# Neprilysin inhibition – additional benefits for cardio-renal disease in diabetes?

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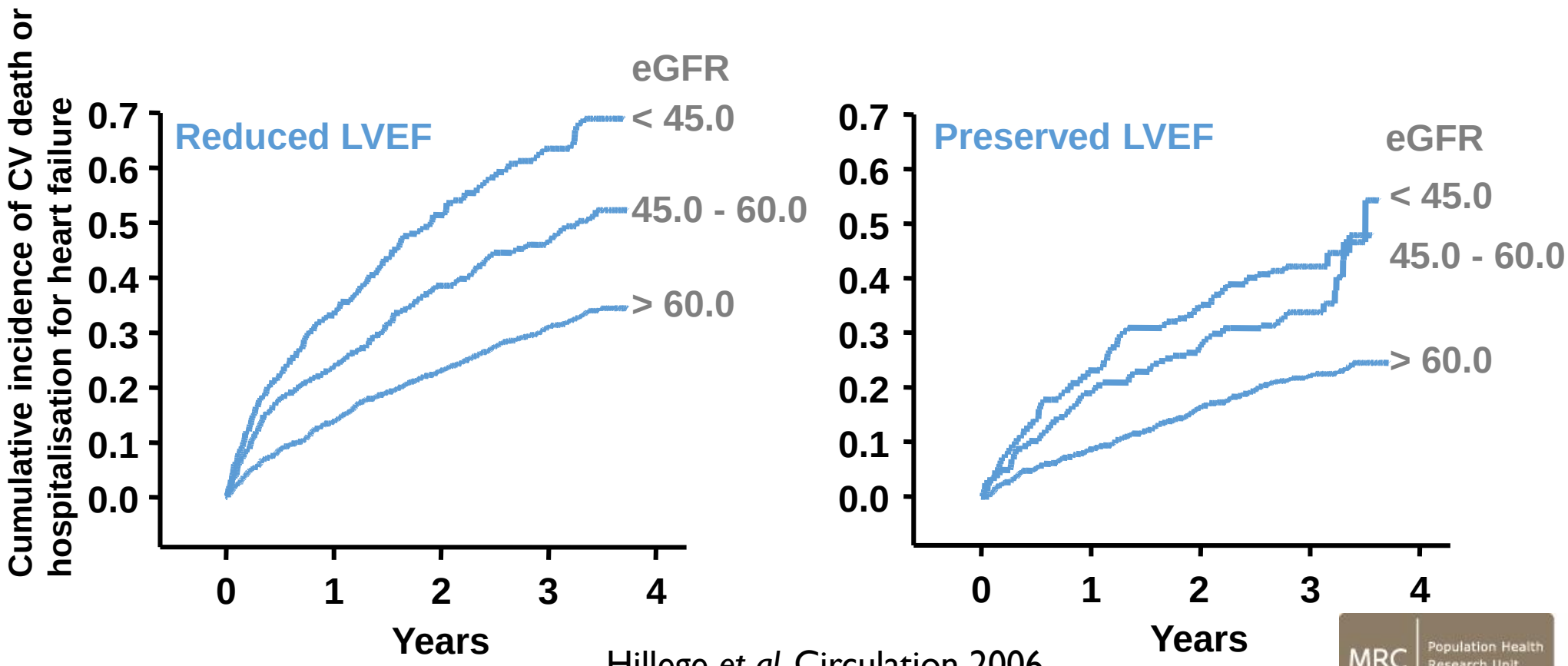
# Overlap between heart failure and CKD

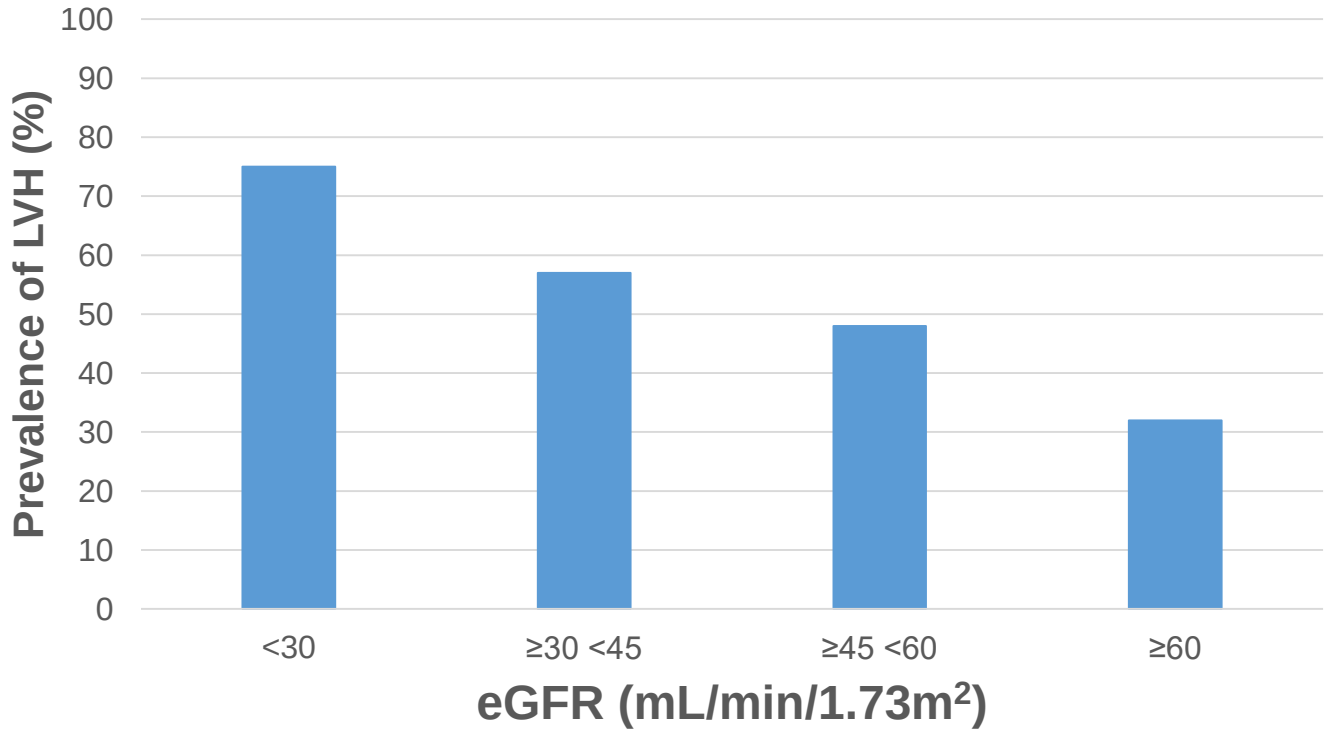
About half of patients with chronic heart failure have CKD




Hillege *et al.* Circulation 2006

# Overlap between heart failure and CKD

Structural heart disease is also very common among patients with CKD




Park *et al.* JASN 2012

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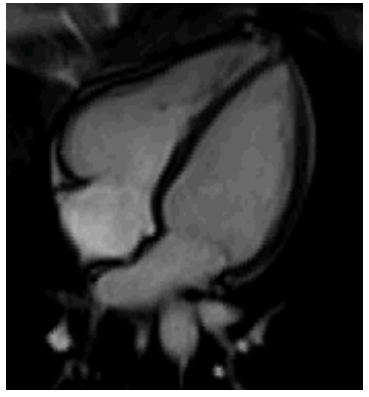
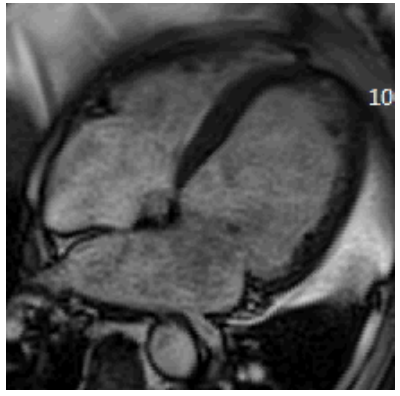
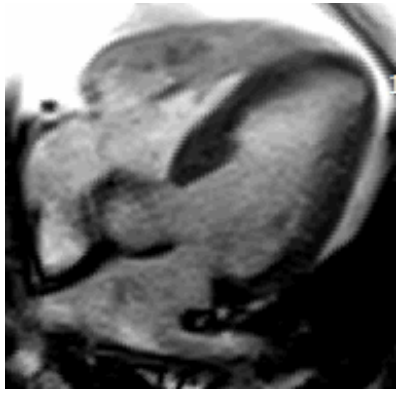
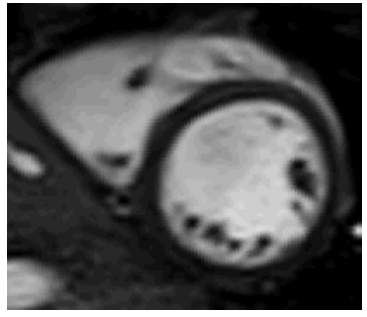
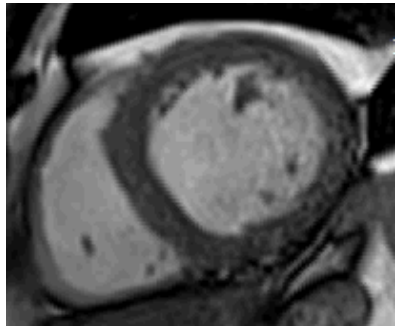
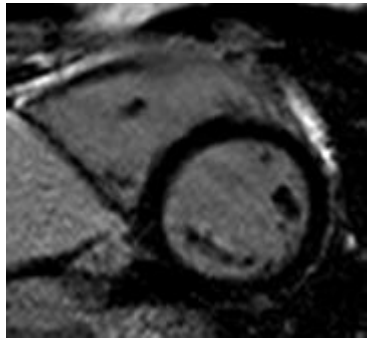
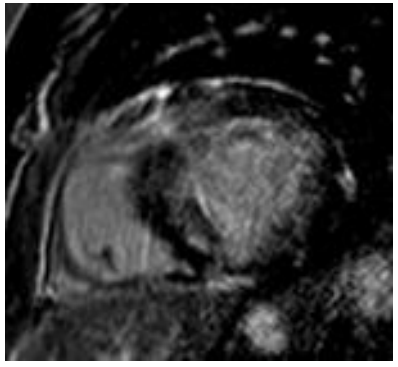
# Overlap between heart failure and CKD

| | Normal | Dilated cardiomyopathy | Post-renal transplant |
|---|---|---|---|
| Cine HLA |  |  |  |
| Cine short-axis |  |  |  |
| LGE |  |  |  |

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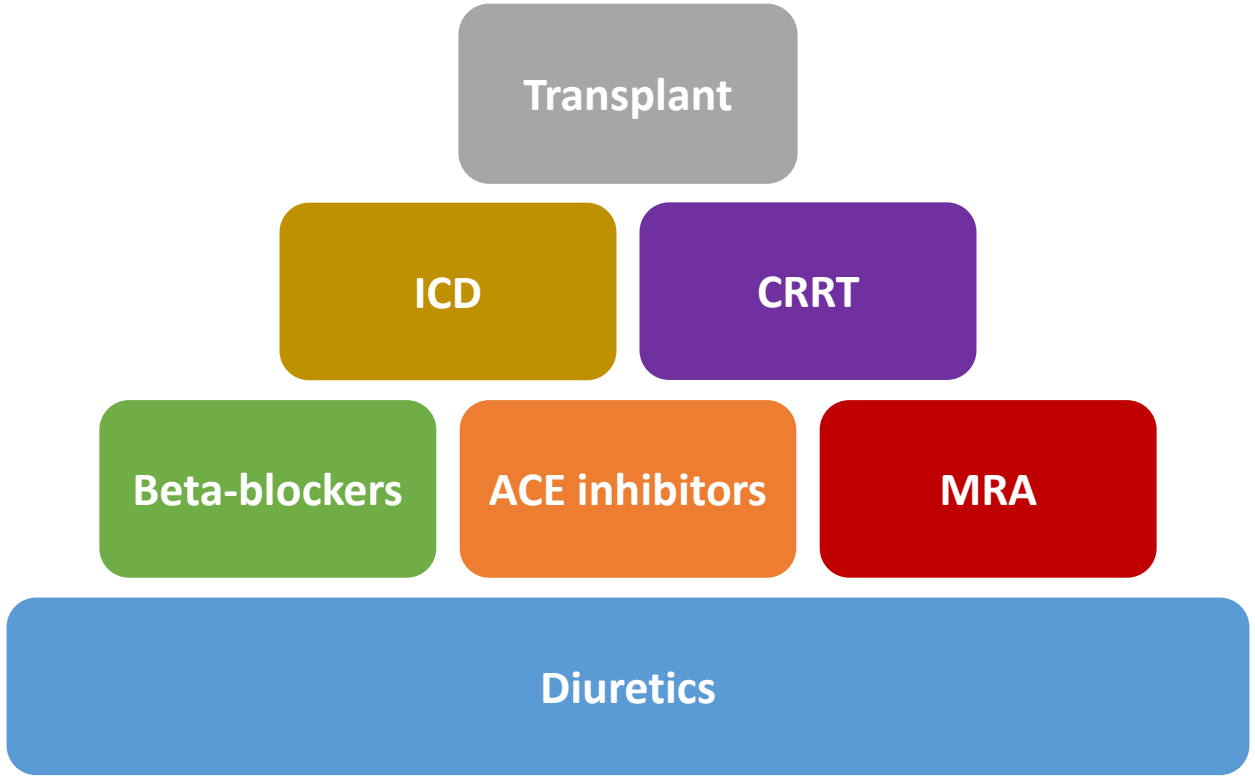
# Therapies for heart failure with reduced ejection fraction (HFrEF)




ESC Guidelines 2016

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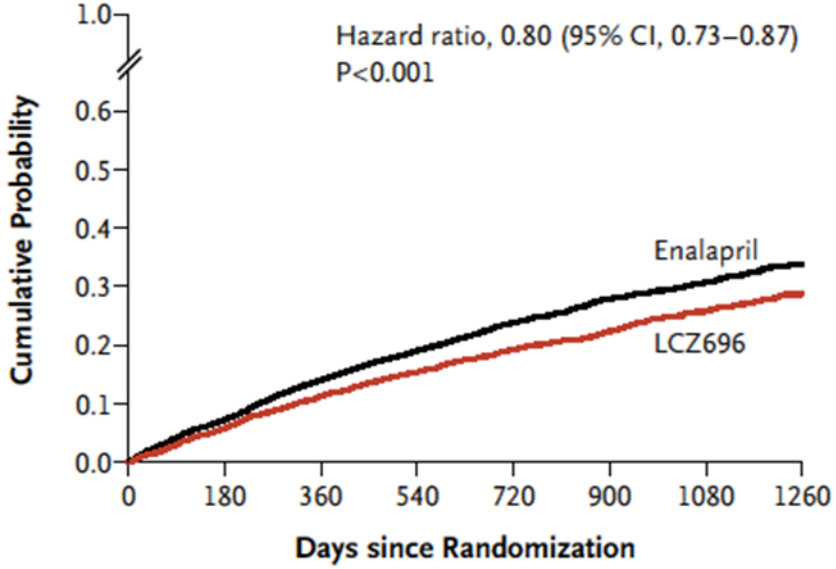
# Have ACEi been replaced in HFrEF?

- PARADIGM-HF: largest trial ever in HFrEF
- Compared LCZ696 *vs* enalapril in 8442 patients with HFrEF (3784 with diabetes)
- Primary outcome: hospitalisation for HF or CV death




McMurray *et al.* NEJM 2014

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# Sacubitril/valsartan: first-in-class angiotensin receptor-neprilysin inhibitor (ARNI)

- Neprilysin (neutral endopeptidase) degrades natriuretic and other vasoactive peptides
- As monotherapy, NEP inhibitors activate renin-angiotensin system
- When given with ACEi, cause excess angioedema (due to bradykinin elevation)
- Safe when combined with ARB

# Potential of NEP inhibition in CKD

- Cardiovascular disease related to underlying structural heart disease in CKD

- NEPi may therefore reduce cardiovascular risk as it does in patients with HFrEF

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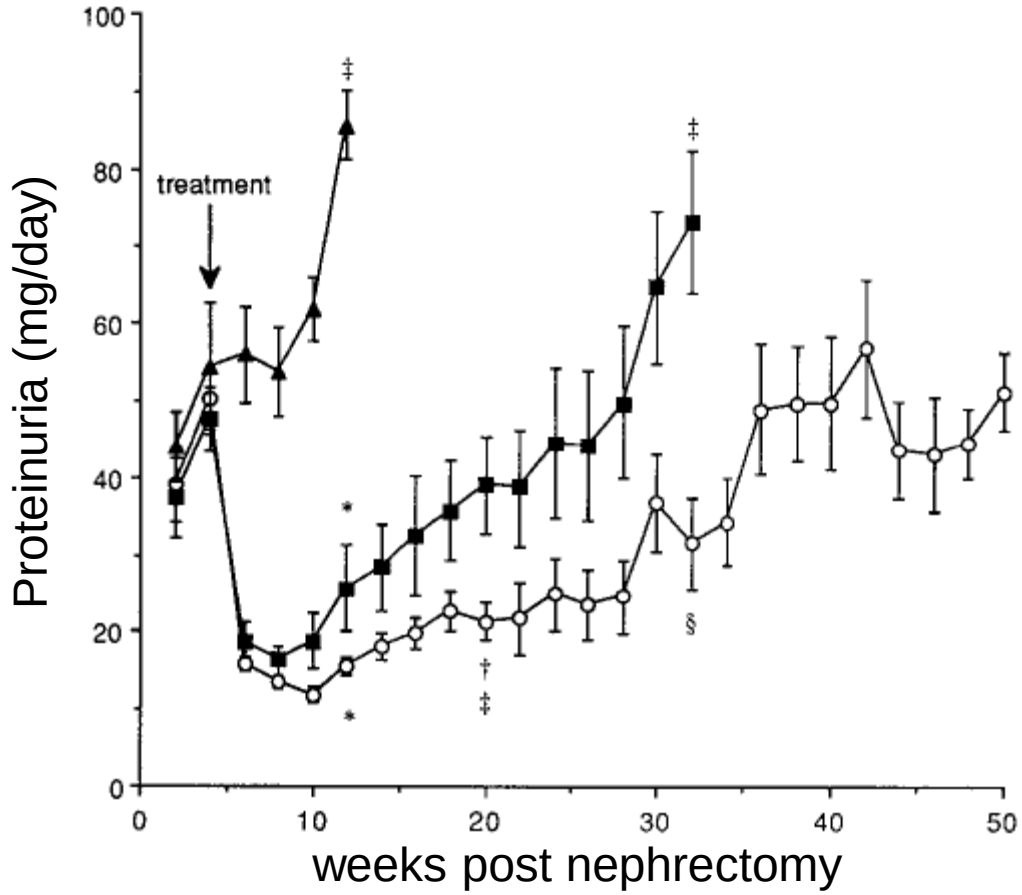
# Effects of NEPi on kidney

- Effects in 5/6 nephrectomy model on proteinuria:




Taal *et al.* JASN 2004

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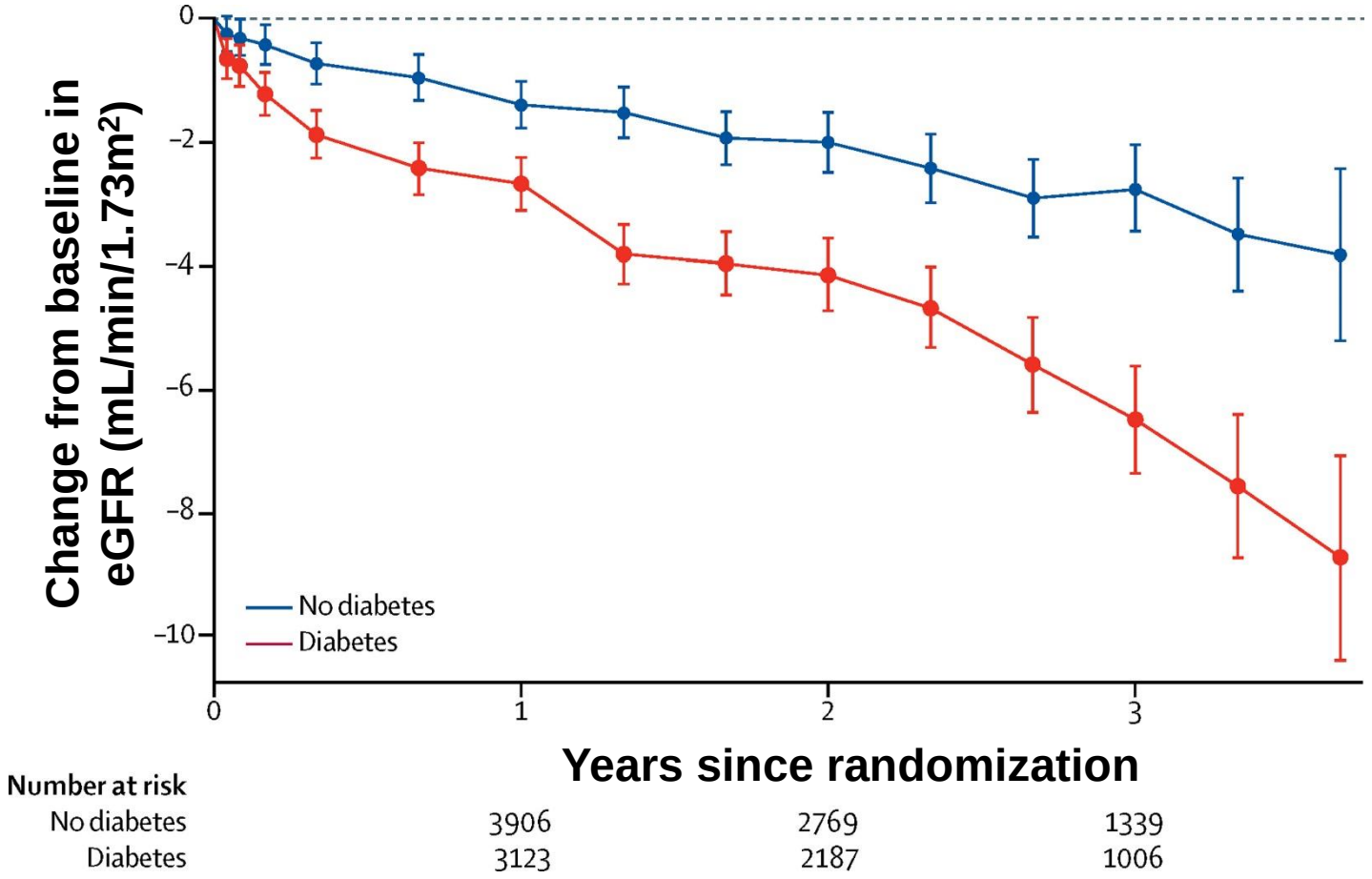
# Effect of sacubitril/valsartan *vs* enalapril on kidney function in HFrEF




Packer *et al.* Lancet Diab Endocrinol 2018

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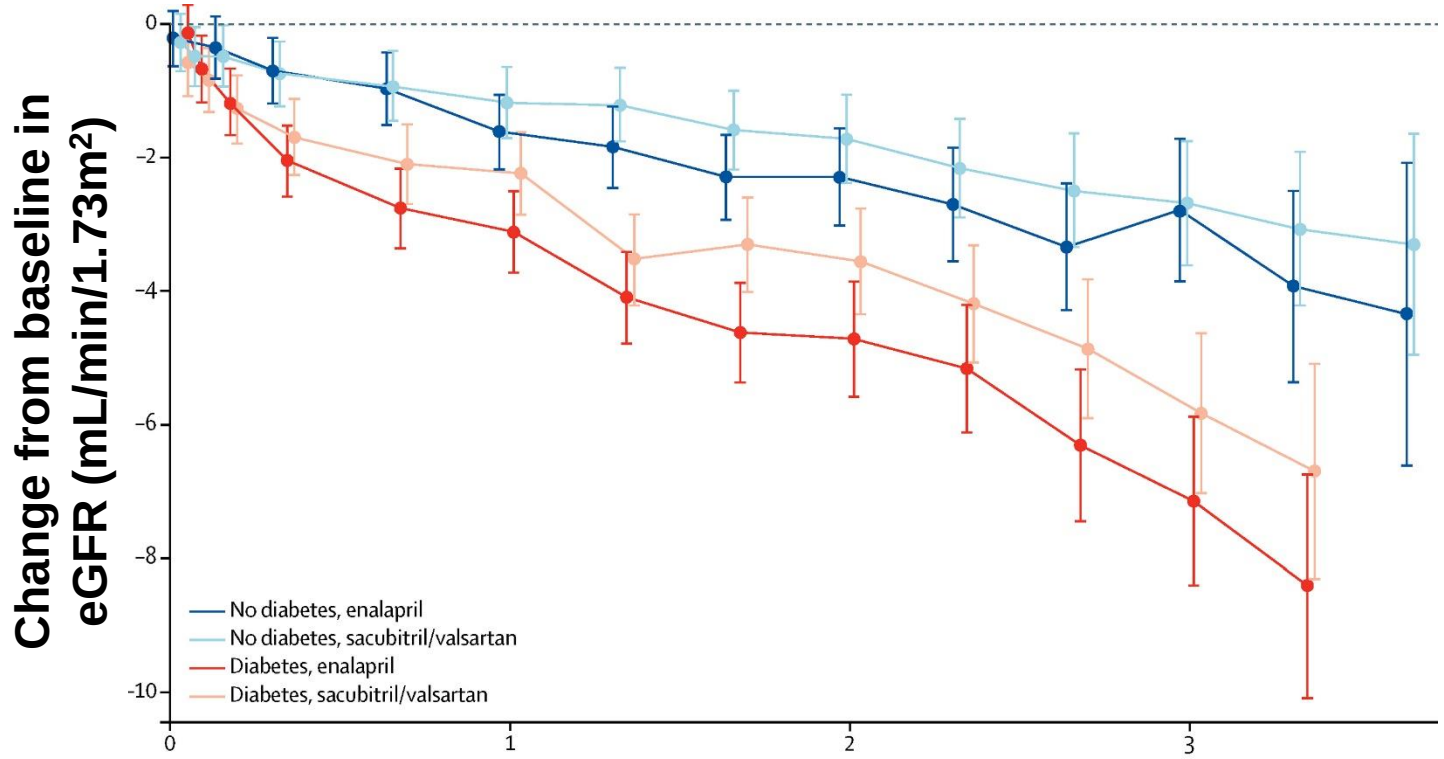
# Effect of sacubitril/valsartan *vs* enalapril on kidney function in HFrEF




| Number at risk | | | |
|---|---|---|---|
| No diabetes, sacubitril/valsartan | 1937 | 1344 | 667 |
| No diabetes, enalapril | 1566 | 1101 | 504 |
| Diabetes, sacubitril/valsartan | 1557 | 1086 | 502 |
| Diabetes, enalapril | | | |

Packer *et al.* Lancet Diab Endocrinol 2018

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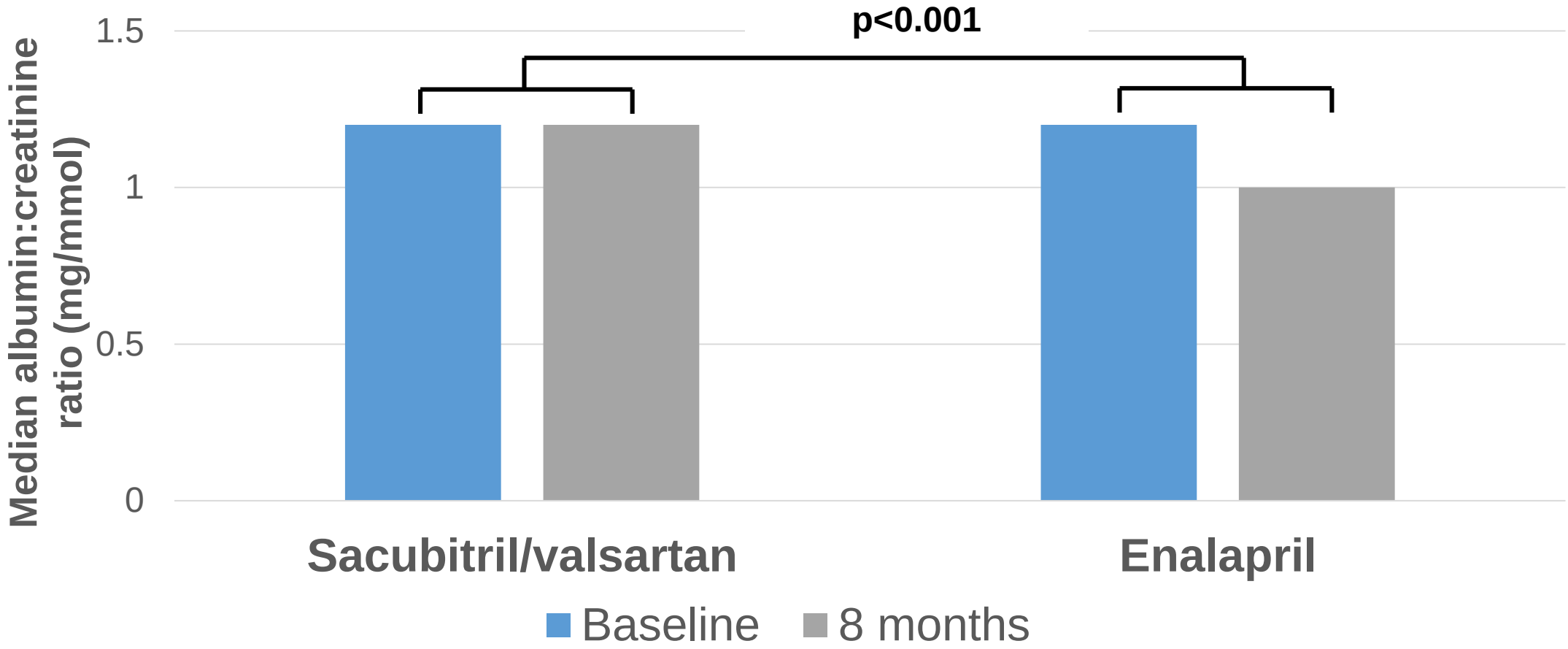
# Effect of sacubitril/valsartan *vs* enalapril on albuminuria in HFrEF



# Need for direct evidence of NEPi in CKD

- Compared to ACEi among patients with HFrEF, sacubitril/valsartan appears to preserve kidney function but increases albuminuria
- Effect on kidney function among patients with more advanced CKD is uncertain
- Before large scale outcomes trial can be planned, pilot trial data required

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# UK HARP-III

- Randomized pilot trial of sacubitril/valsartan *vs* irbesartan among patients with CKD
  - eGFR 20-45 mL/min/1.73m$^2$; or
  - eGFR 45-60 mL/min/1.73m$^2$ + uACR >20 mg/mmol
- Sacubitril/valsartan 97/103 mg bd *vs* irbesartan 300 mg od
- Outcomes:
  - Measured GFR
  - eGFR, uACR
  - BP, cardiac biomarkers
  - Safety and tolerability

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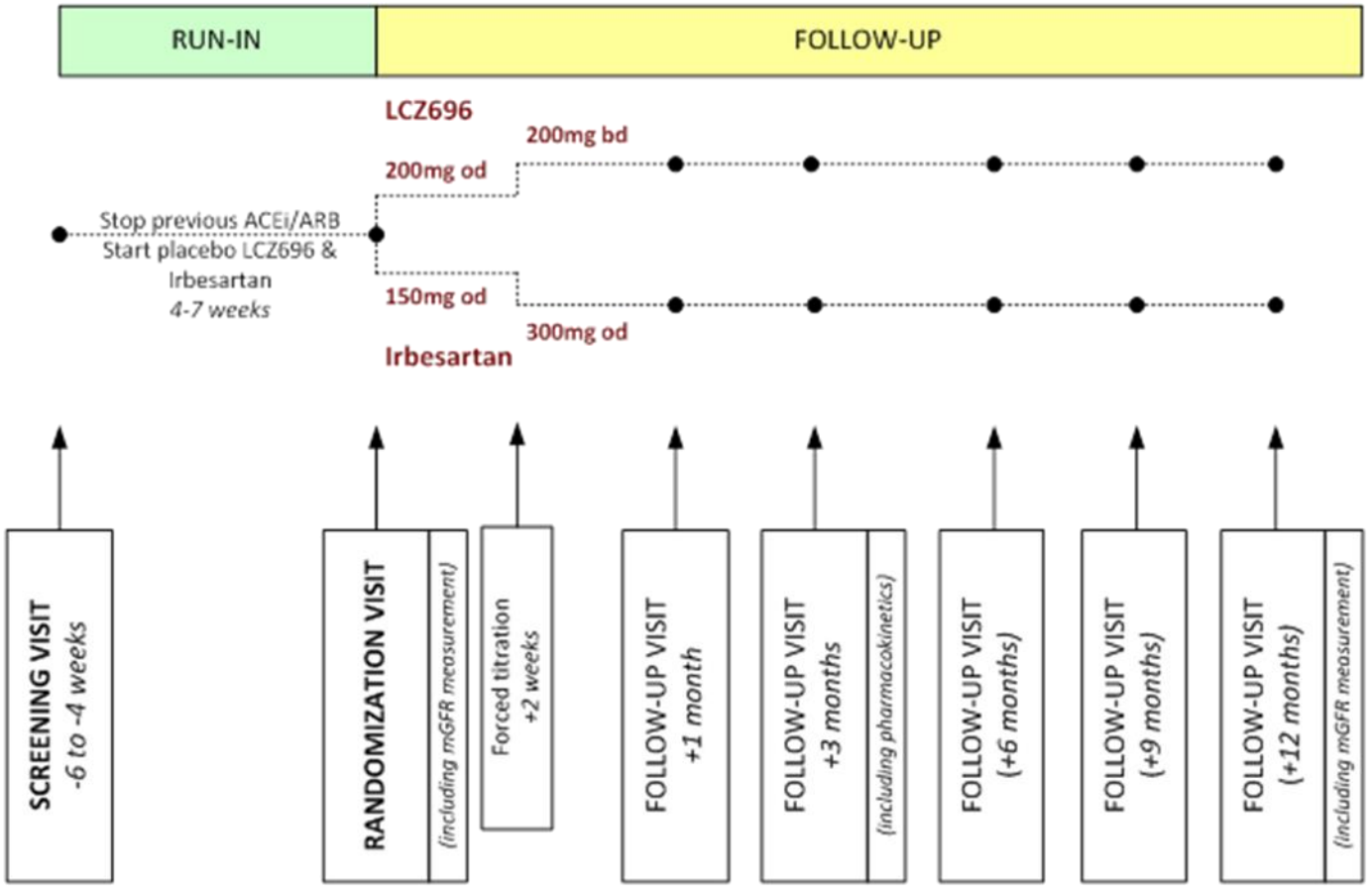
# UK HARP-III: design

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# UK HARP-III: baseline characteristics

| Characteristic | Sacubitril/valsartan (n=207) | Irbesartan (n=207) |
|---|---|---|
| Mean age (years) | 62.0 (14.1) | 63.6 (13.4) |
| Male sex | 148 (71%) | 150 (72%) |
| Diabetes mellitus | 81 (39%) | 83 (40%) |
| Mean systolic BP (mmHg) | 146 (16) | 146 (16) |
| Mean diastolic BP (mmHg) | 82 (11) | 80 (11) |
| Mean eGFR (mL/min/1.73m$^2$) | 35.4 (11.0) | 35.5 (11.0) |
| Geometric mean uACR (mg/mmol) | 34 (5) | 34 (5) |
| Cause of kidney disease: | | |
| Glomerular disease | 60 (29%) | 51 (25%) |
| Tubulointerstitial disease | 18 (9%) | 32 (15%) |
| Diabetic kidney disease | 36 (17%) | 47 (23%) |

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# Tolerability of sacubitril/valsartan

| Reason for stopping | Sacubitril/valsartan (n=207) | Irbesartan (n=207) |
|---|---|---|
| Serious adverse event | 4 (2%) | 7 (3%) |
| Non-serious adverse reaction | 18 (9%) | 12 (6%) |
| Other reason | 11 (5%) | 15 (7%) |
| | | |
| **Any reason** | **33 (16%)** | **34 (16%)** |

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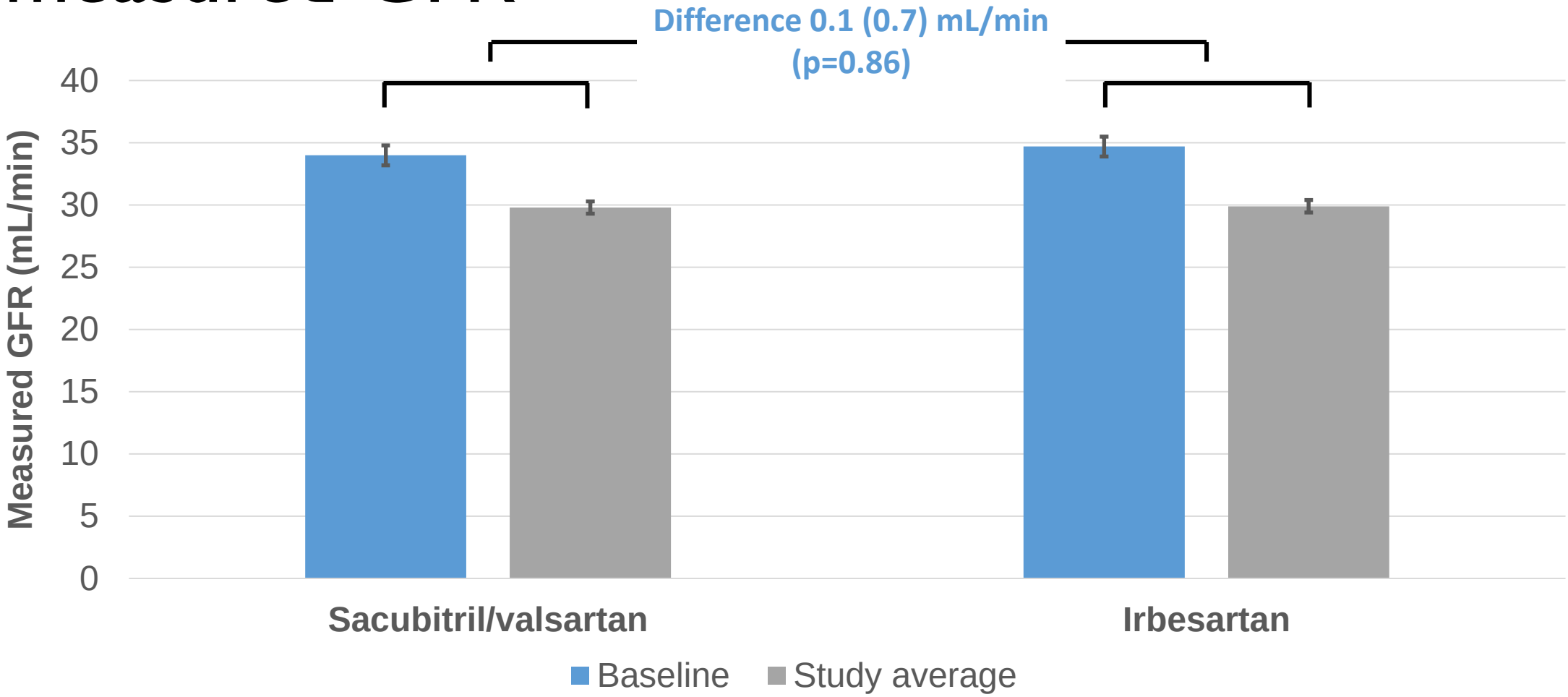
# Effect of sacubitril/valsartan *vs* irbesartan on measured GFR

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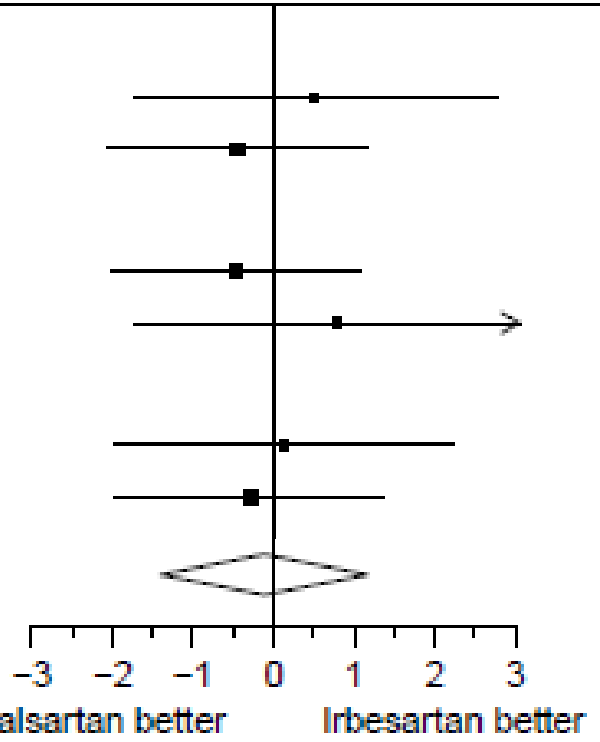
# Effect of sacubitril/valsartan *vs* irbesartan on measured GFR, by diabetes status

| | Mean (SE) mGFR (mL/min/1.73m$^2$) | | Difference in means (95% CI) |
|---|---|---|---|
| | Sacubitril/valsartan | Irbesartan | |
| **Age ($\chi^2_1 = 0.45$; p=0.50)** | | | |
| ≤60 years | 29.9 (0.8) | 29.5 (0.8) | 0.5 (−1.7 to 2.7) |
| >60 years | 29.7 (0.6) | 30.2 (0.6) | −0.4 (−2.0 to 1.2) |
| **Sex ($\chi^2_1 = 0.70$; p=0.40)** | | | |
| Male | 29.6 (0.5) | 30.1 (0.5) | −0.5 (−2.0 to 1.0) |
| Female | 30.3 (0.9) | 29.5 (0.9) | 0.8 (−1.7 to 3.3) |
| **Prior diabetes ($\chi^2_1 = 0.10$; p=0.76)** | | | |
| Yes | 29.2 (0.8) | 29.1 (0.7) | 0.1 (−2.0 to 2.2) |
| No | 30.2 (0.6) | 30.5 (0.6) | −0.3 (−1.9 to 1.3) |
| **All participants** | **29.8 (0.5)** | **29.9 (0.5)** | **−0.1 (−1.4 to 1.2)** |

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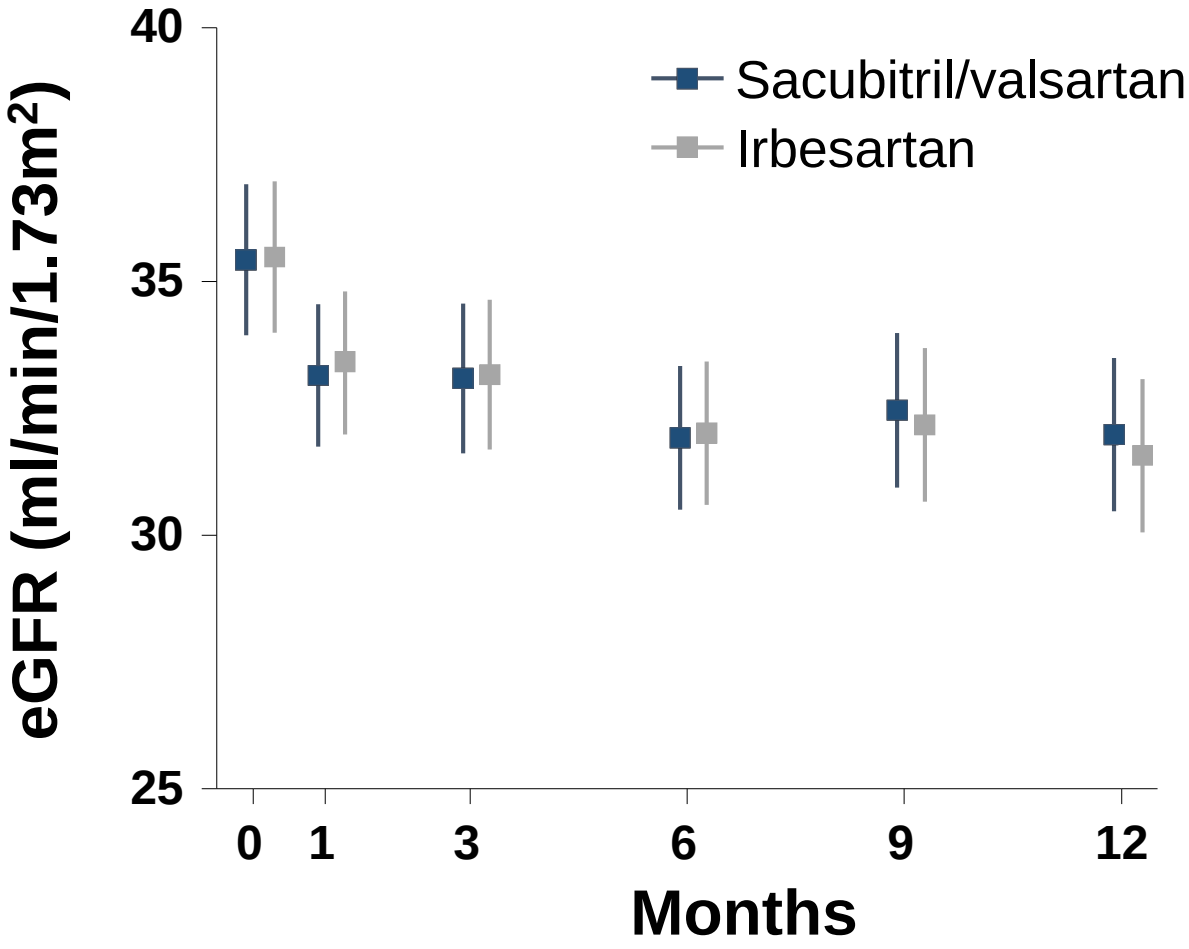
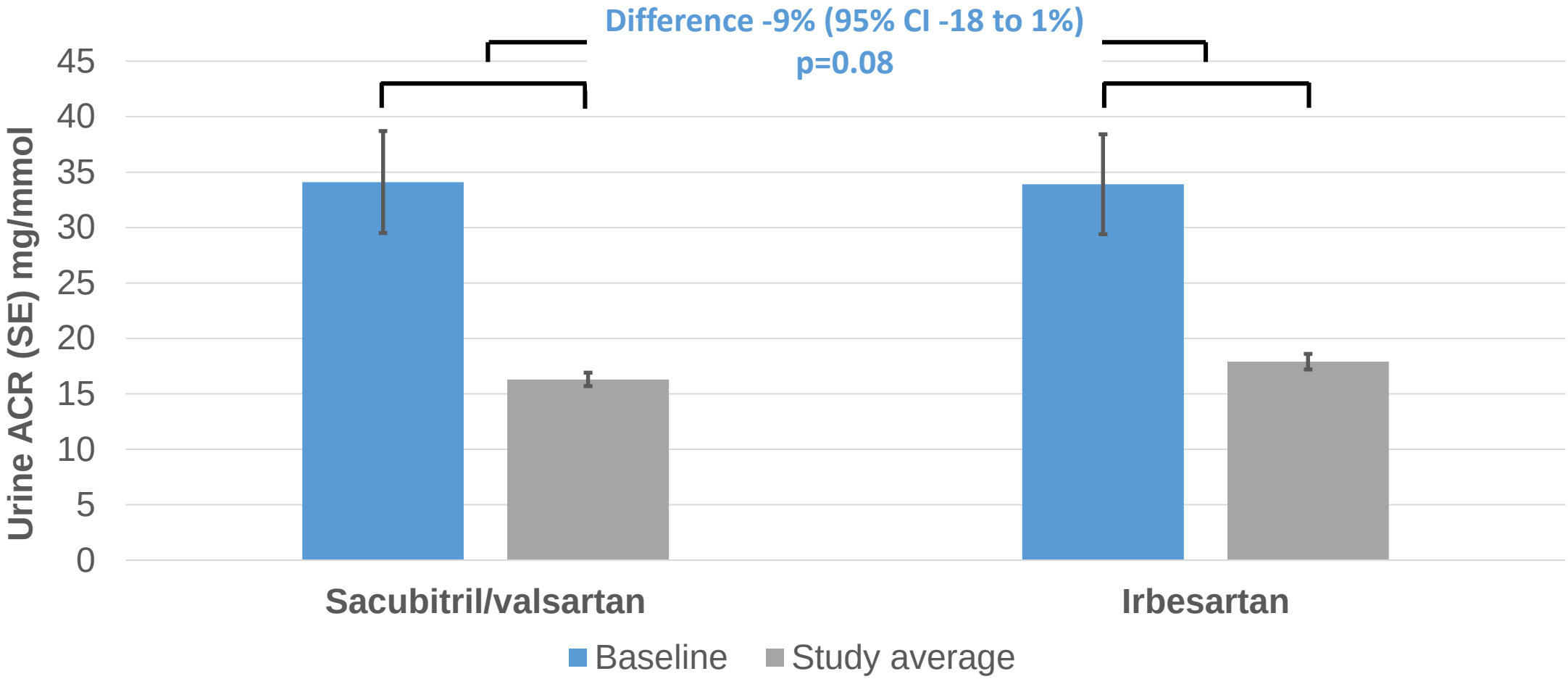
# Effect of sacubitril/valsartan *vs* irbesartan on eGFR



# Effect of sacubitril/valsartan *vs* irbesartan on urine albumin:creatinine ratio

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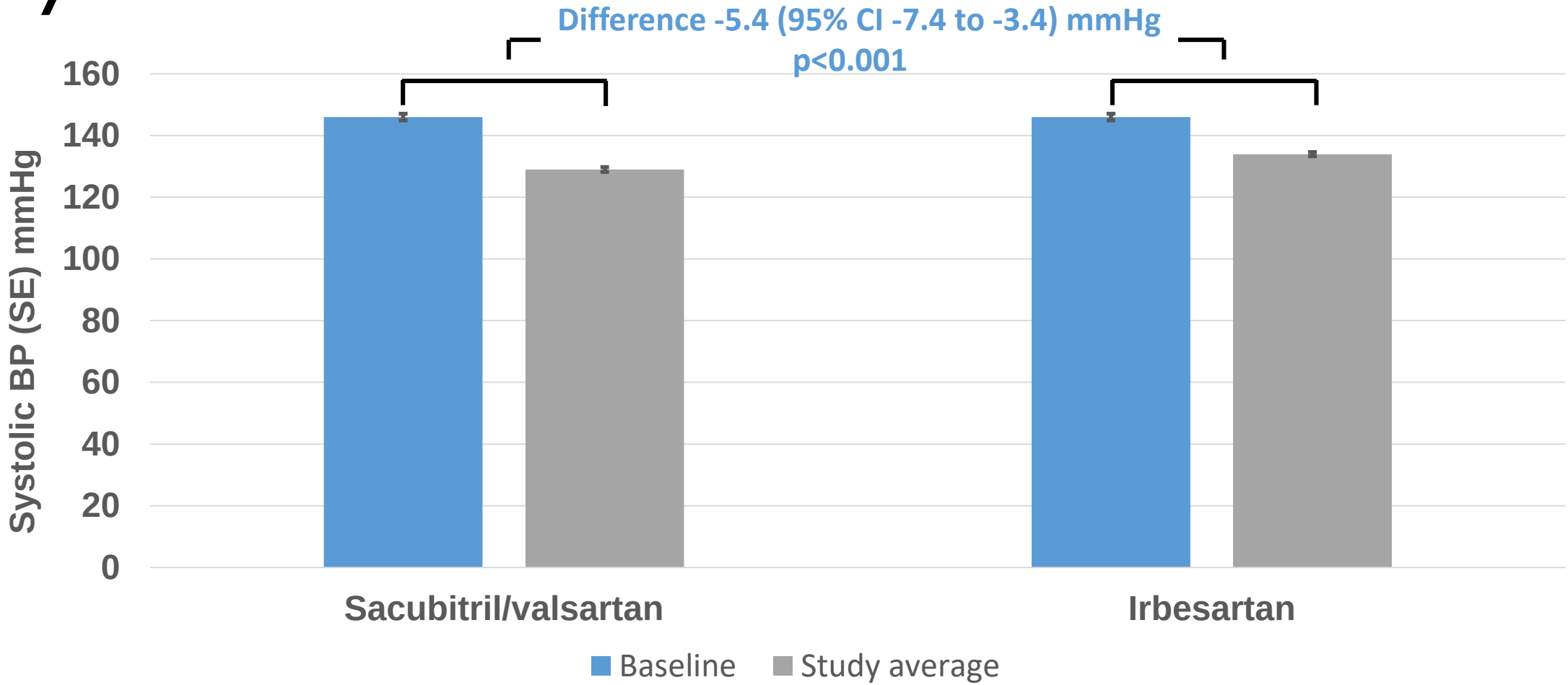
# Effect of sacubitril/valsartan *vs* irbesartan on systolic BP

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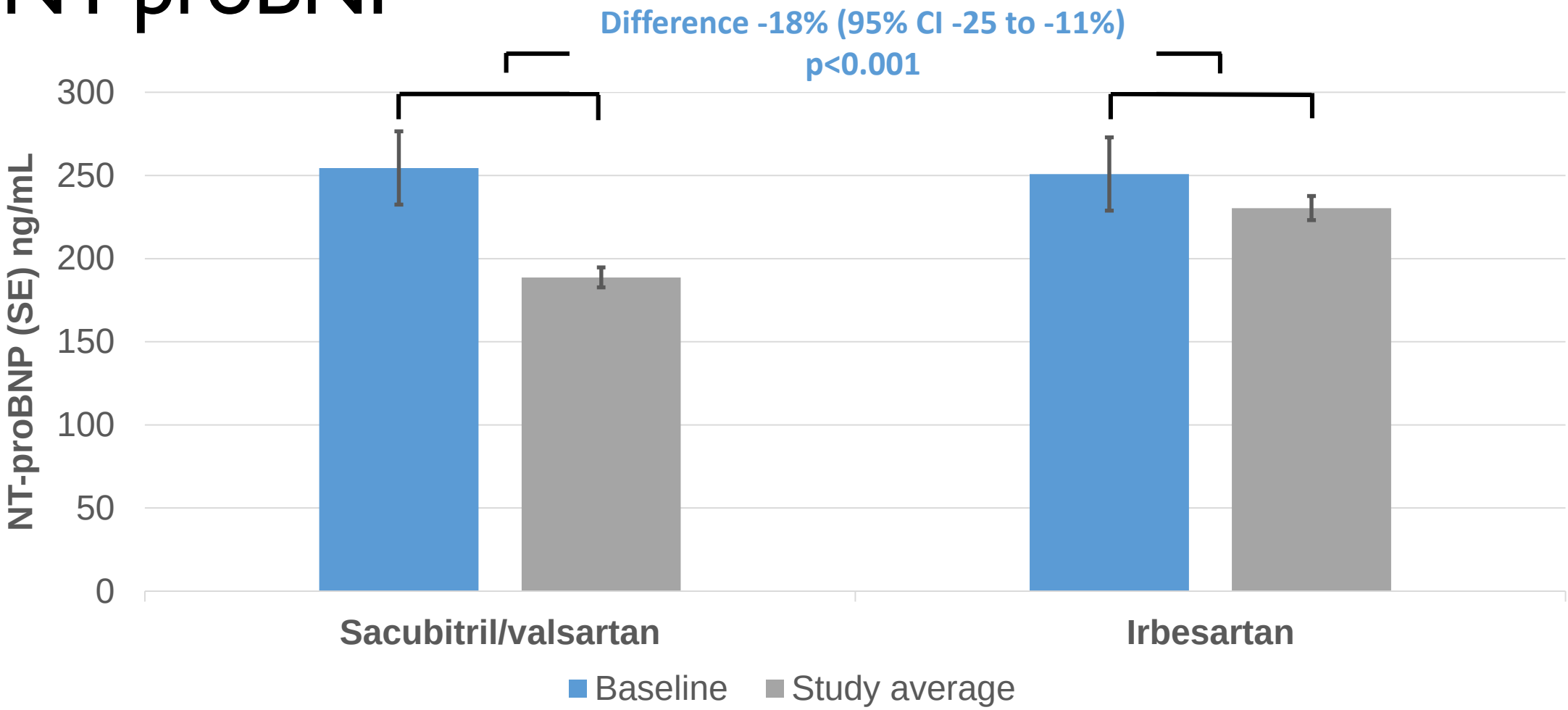
# Effect of sacubitril/valsartan *vs* irbesartan on NT-proBNP

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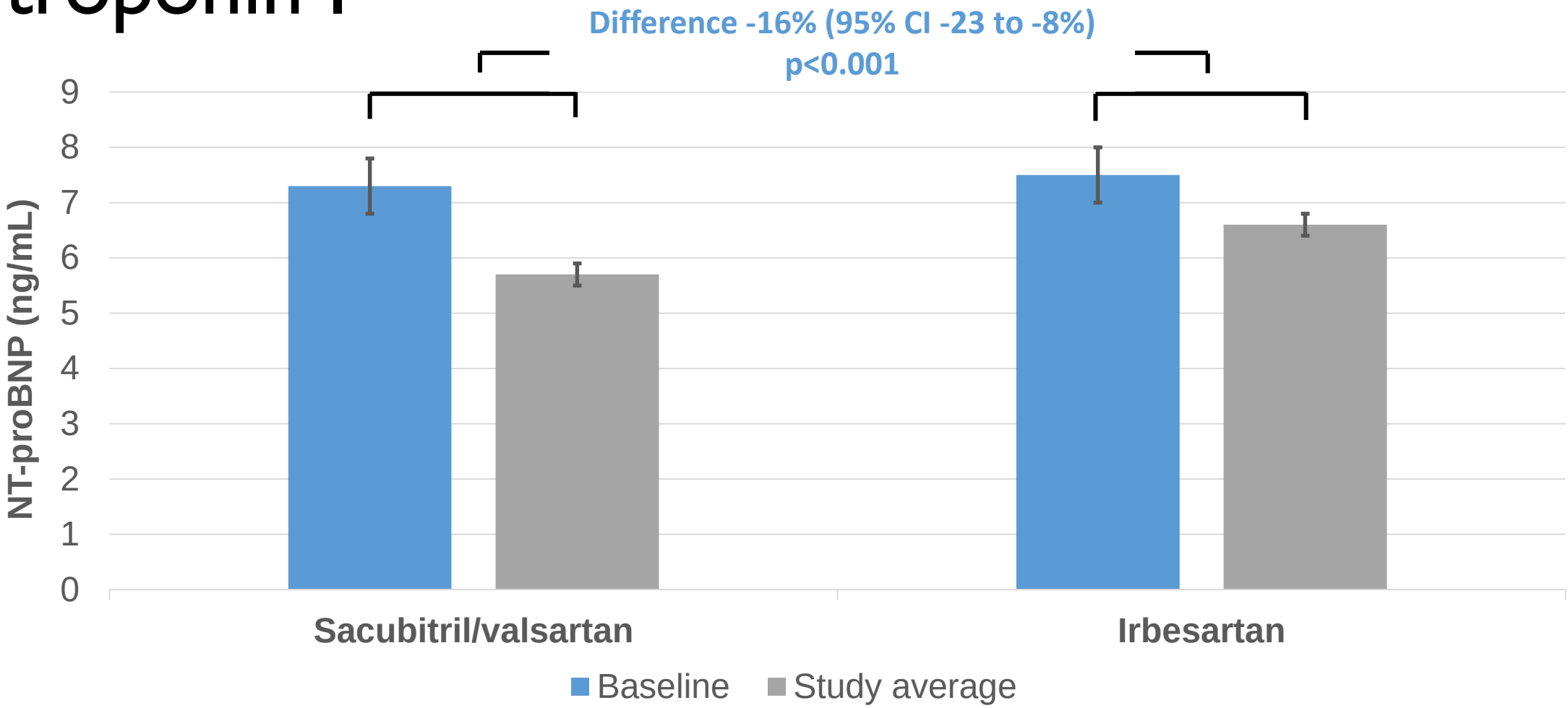
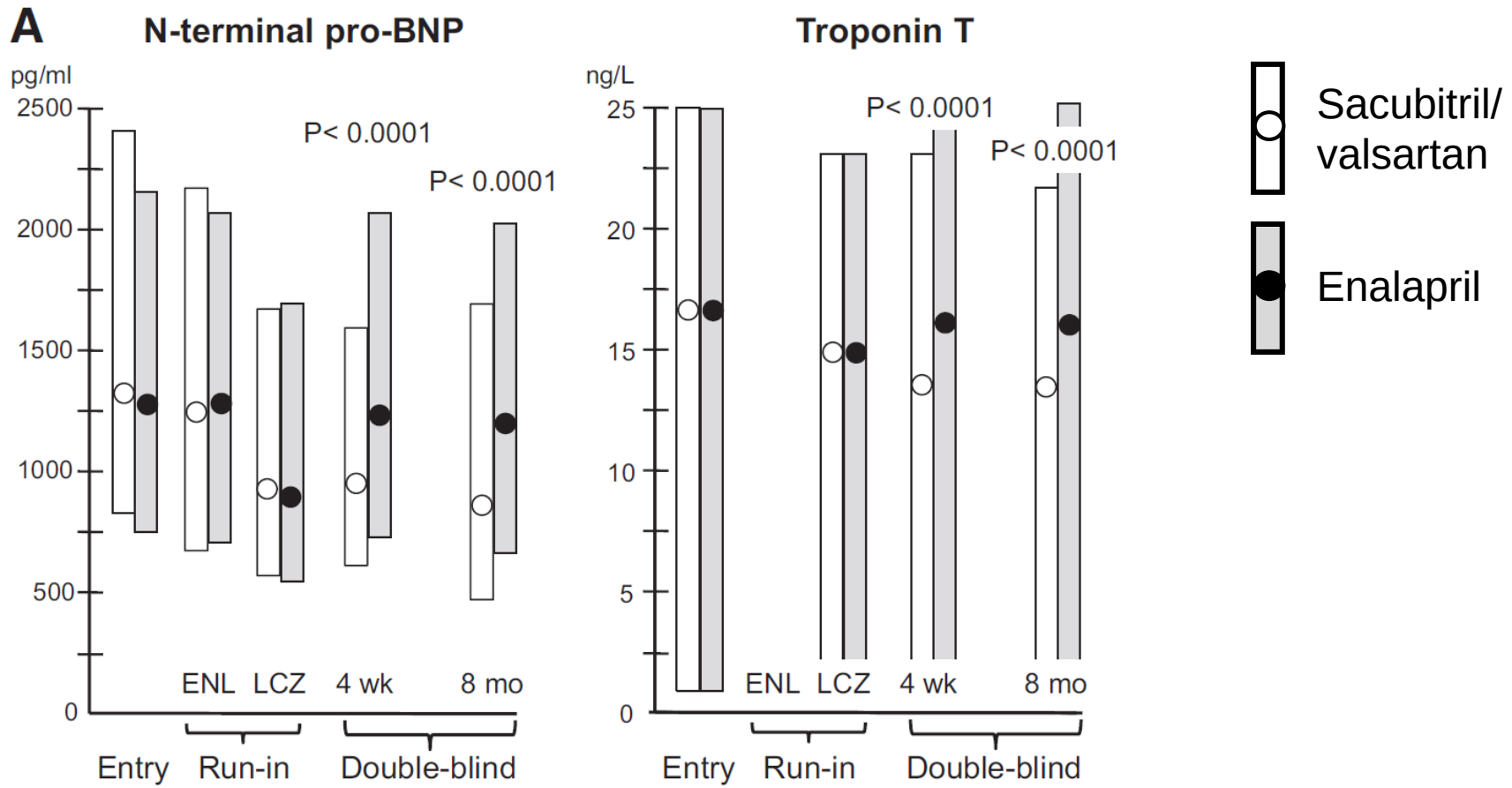
# Effect of sacubitril/valsartan *vs* irbesartan on troponin I



# Effect of sacubitril/valsartan *vs* enalapril on cardiac biomarkers in HFrEF




Packer *et al.* Circulation 2015

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# Summary

- ARNI has no additional effect on kidney function when compared to angiotensin receptor blockade (ARB)
- ARNI lowers BP further than ARB alone
- ARNI reduces cardiac biomarkers further than ARB alone (c.f. data in HFrEF)
- These results suggest ARNI may reduce cardiovascular risk among patients with CKD (and do not exclude a benefit on kidney function)

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# Acknowledgements


- Most importantly to the participants in UK HARP-III

- The UK HARP-III doctors and research coordinators at our 25 sites in the UK

- Data Monitoring Committee (Keith Wheatley, Charlie Tomson, Paul Roderick)

- Steering Committee


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