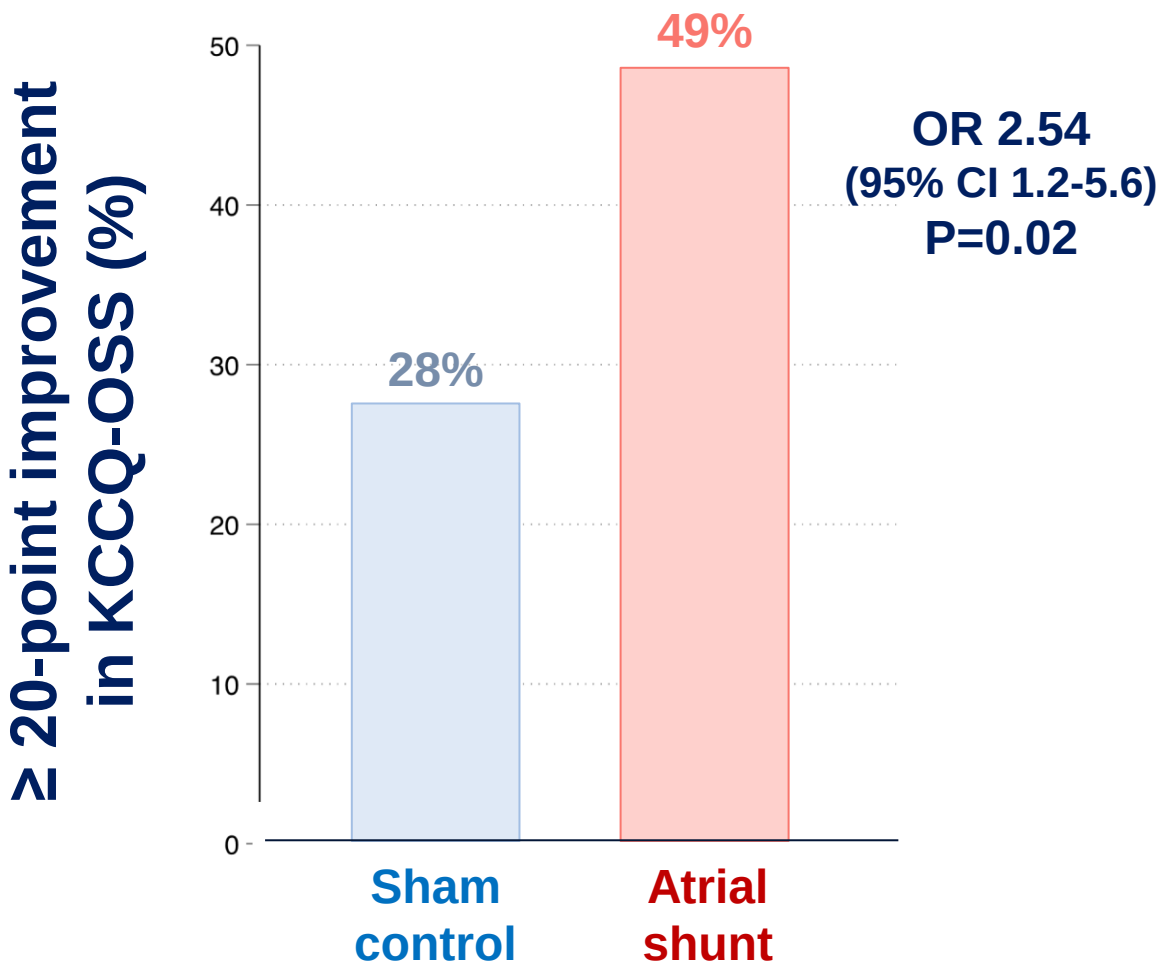
Responder group: Cumulative (total) HF events



Responder group: ΔKCCQ-OSS (baseline to 60 months)





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All patients: Safety results

Safety endpoints through 5 years	Atrial shunt (n=309)	Sham control (n=312)	P-value
Composite safety endpoint	39.0%	34.6%	0.33
Cardiovascular death	12.1%	8.9%	0.27
Non-fatal ischemic stroke	4.0%	2.3%	0.32
New-onset/worsening kidney dysfunction	18.1%	21.0%	0.42
MACE	16.9%	10.3%	0.042
Cardiac death	11.2%	7.9%	0.23
Myocardial infarction	6.4%	3.3%	0.13
Cardiac tamponade	1.2%	0.0%	—
Emergency cardiac surgery	0.4%	0.0%	—
Thromboembolic complications	1.6%	1.4%	0.86
Transient ischemic attack	1.6%	1.4%	0.86
Systemic embolic events	0.0%	0.0%	—
Newly-acquired persistent/permanent AF/flutter	7.6%	6.5%	0.65

Responder group: Safety results

Safety endpoints through 5 years	Atrial shunt (n=309)	Sham control (n=312)	P-value
Composite safety endpoint	33.9%	41.4%	0.24
Cardiovascular death	8.5%	6.7%	0.62
Non-fatal ischemic stroke	2.3%	1.9%	0.84
New-onset/worsening kidney dysfunction	16.2%	26.0%	0.067
MACE	13.1%	8.7%	0.29
Cardiac death	7.7%	5.8%	0.56
Myocardial infarction	6.2%	3.9%	0.43
Cardiac tamponade	1.5%	0.0%	—
Emergency cardiac surgery	0.0%	0.0%	—
Thromboembolic complications	1.5%	2.9%	0.49
Transient ischemic attack	1.5%	2.9%	0.49
Systemic embolic events	0.0%	0.0%	—
Newly-acquired persistent/permanent AF/flutter	9.2%	11.5%	0.56

Conclusions: REDUCE LAP-HF II 5-year follow-up

- **Overall cohort** (n=621): No difference in the composite endpoint of CV death, non-fatal ischemic stroke, KCCQ-OSS at 5 years
- **Responder group** (n=313): ↓HF events in shunt- vs. sham patients (15 vs. 10 HF events per 100 patient-years)
- **In responder group, KCCQ-OSS improved ~12 points greater in sham vs. shunt patients** (2.5x increased odds of 20-point or greater improvement)
- **Responder group:** Safety endpoints similar in shunt vs. sham

Conclusions: REDUCE LAP-HF II 5-year follow-up

- **Beneficial effect and safety of Corvia atrial shunt in the previously described responder group persisted through 5 years of follow-up, with ↓HF events and ↑KCCQ improvement compared to sham**
- **Results continue to support confirmatory RESPONDER-HF trial, which is ongoing and will definitively determine whether atrial shunting is beneficial in responder phenotype (HF, EF ≥40%, peak PVR <1.75 WU, no PPM/ICD)**