ACE, DPP4 and NEP inhibitors

Understanding Mechanisms to Optimize Cardiovascular Benefit

Disclosures

Grant support: NIH, AHA, Novo Nordisk, Shire Pharmaceuticals

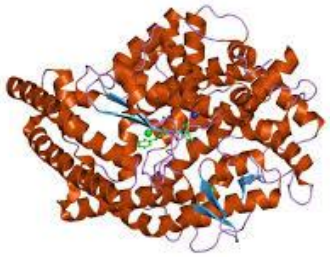
Consulting: Novartis Pharmaceuticals, Shire Pharmaceuticals, Selenity Pharmaceuticals, Alnylam Pharmaceuticals

Institutional: Bayer/Vanderbilt Alliance

I will reference unlabeled or unapproved uses of drugs or other products: bradykinin, icatibant, substance P, brain-type natriuretic peptide, neuropeptide Y

Three peptidase inhibitors

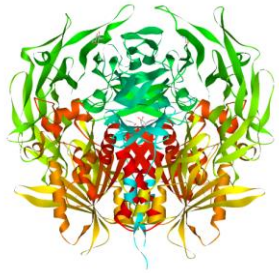
Angiotensin-converting enzyme



Captopril
1981

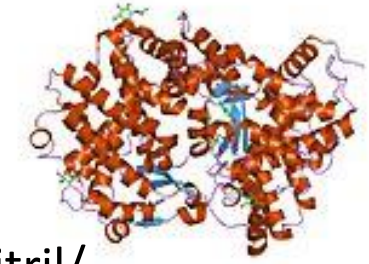
Losartan
1995

Dipeptidyl peptidase-4



Sitagliptin
2006

Neutral endopeptidase

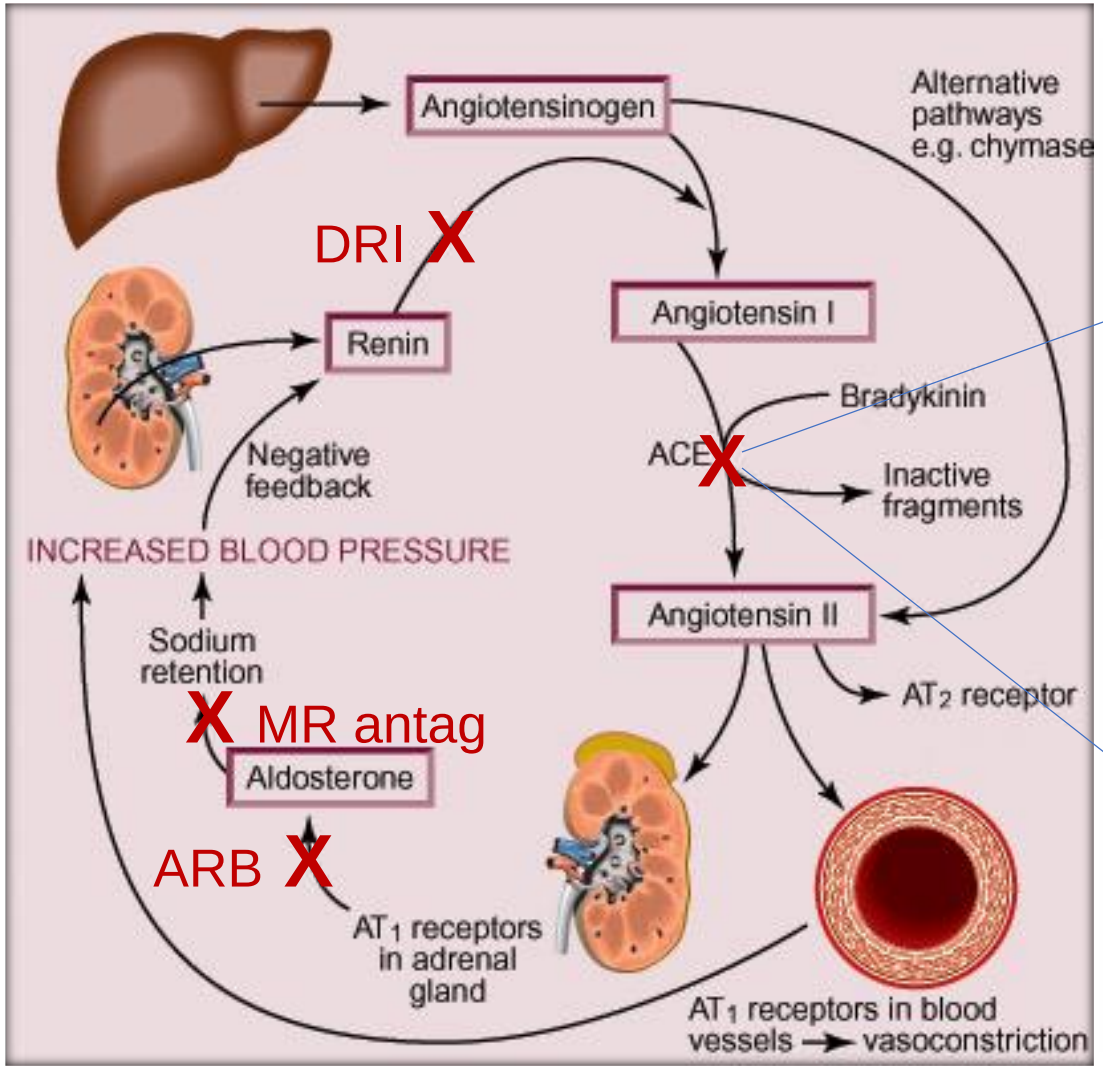


Sacubitril/
Valsartan
2015

Peptidase Inhibitors: Common themes

- The enzymes these drugs inhibit are “promiscuous.” Beneficial and adverse effects of the inhibitors often result blocking the degradation of more than one biologically active peptide.
- The peptidases share many substrates, creating the possibility of drug-drug interactions among inhibitors.
- The peptide substrates of the enzymes are difficult to measure and degraded through multiple pathways.

Angiotensin-converting enzyme (ACE) inhibitors



Comparative effectiveness of ACEi vs ARB in ischemic heart disease

TABLE 3 General Summary of Outcomes and Strength of Evidence Addressing Key Questions 1 and 2

	Key Question 1: ACE Inhibitors Versus Placebo[a,b]	Key Question 1: ARBs Versus Placebo	Key Question 2: Combined Therapy Versus ACE Inhibitor
Total mortality	↓↓↓	– –	– –
Cardiovascular mortality	↓↓	– –	– –
MI[c]	↓↓↓	NE	– –
Stroke	↓↓	– –	– –
Composite of cardiovascular mortality, nonfatal MI, and stroke	– –	↓↓	– –
Study withdrawal due to adverse events	↑	NE	↑↑
Hypotension	–	NE	↑↑
Syncope	↑	NE	↑↑
Cough	↑	NE	– –

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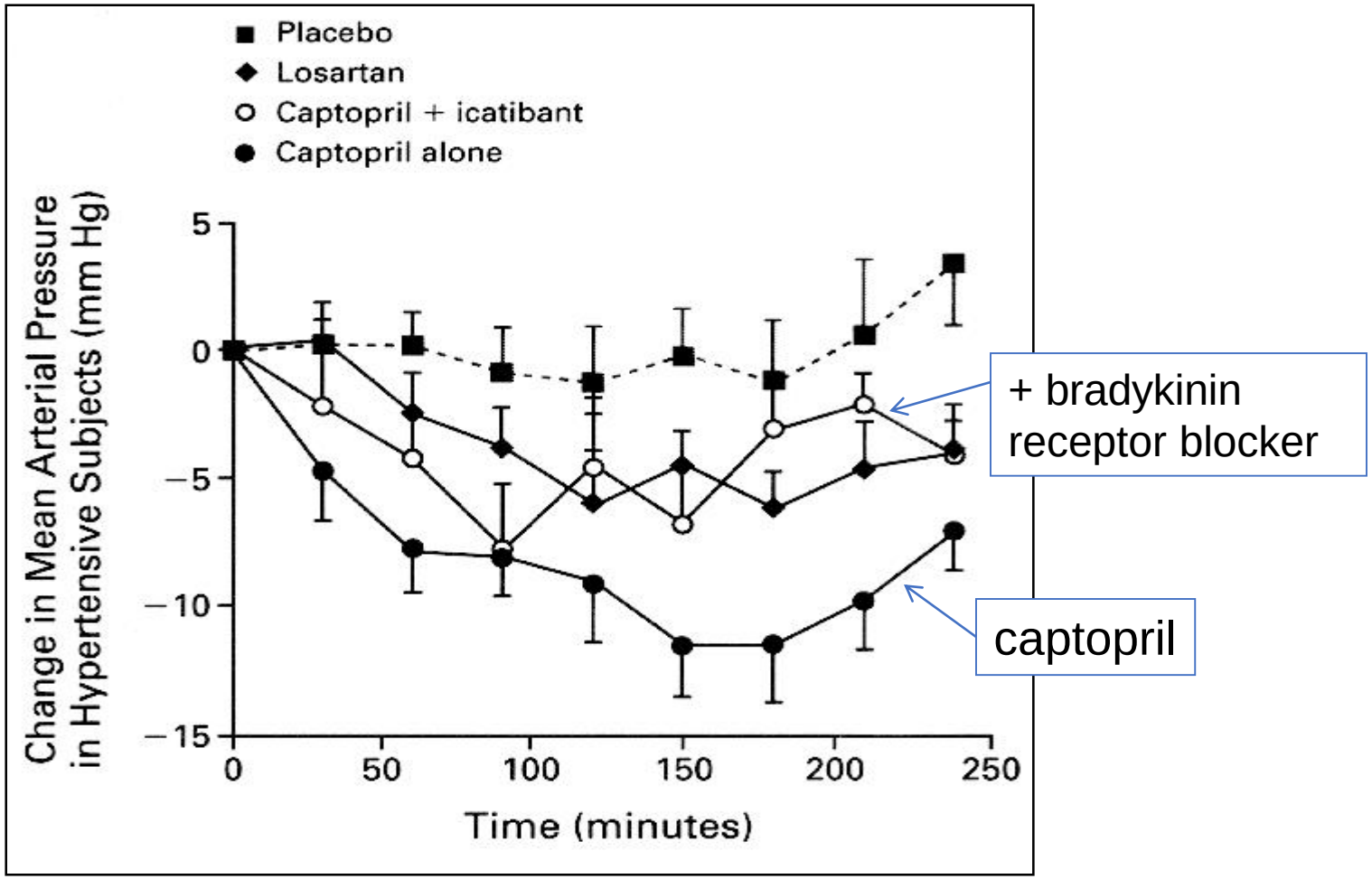
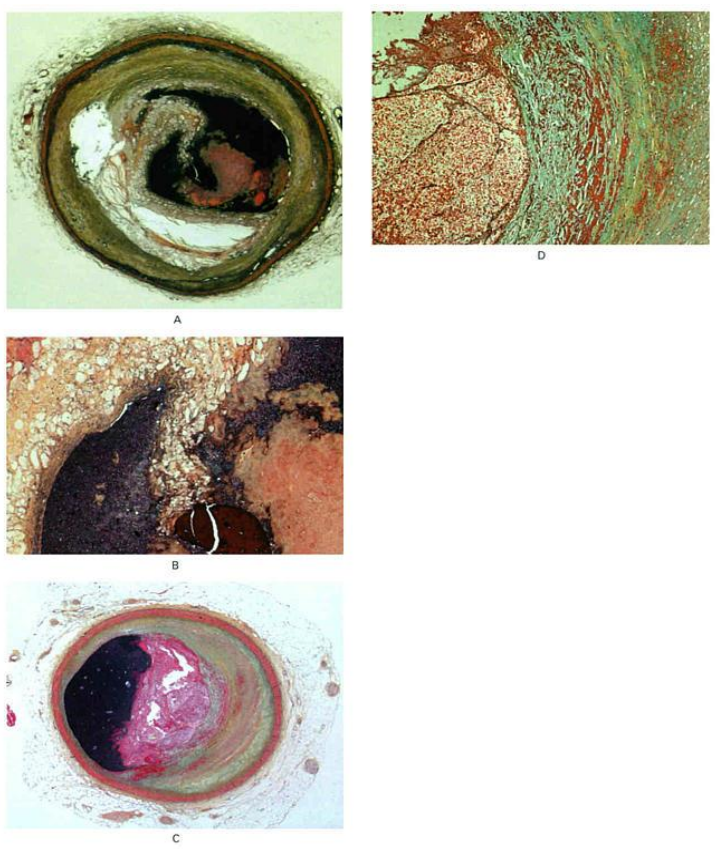
White and Greene *J Man Care Pharmacy* 2011

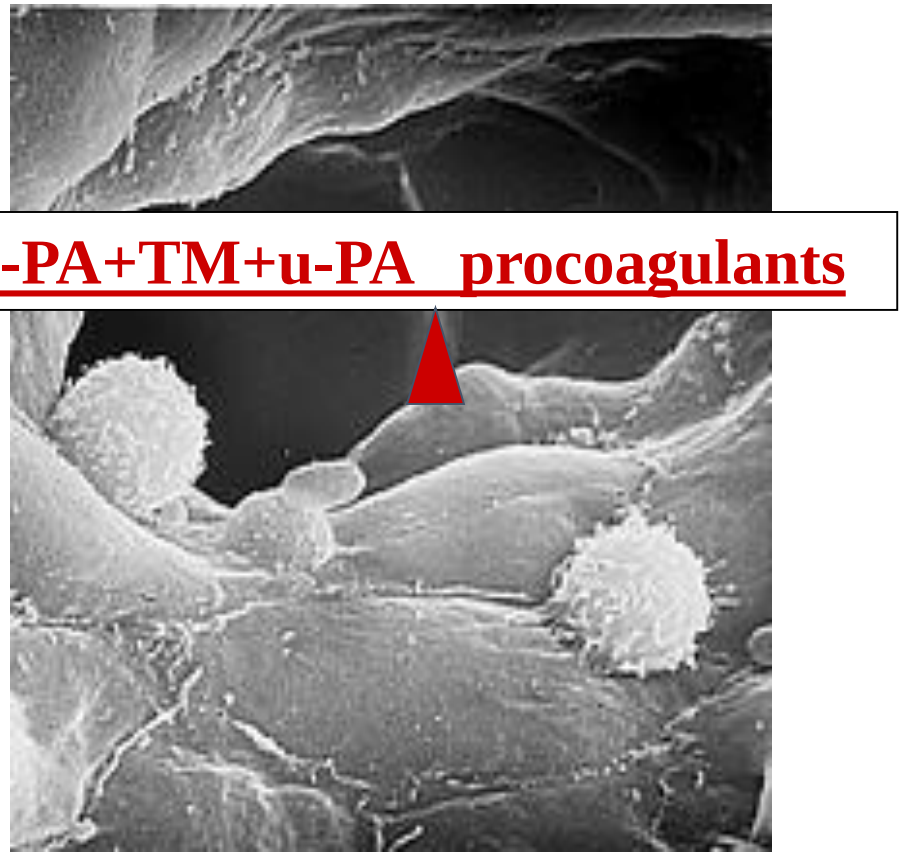
Bradykinin contributes to the blood pressure response to ACE inhibition



Gainer et al *NEJM* 1998

Endogenous bradykinin stimulates t-PA release during ACE inhibition

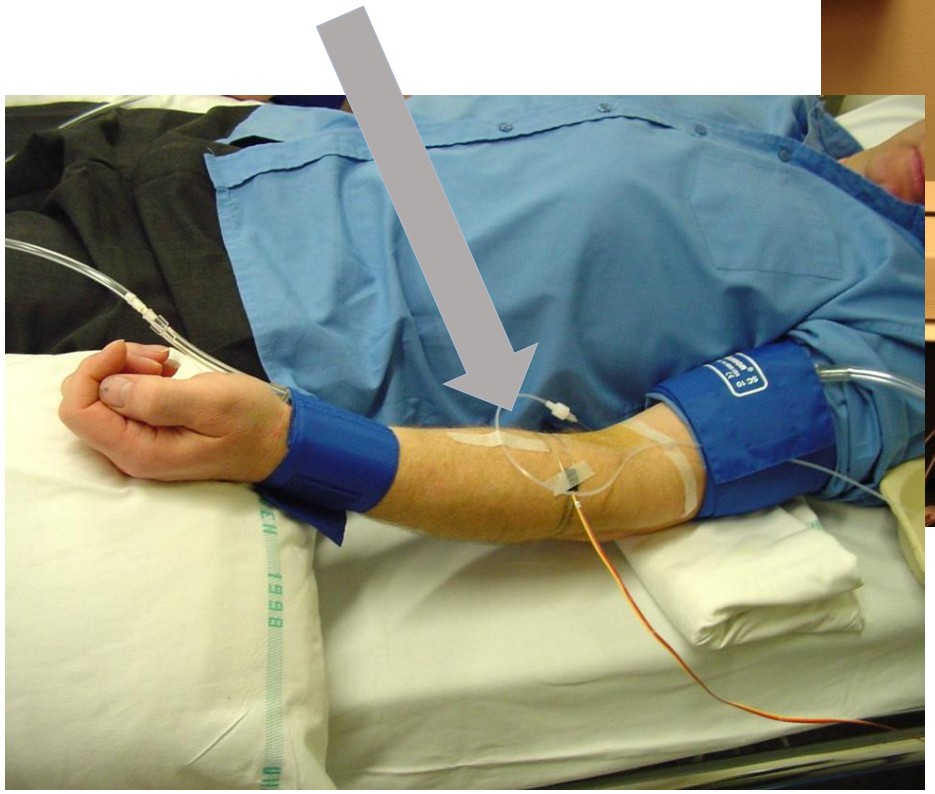




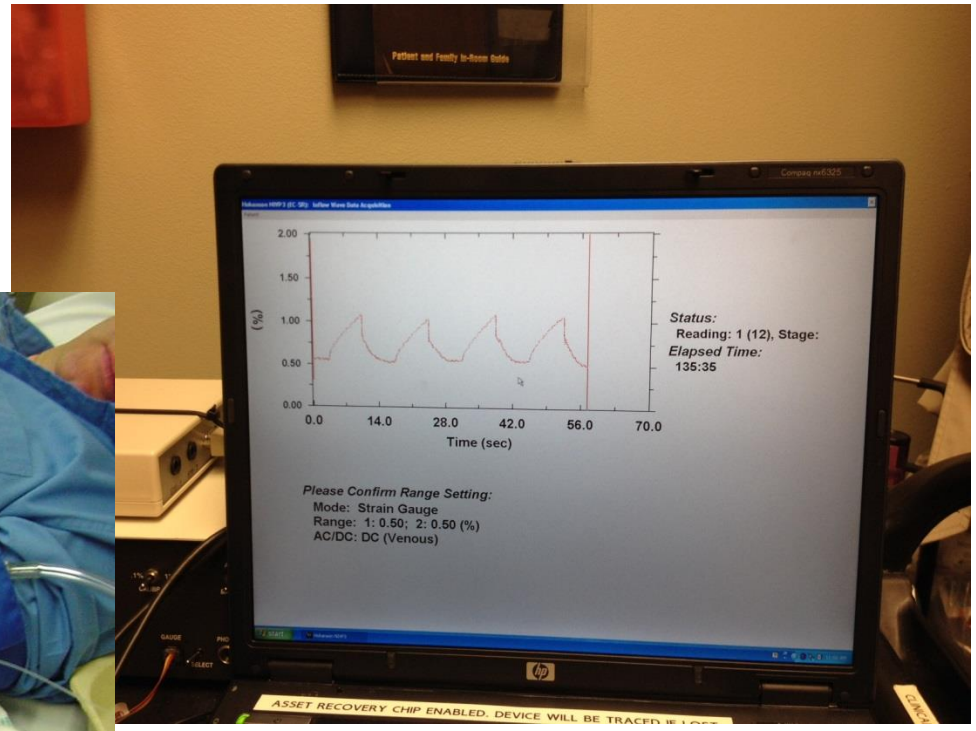
Burke et al *New Engl J Med* 1997

Assessing effect of peptidase (ACE) inhibitors on responses to vascular peptides

Arterial Line (brachial artery) &
Adjacent Peripheral IV

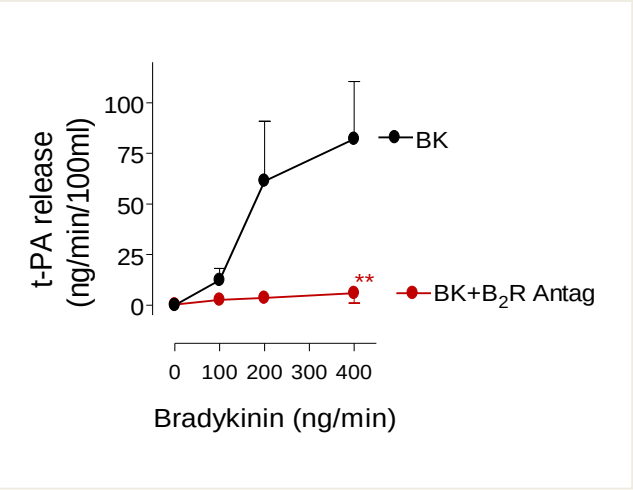


Strain Gauge Plethysmography

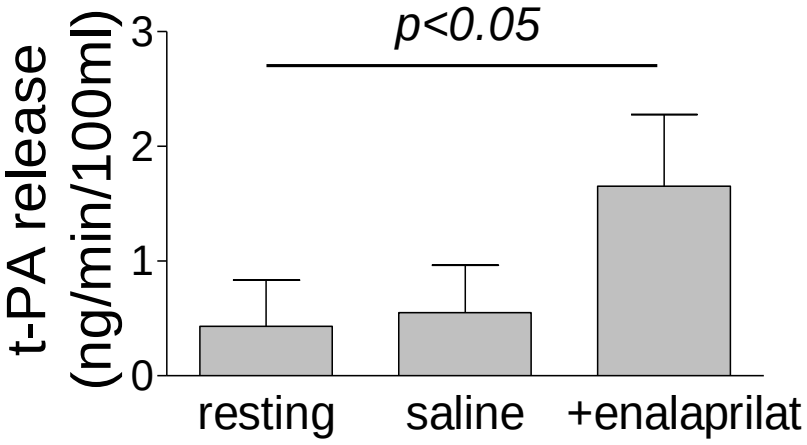


Forearm Blood Flow Readings

During ACE inhibition, endogenous bradykinin increases vascular t-PA release



Brown et al *Circulation* 2000



Pretorius et al, *Circulation* 2003

Forearm t-PA release reflects coronary endothelial fibrinolytic function

Coronary t-PA release parallels forearm t-PA release

Minai et al *JACC* 2001

Forearm t-PA release predicts cardiovascular events

Robinson et al *ATVB* 2007

Cardiovascular risk factors are associated with impaired endothelial fibrinolysis

Hypertension

Ridderstrale et al *Hypertension*

Obesity and insulin resistance

Carnassi et al *Thromb Res*

Smoking

Pretorius et al *ATVB*

Male sex

Pretorius et al *Circulation, ATVB, Hypertension*

Exposure to diesel exhaust

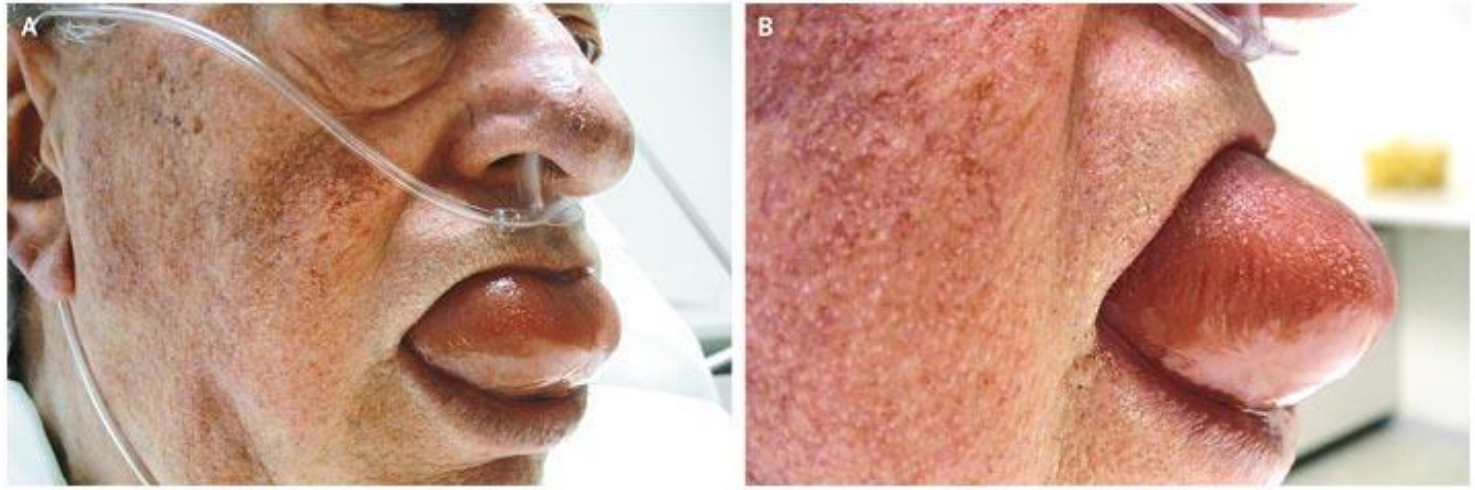
Tornquist et al *Am J Resp Crit Care*

- ACE inhibitors decrease the degradation of peptides such as angiotensin I to II and bradykinin to inactive products
- Endogenous bradykinin contributes to favorable effects of ACE inhibitors on blood pressure and endothelial t-PA release

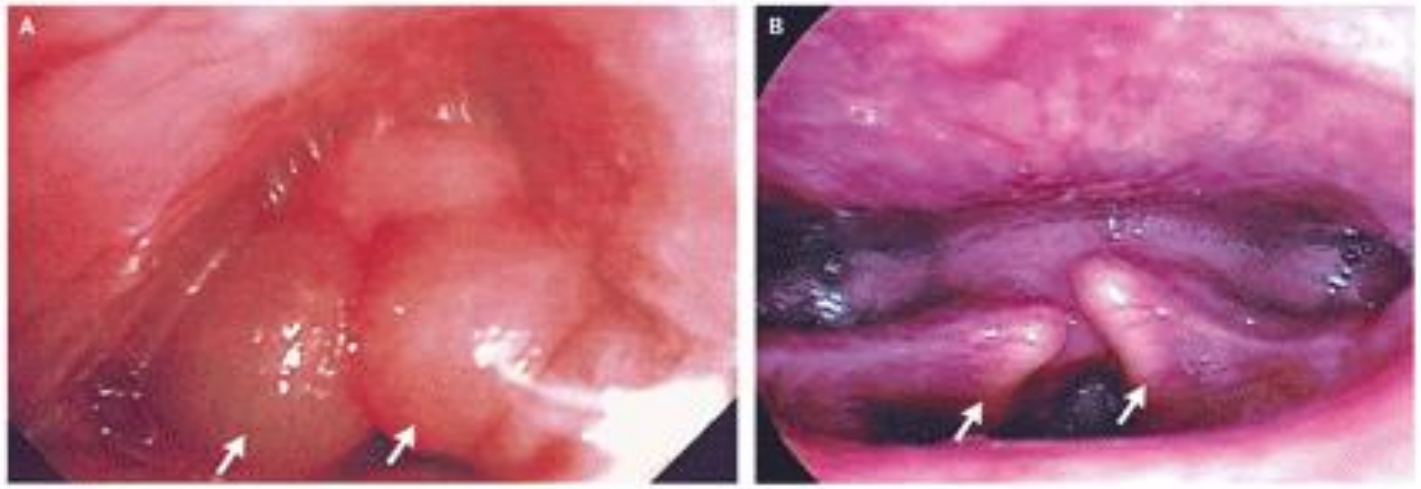
- But…

Bradykinin Is a Double-Edged Sword

ACE inhibitor-associated angioedema: an effect of bradykinin?



NEJM 2006 July 20;355(3):295



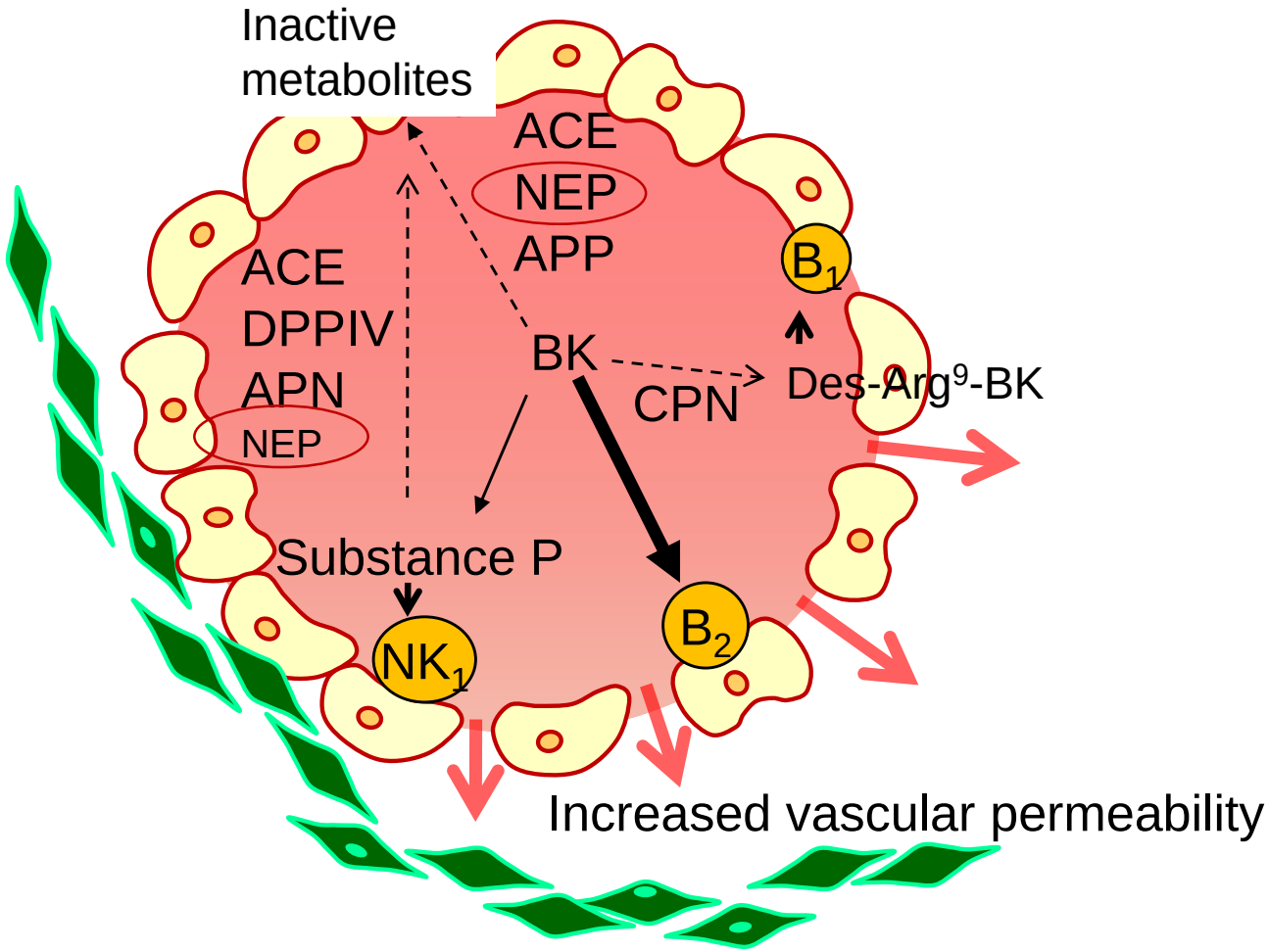
NEJM 2005 Oct 27;353(17):e15

Angiotensin-converting enzyme inhibitor-associated angioedema: risk factors

Risk factor	Odds Ratio (95% CI)	P value
African American race	2.97 (2.24,3.92)	<0.0001
Current smoker	2.49 (1.86, 3.34)	<0.0001
Female gender	1.49 (1.16, 1.91)	0.002
Seasonal allergies	1.52 (1.12, 2.06)	0.008
Former smoker	1.47 (1.09, 1.99)	0.013
History of diabetes	0.58 (0.38, 0.90)	0.014

BMS on file and Kostis et al. *J Clin Hypertens (Greenwich)* 2008;10:82-94

Hypothesized mechanism of ACE inhibitor-associated angioedema



Angioedema during combined ACE/neutral endopeptidase (NEP) inhibition

WALL STREET JOURNAL APRIL 2000

…the FDA raised questions about four patients on the drug who had a severe reaction that closed down their airways. The patients were among 7,000… The four patients had a severe form of angioedema, which is typically characterized by a mild, temporary swelling of the lips, cheeks or tongue.

Some 40 other patients developed the milder angioedema….

Among the four patients with the severe reaction, two were white and two were black, but the overall incidence of angioedema, though low, was four times higher among blacks….

Am. J. Hum. Genet. 77:617–626, 2005

A Variant in *XPNPEP2* Is Associated with Angioedema Induced by Angiotensin I–Converting Enzyme Inhibitors

Qing Ling Duan,[1,2,*] Borzoo Nikpoor,[1,*] Marie-Pierre Dubé,[3] Giuseppe Molinaro,[4] Inge A. Meijer,[1] Patrick Dion,[1] Daniel Rochefort,[1] Judith Saint-Onge,[1] Leah Flury,[5] Nancy J. Brown,[6] James V. Gainer,[6] Jean L. Rouleau,[3] Angelo Agostoni,[7] Massimo Cugno,[7] Pierre Simon,[8] Pierre Clavel,[9] Jacky Potier,[11] Bassem Wehbe,[12] Seddik Benarbia,[13] Julien Marc-Aurèle,[14] Jacques Chanard,[10] Tatiana Foroud,[5] Albert Adam,[4] and Guy A. Rouleau[1]

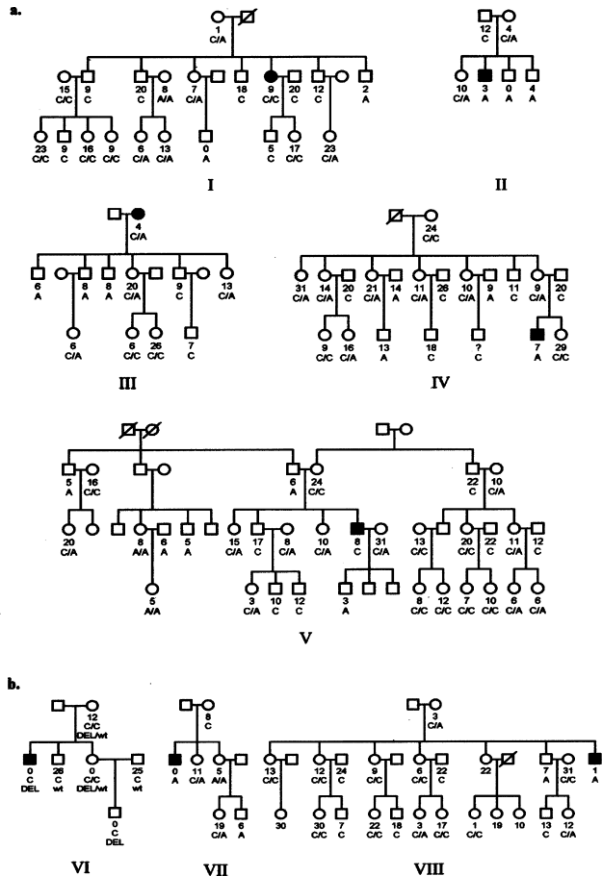


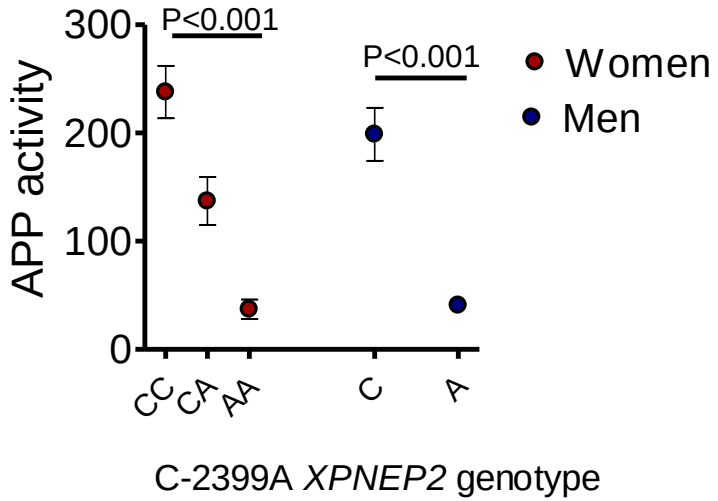
Table 2

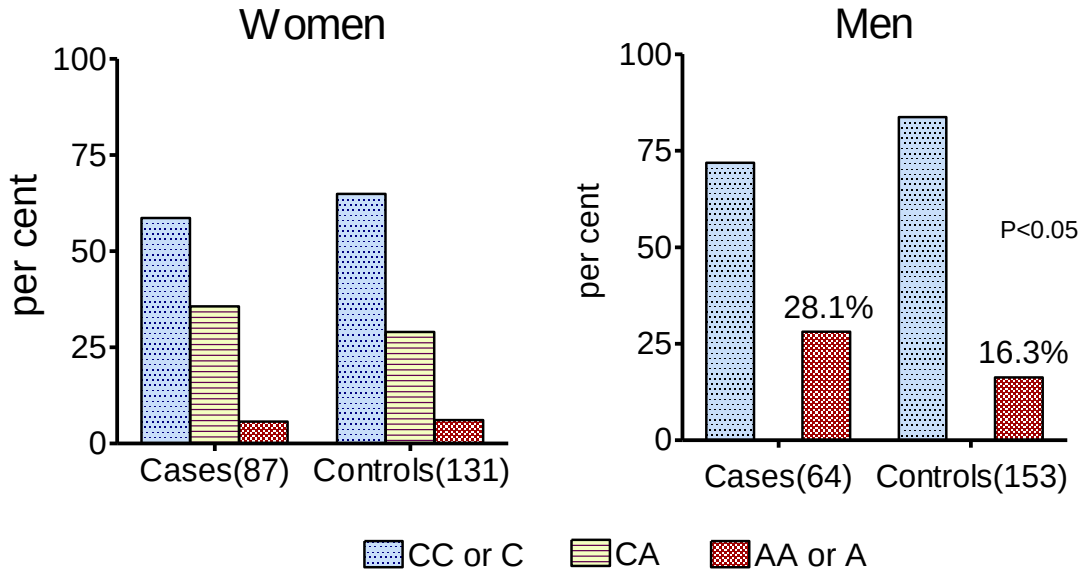
C-2399A SNP Genotypes in ACEi-Associated AE Cases and Matched Controls

	AE-ACEi Cases ($n = 20$)			Controls ($n = 60$)	
C-2399A SNP Genotype	No. of Males	No. of Females	Mean APP ± SE (units)	No. of Males	No. of Females
CC or C	4	8	18 ± 4	18	31
CA	–	4	10 ± 5	–	8
AA or A	3	1	2 ± 2	3	0
All			13 ± 3		

NOTE.—Mean APP activity is represented as units of arginine released per minute per milliliter of plasma sample.

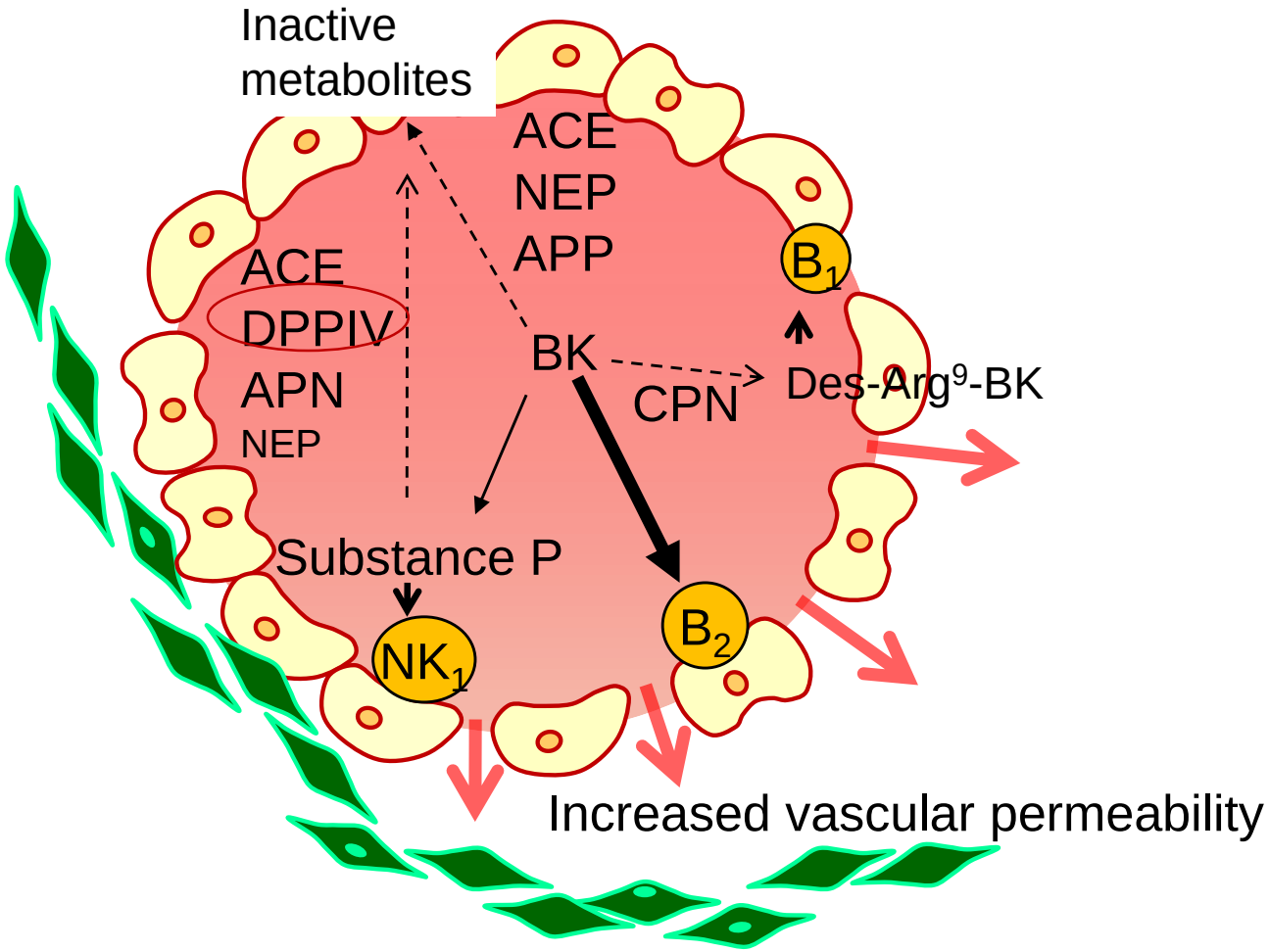
Aminopeptidase P deficiency contributes to anaphylactoid reactions but less likely to ACE inhibitor-associated angioedema



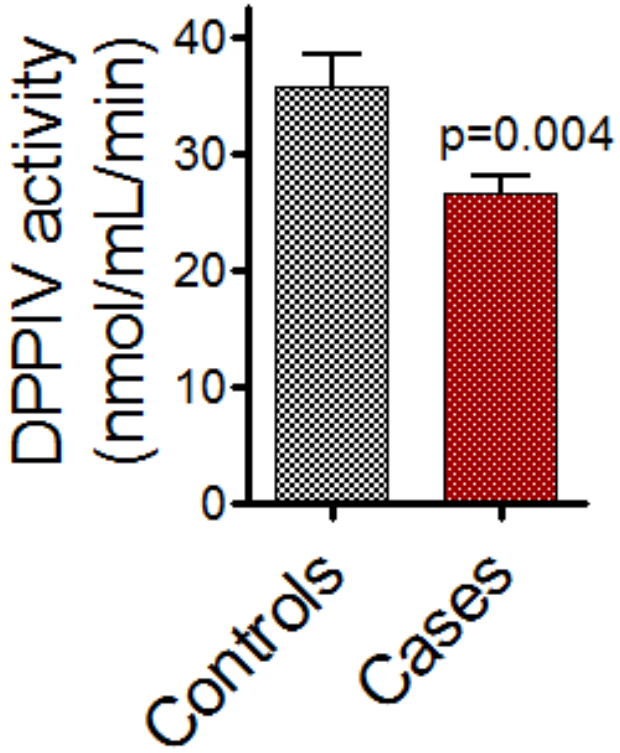


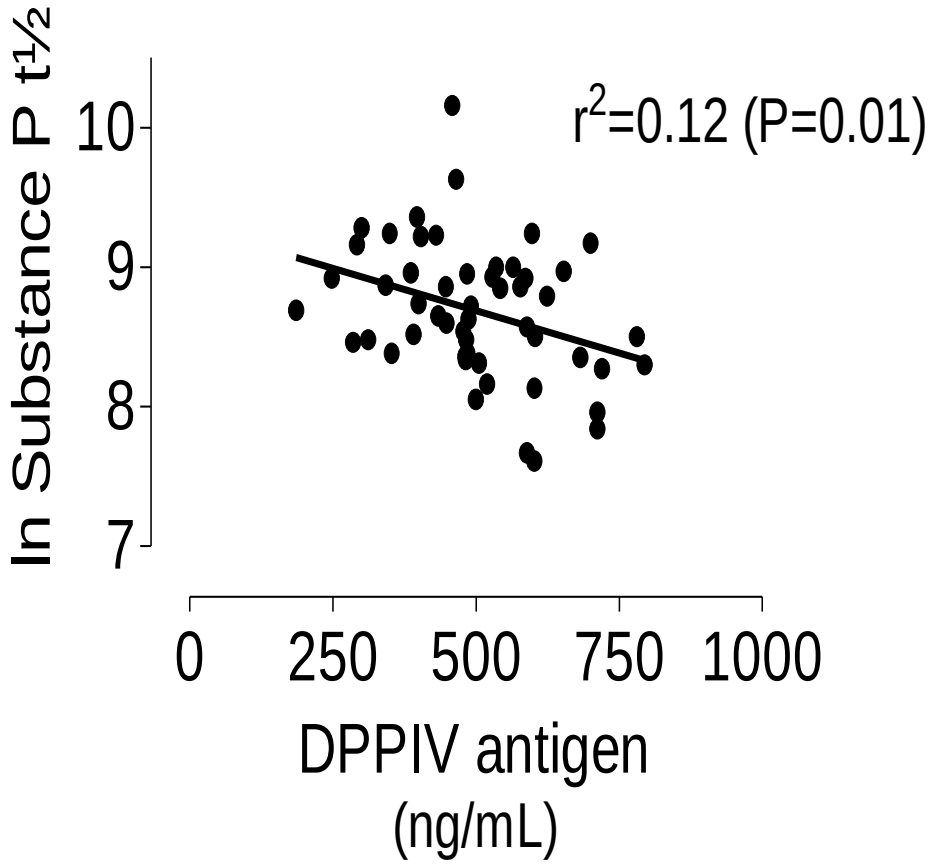
Adam et al Lancet 2002
Woodard-Grice 2010

Hypothesized mechanism of ACE inhibitor-associated angioedema



DPP4 activity is decreased in plasma during ACEI-associated angioedema





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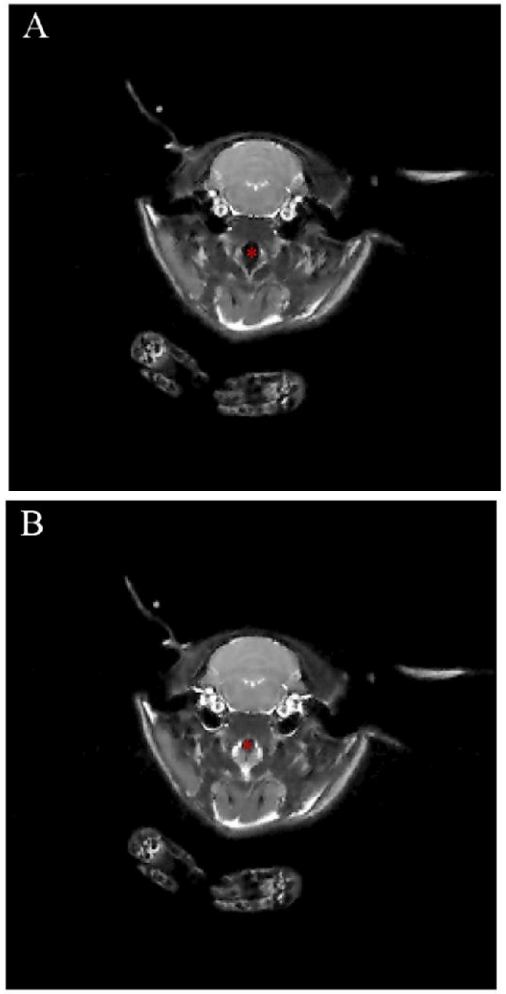
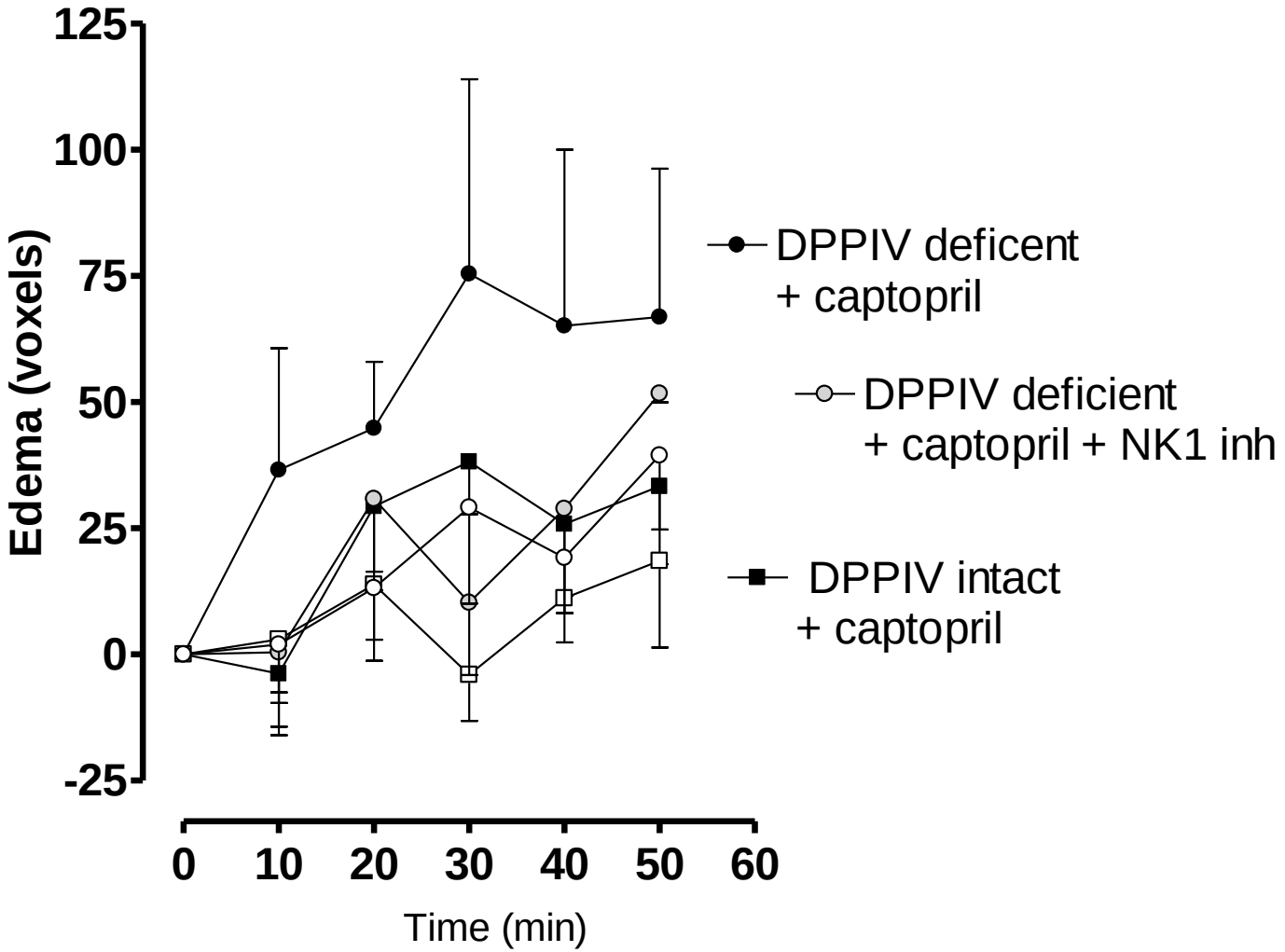
Byrd et al *Hypertension* 2008

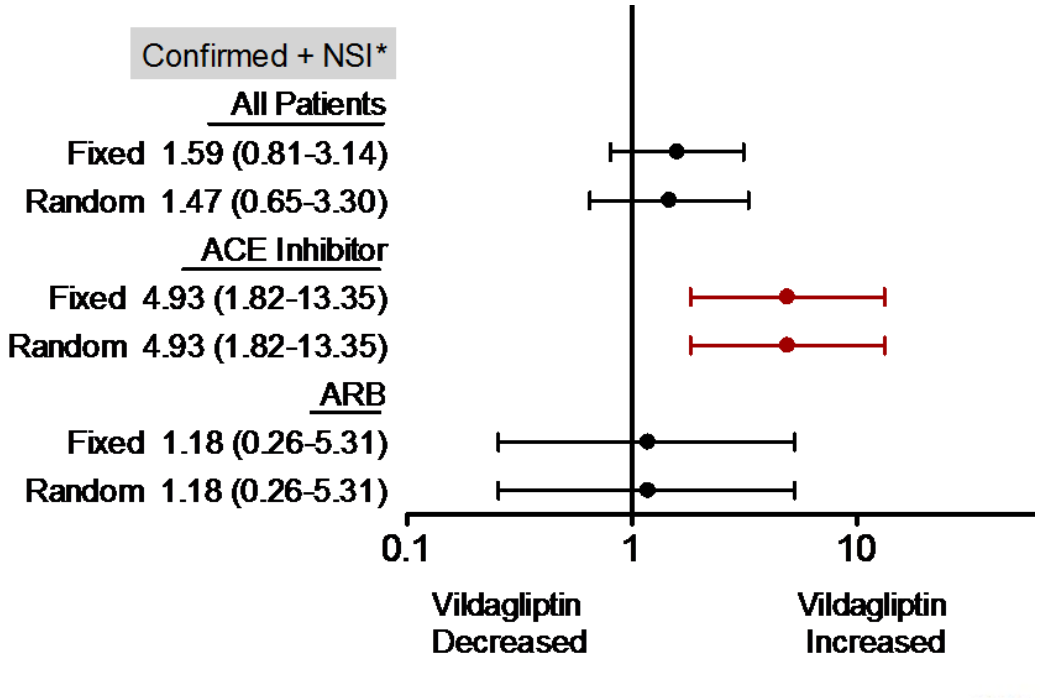
DPPIV deficiency increases susceptibility to ACE inhibitor-induced peritracheal edema through NK1





Byrd et al *J Allergy Clin Immunol* 2008

DPP4 inhibitor use is associated with increased risk of ACEi angioedema



Brown et al *Hypertension* 2009

Increased angioedema in saxaglitpin-treated in SAVOR-TIMI 53

SAFETY END POINTS

The prespecified safety end points are listed in Table 3. The numbers of patients with thrombocytopenia, lymphocytopenia, infections, cancers, hypersensitivity or skin reactions, bone fractures, or liver abnormalities were similar in the saxagliptin and placebo groups. Hospitalization for hypoglycemia occurred infrequently, and the rate was similar in the two groups: 0.6% according to 2-year Kaplan–Meier estimates (53 patients) in the saxagliptin group and 0.5% according to 2-year Kaplan–Meier estimates (43 patients) in the placebo group (hazard ratio with saxagliptin, 1.22; 95% CI, 0.82 to 1.83; P=0.33). However, significantly more patients in the saxagliptin group than in the placebo group reported at least one hypoglycemic event (1264 patients [15.3%] vs. 1104 patients [13.4%], P<0.001); major hypoglycemic events occurred in 177 patients (2.1%) in the saxagliptin group as compared with 140 patients (1.7%) in the placebo group (P=0.047), [0.3%] in the saxagliptin group and 21 patients [0.3%] in the placebo group, P=0.77). Definite or possible acute pancreatitis occurred in 22 patients (0.3%) in the saxagliptin group and in 16 patients (0.2%) in the placebo group (P=0.42), definite acute pancreatitis in 17 patients (0.2%) and 9 patients (0.1%) in the two groups, respectively (P=0.17), and chronic pancreatitis in 2 patients (<0.1%) and 6 patients (0.1%), respectively (P=0.18). There were 5 cases of pancreatic cancer in the saxagliptin group and 12 in the placebo group (P=0.095). There were no cases of fatal angioedema; nonfatal angioedema occurred in 8 patients in the saxagliptin group and 1 in the placebo group (P=0.04).

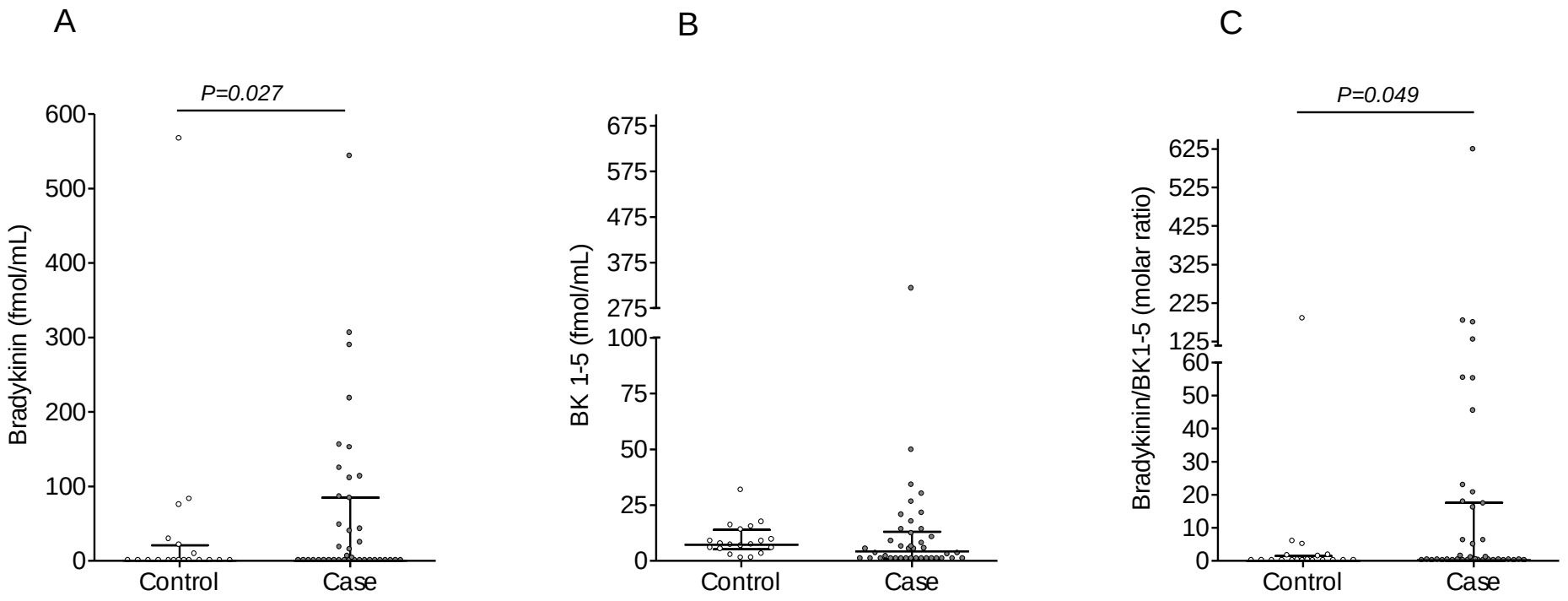
DISCUSSION

In this randomized, placebo-controlled trial, the DPP-4 inhibitor saxagliptin neither reduced nor increased the risk of the primary composite end point of cardiovascular death, myocardial infarction, or ischemic stroke, when added to the stan-

Comparisons of clinical trials of B2 receptor antagonist in ACE inhibitor-associated angioedema

Study	Baş et al	Straka et al	Sinert et al
N	27 per protocol	30	121
Patient Characteristics	37% female	63% female	61.2% female
	0% African descent	67% African descent	69.4 % African descent
Comparator group	500 mg prednisolone, Clemastine 2 mg	Both groups received standard therapy	Both groups received standard therapy
Symptoms to treatment (hr)	6.1 (3.0 to 10.0)	10.3 ± 0.56	7.8 (5.5 to 9.6)
Finding	Icatibant superior	No difference	No difference
	NEJM 2015	*J All Clin Immunol* 2017	*J All Clin Immunol Pract* 2017

Bradykinin and bradykinin: BK1-5 ratio increased in ACE inhibitor-associated angioedema compared to ACE inhibitor-treated controls



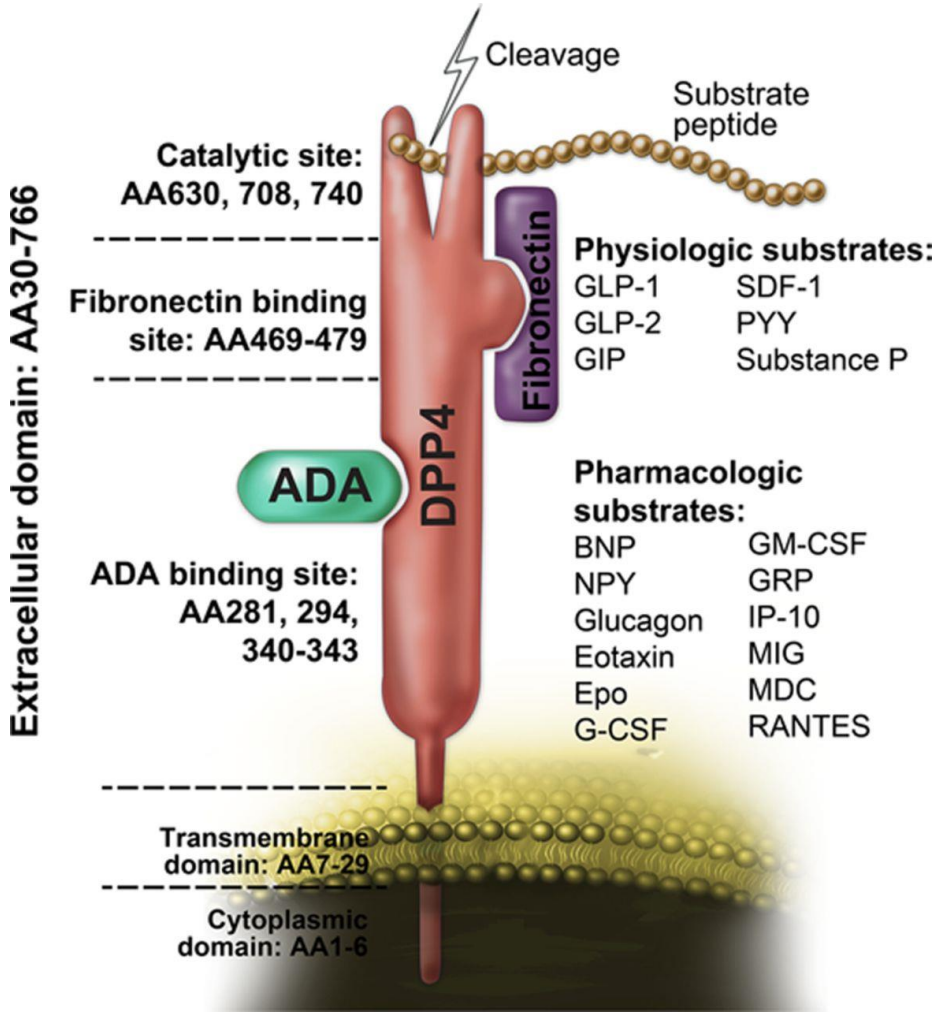
Hubers et al *J Allergy Clin Immunol* 2018

Interim Summary

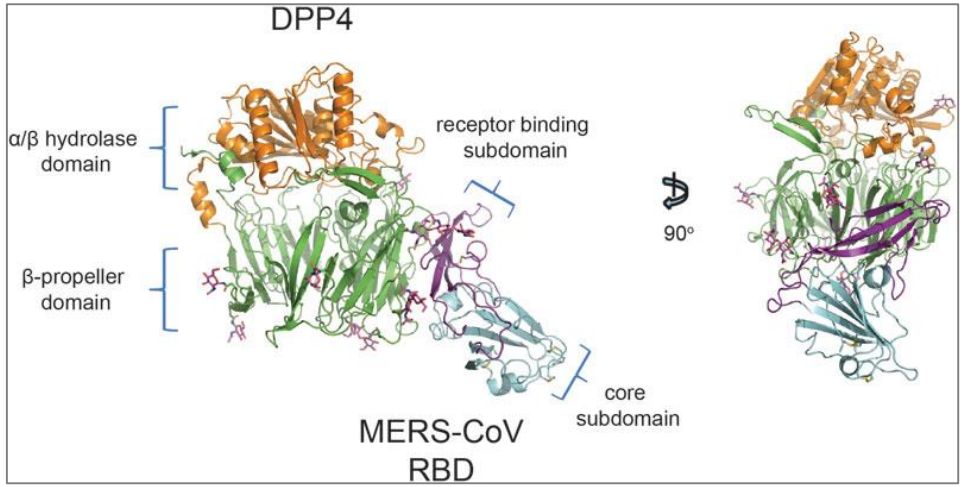
- ACE and DPP4 share many peptide substrates.
- In patients taking an ACE inhibitor, use of a DPP4 inhibitor increases the risk of angioedema.

Could there be a favorable interactive effect of ACE inhibitors and DPP4 inhibitors on blood pressure?

Dipeptidyl peptidase 4 (CD26)



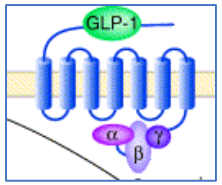
Zhong et al. *Circ Res*. 2015;116:1491-1504



Wang et al *Cell Research* (2013) 23:986–993

GLP-1 causes vasodilation through GLP-1 receptor-dependent and -independent pathways

GLP-1 (7-36) → DPP4 → GLP-1 (9-36)



?

GLP-1 receptor dependent

NO – independent vasodilation
(not blocked by NOS inhibitor)

GLP-1 receptor independent
(see in *GLP-1R -/-* mice)

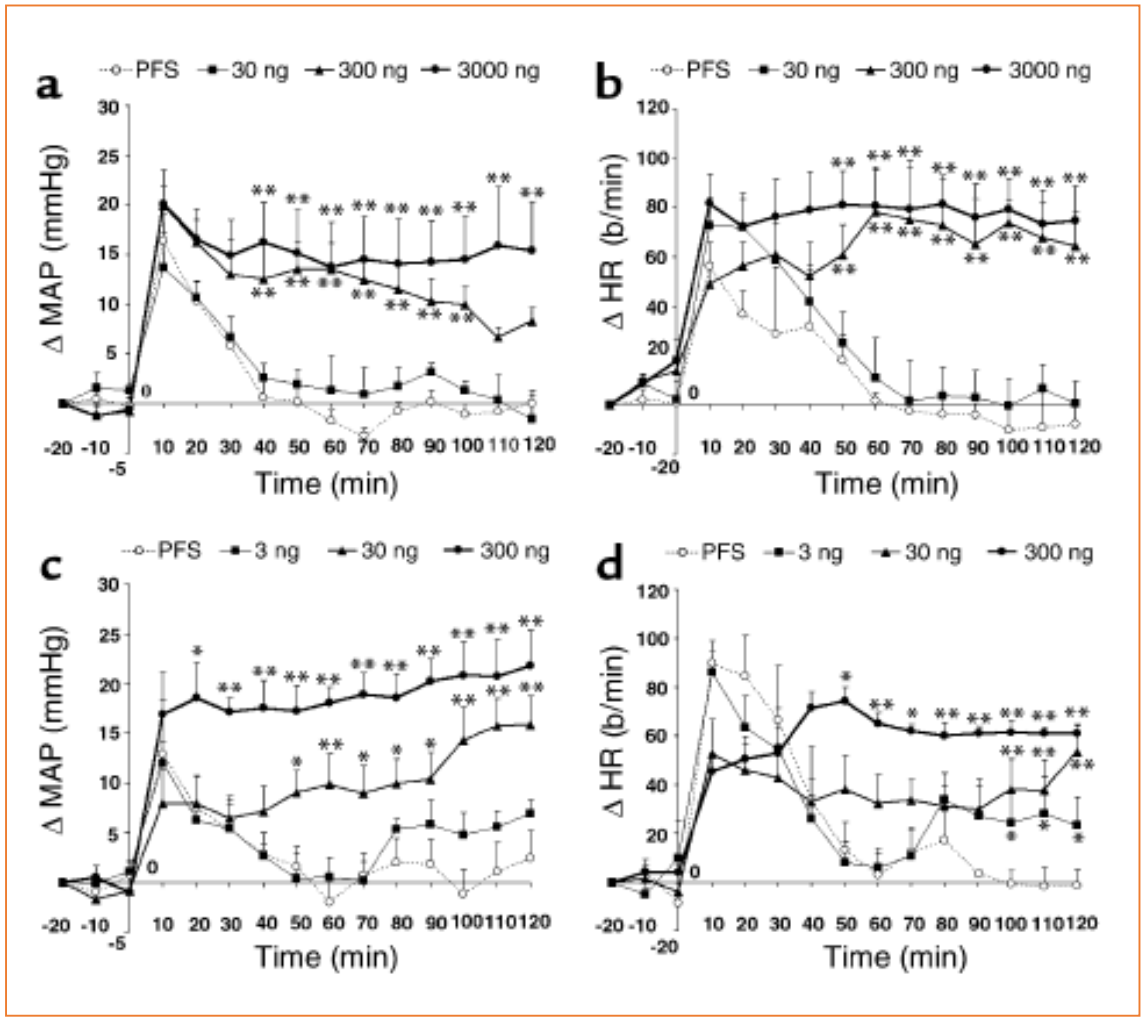
NO-dependent vasodilation
(blocked by L-NNA)

Ban et al *Circulation* 2008

GLP-1 receptor stimulation increases blood pressure and heart rate

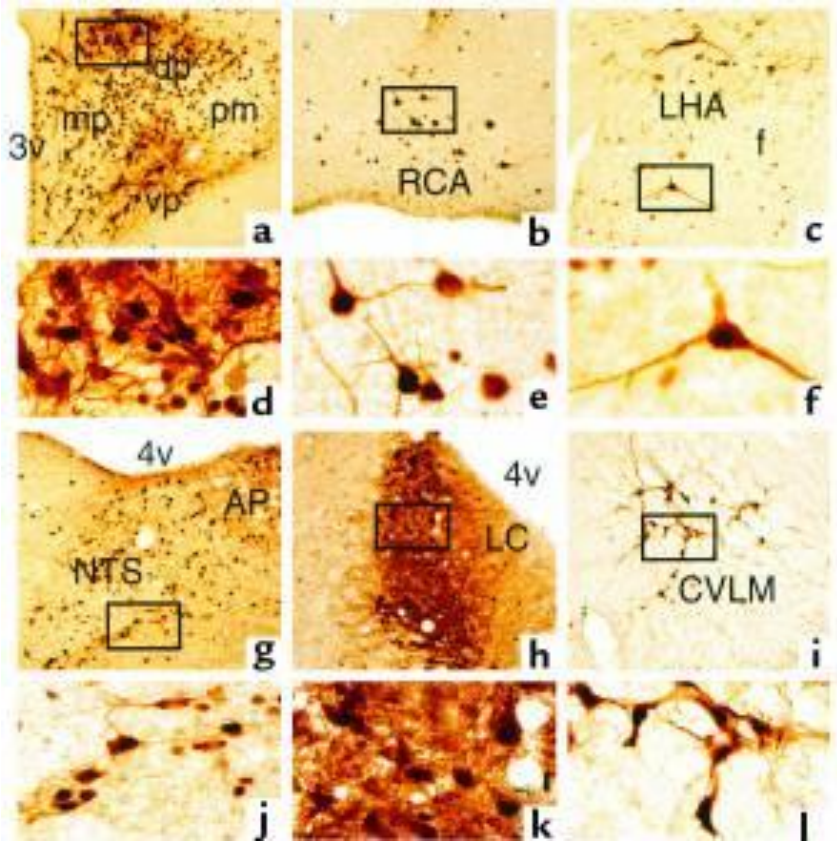
Intravenous Exendin 4

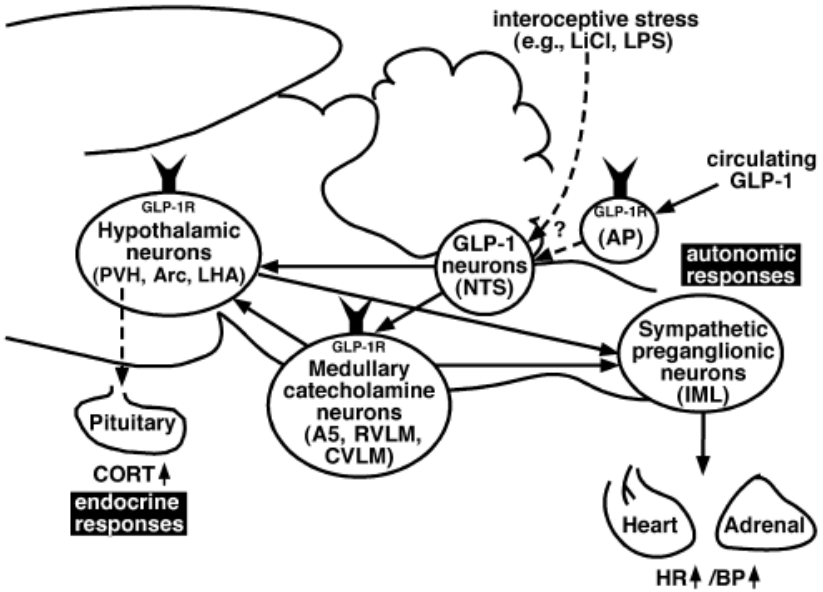
Intraventricular Exendin 4



Yamamoto et al *J Clin Invest* 2002

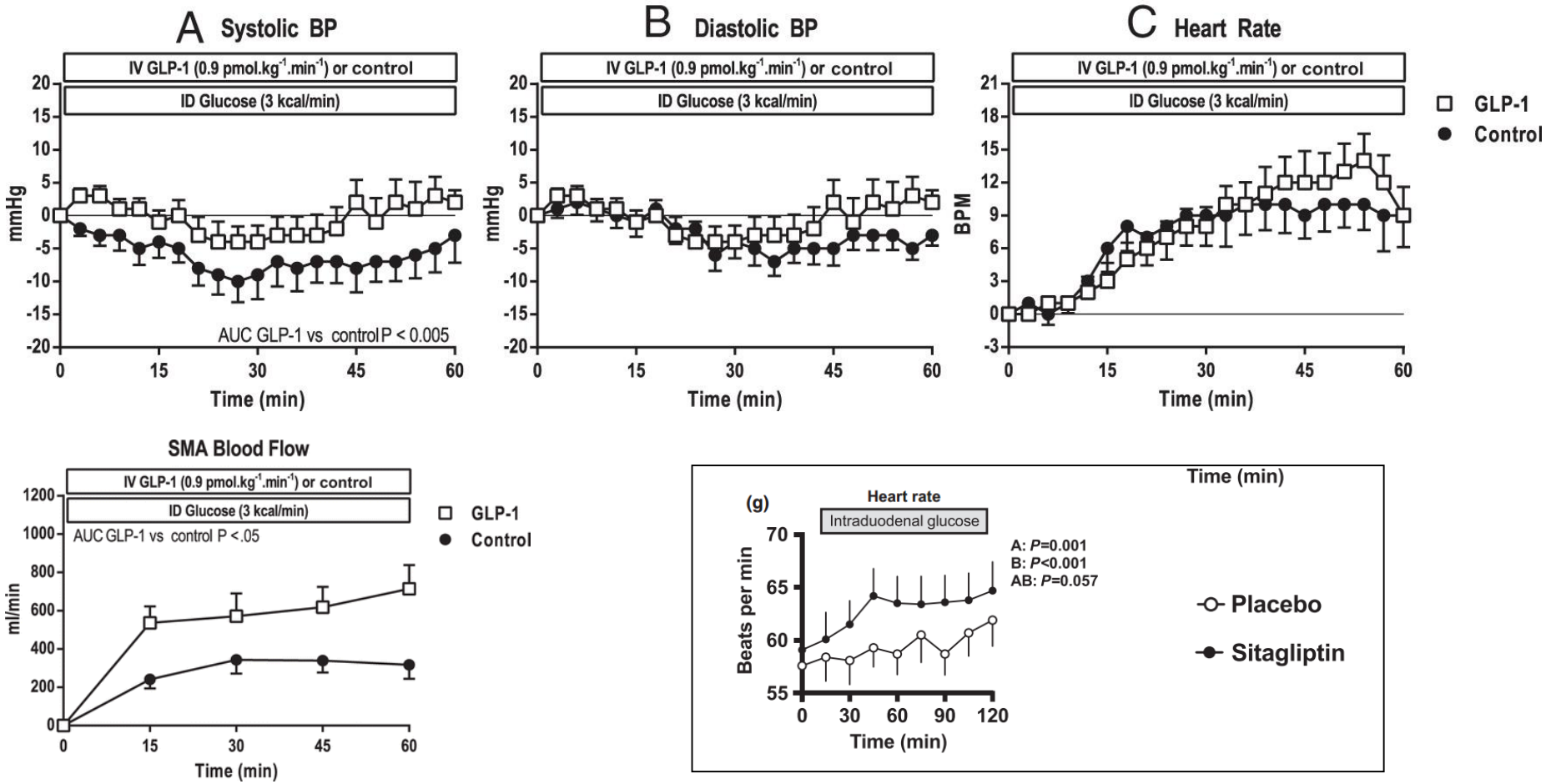
GLP-1R stimulation activates autonomic regulatory neurons





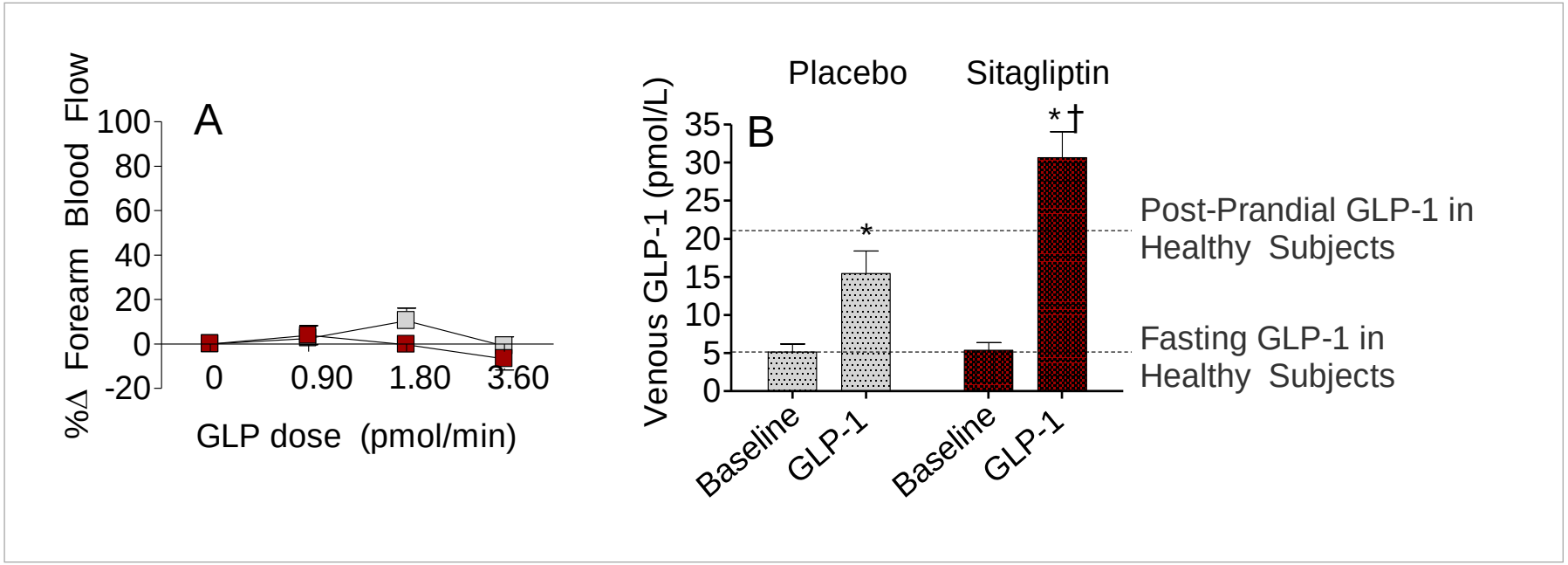
Yamamoto et al *J Clin Invest 2002*

GLP-1 increases blood pressure and heart rate during intra-duodenal (ID) glucose



Trahair et al *J Clin Endocrinol Metab* 2014 Wu et al *Diabetic Med* 2014

GLP-1 does not cause direct vasodilation in human forearm



Devin et al *JAHA* 2014

Interim Summary

- In rodents, GLP-1 causes vasodilation through GLP-1 receptor-dependent and -independent mechanisms.
- GLP-1 also activates the sympathetic nervous system.
- GLP-1 does not cause vasodilation in the human forearm vasculature.
- Acute GLP-1 administration may increase blood pressure and heart rate when given during caloric intake.
- With chronic administration of GLP-1 analogues, blood pressure decreases, but this may be due to weight loss.

Vasoactive substrates of DPP4

Substance P

RPKPQQFFGLM

Brain natriuretic peptide

SPKMVQGSGCFGRKMDRISSSSGLGCKVLRRH

Neuropeptide Y

NPYYPSKPDNPOEDAPAEDLARYYSALRHYINLITRQRY

Peptide YY

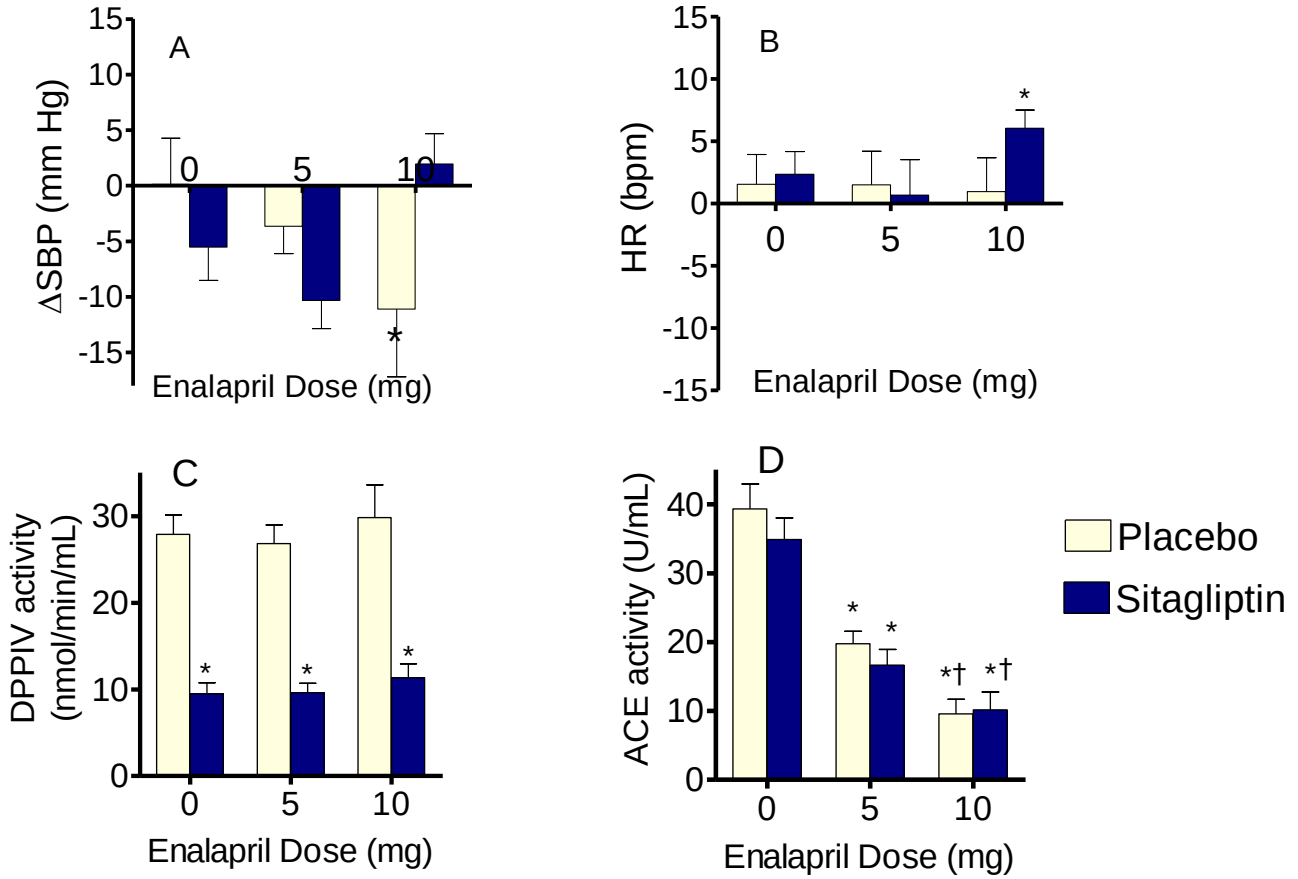
YPSKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY

Effect of DPP4 inhibitor on acute response to ACE inhibitor

Figure 1. Study protocol.

Marney et al *Hypertension* 2010

DPP4 inhibition attenuates BP response to acute maximal ACE inhibition



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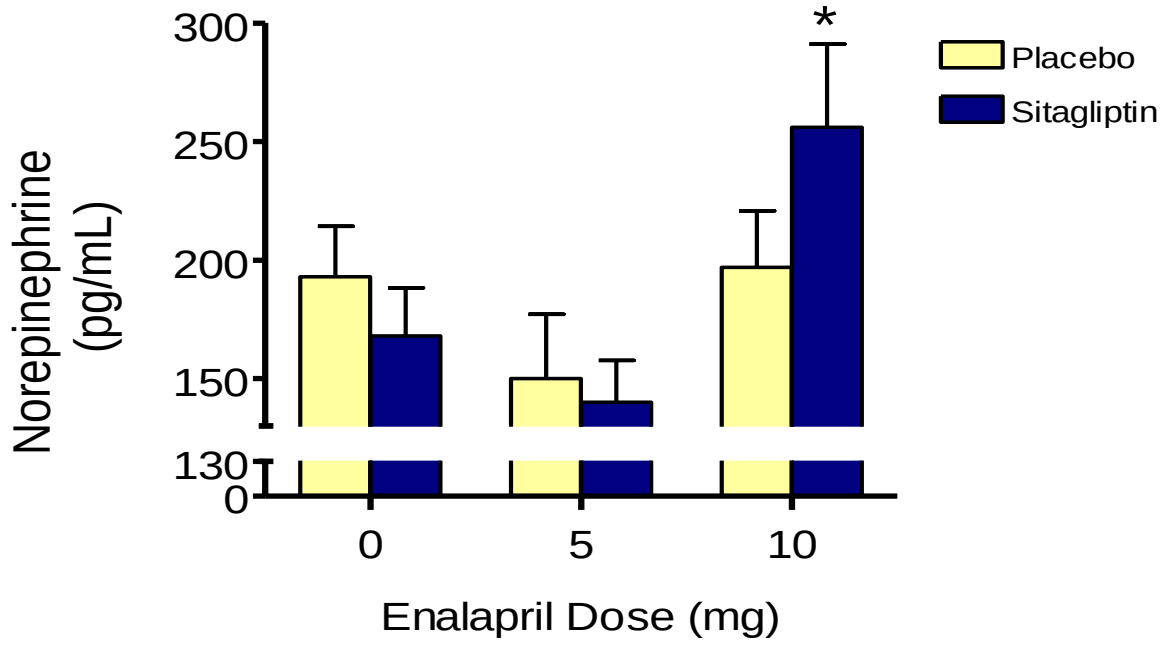
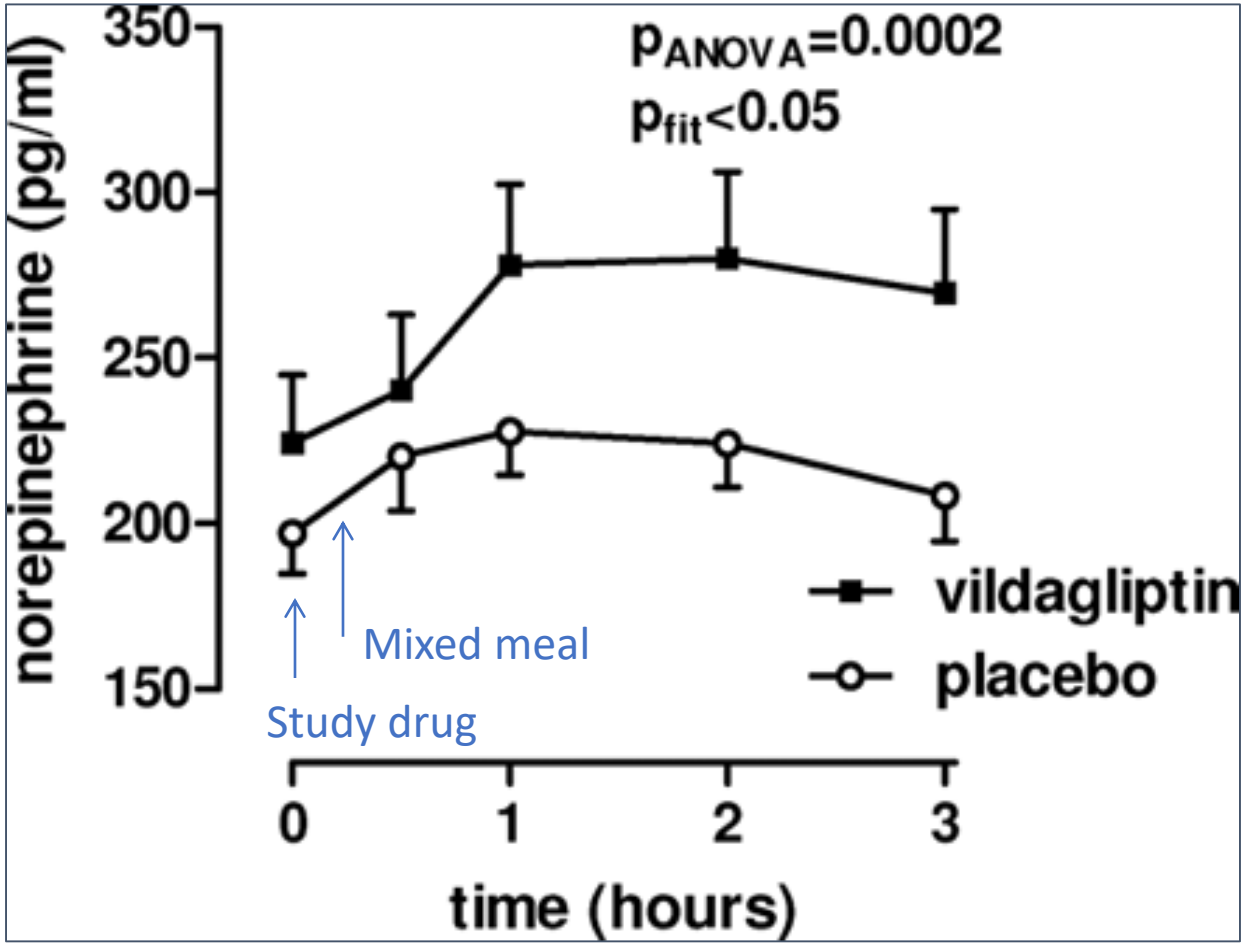
Marney et al *Hypertension* 2010

Full-dose ACE inhibition increases sympathetic activity when DPP4 is inhibited



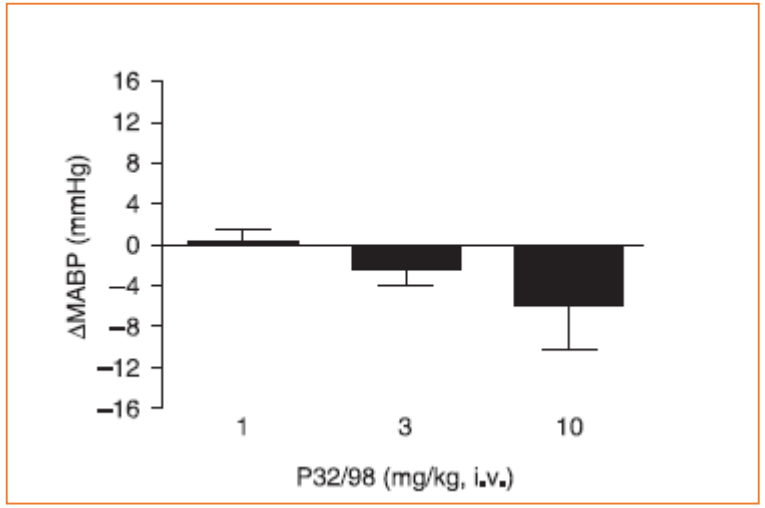
Marney et al *Hypertension* 2010

DPP4 inhibition increases post-prandial catecholamines



Boschmann et al *J Clin Endocrinol Metab* 2009

Non-pretreated



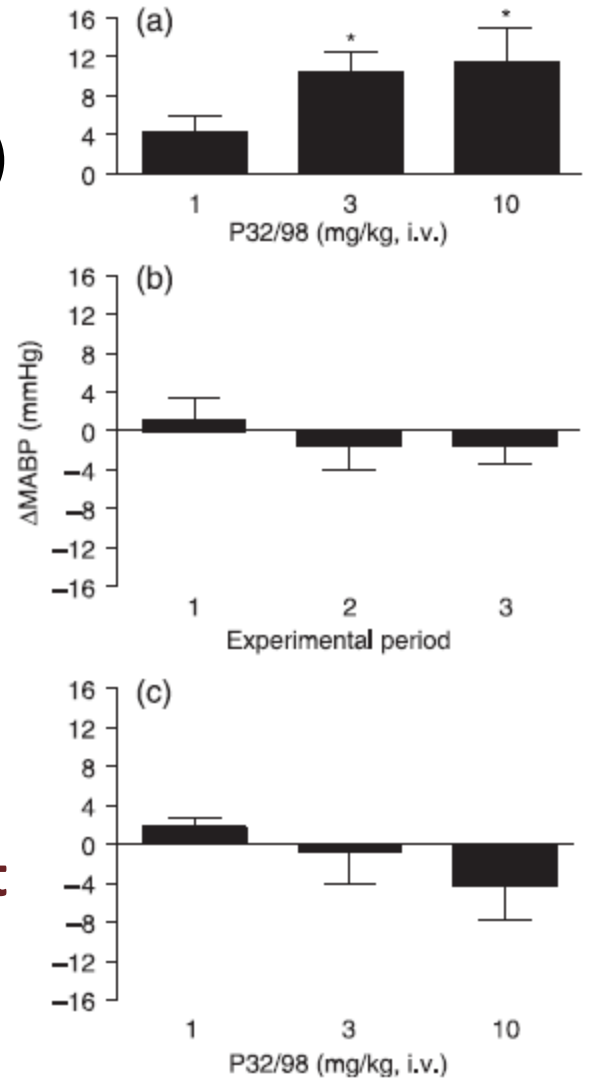
DPPIV inhibitor (P32/98)

vehicle

DPPIV inhibitor (P32/98)

+ NPY1 receptor antagonist

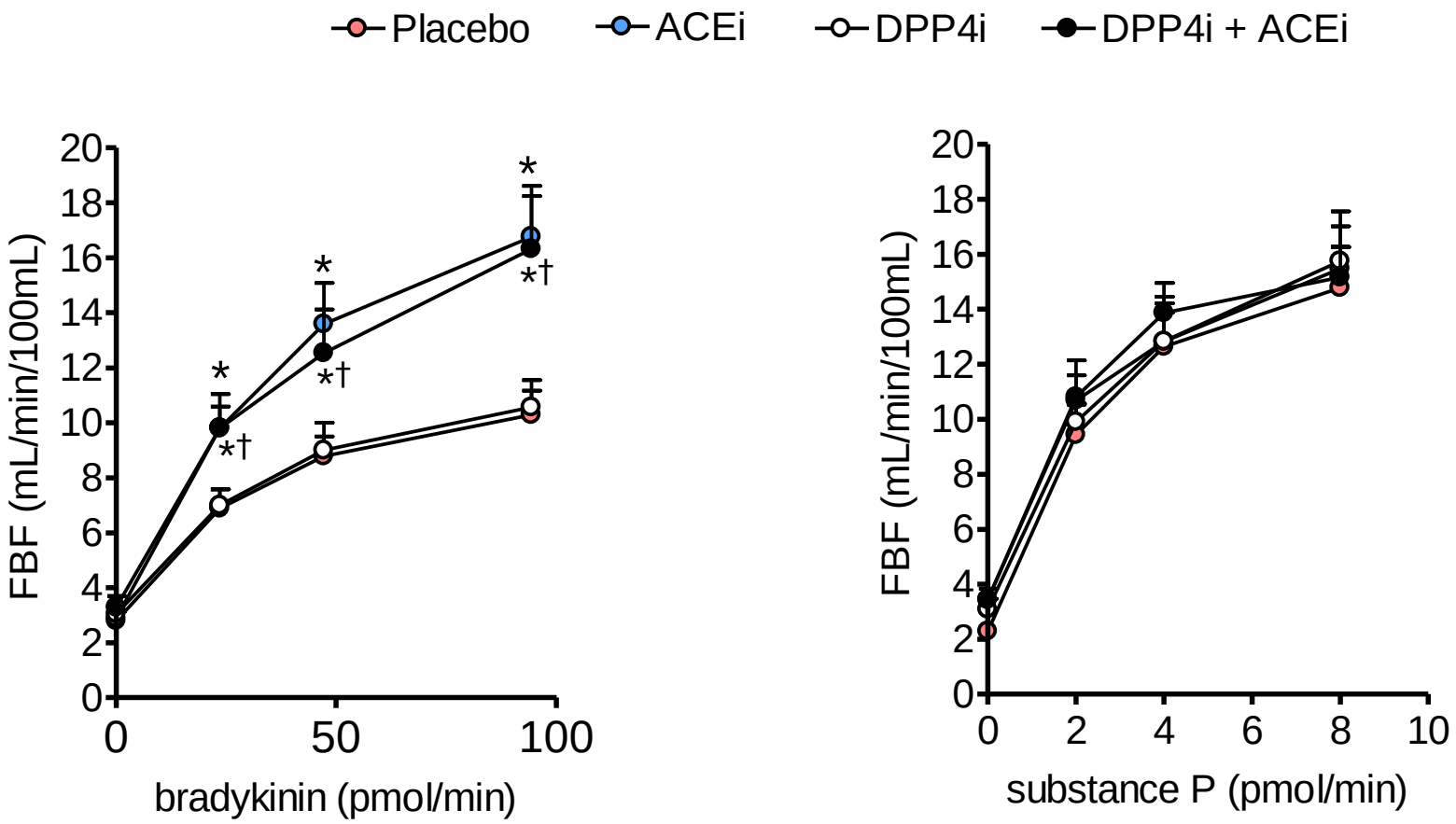
Captopril -pretreated



VANDERBILT HEALTH

Jackson et al *Clin.Exp.Pharmacol.Physiol* 2008

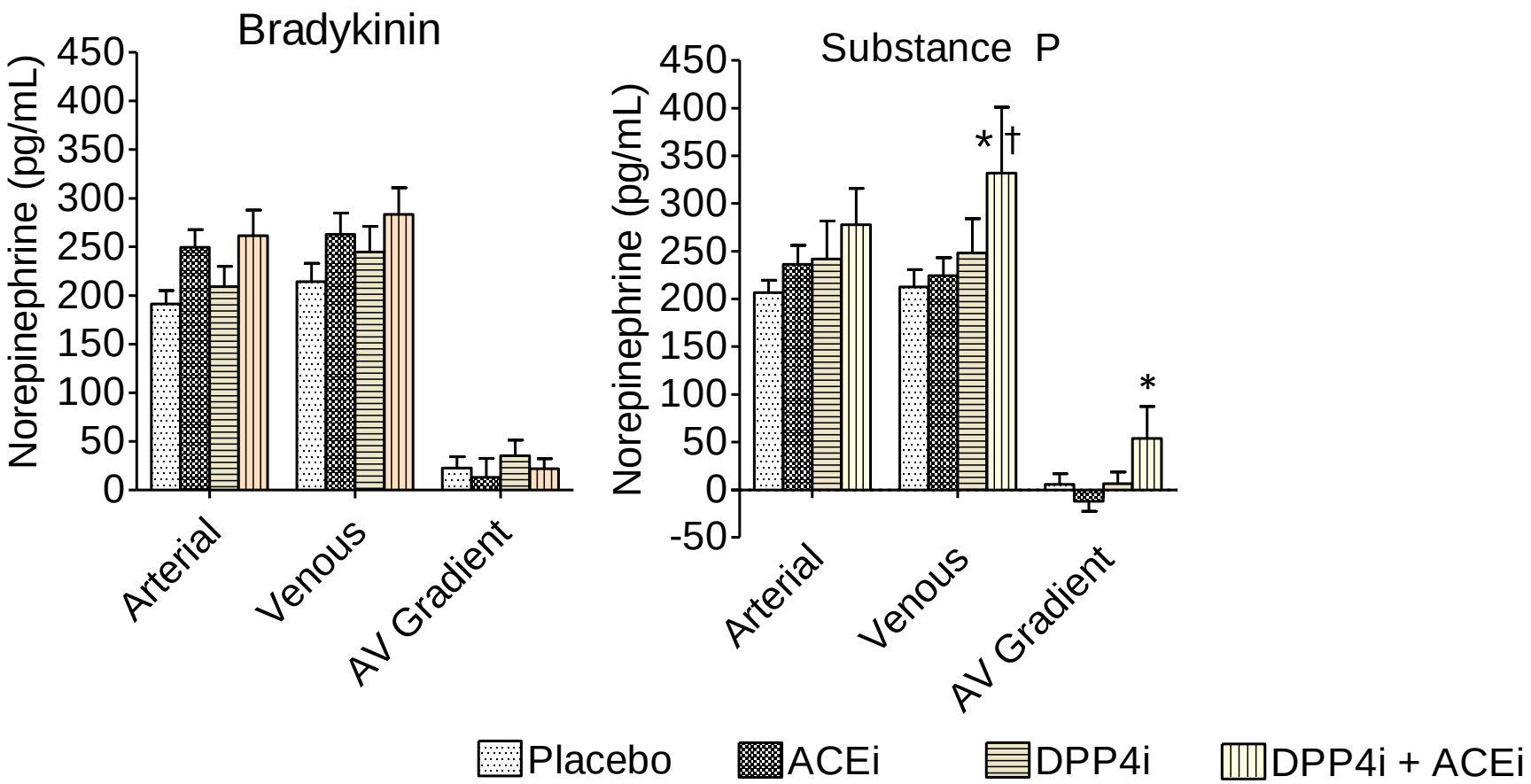
No effect of DPP4 inhibition on vasodilation in response to bradykinin or substance P



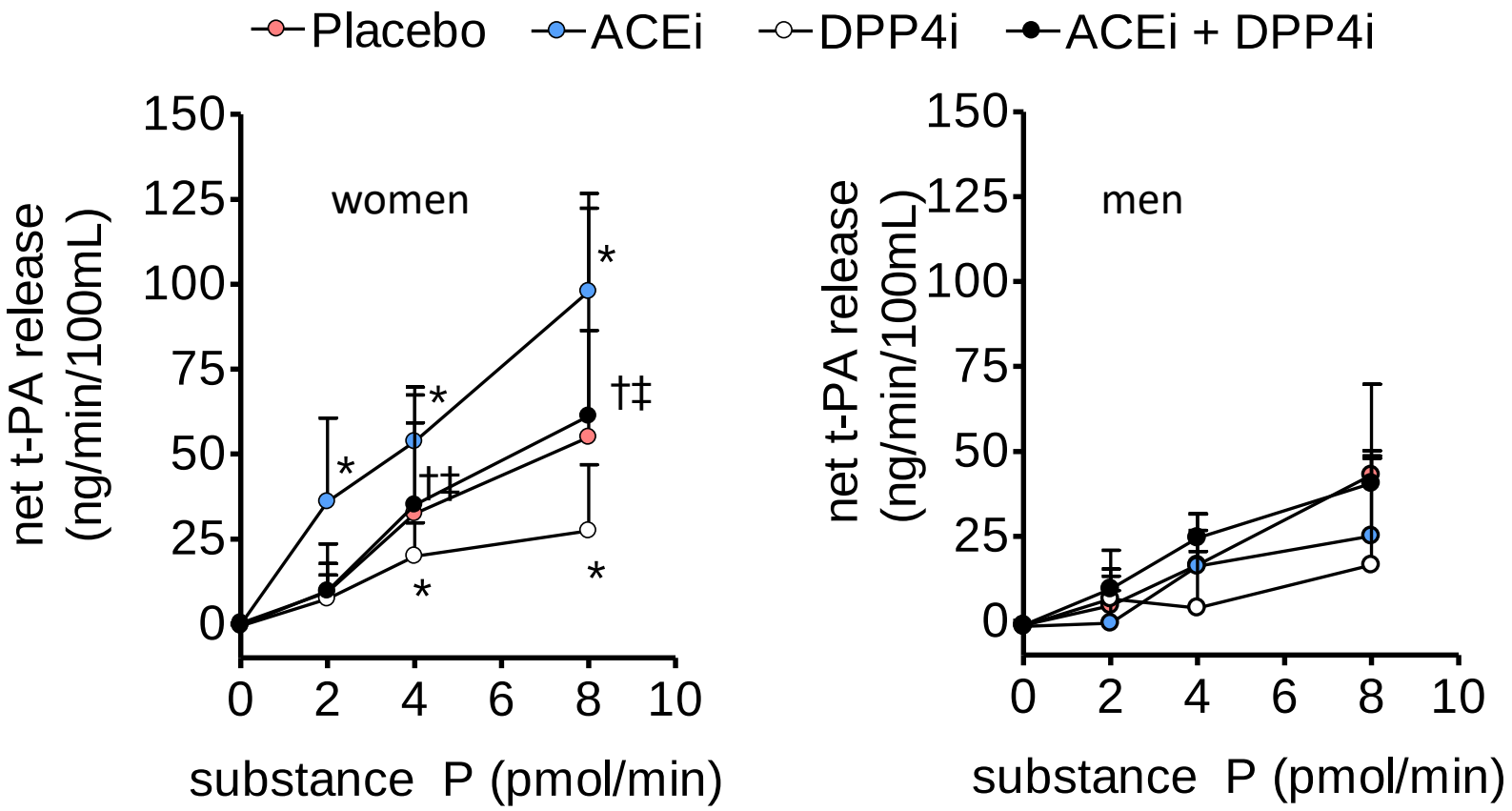
VANDERBILT HEALTH

Devin et al *Hypertension* 2014

Substance P stimulates local NE release during ACE and DPP4 inhibition



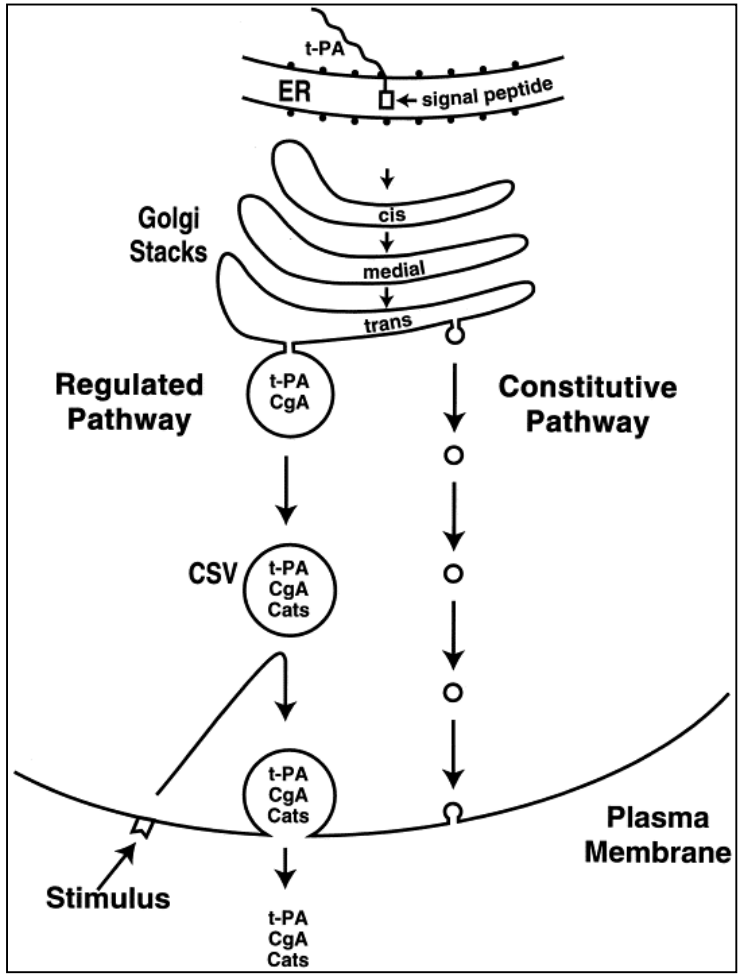
Effect of ACE and DPP4 inhibition on t-PA release in response to substance P



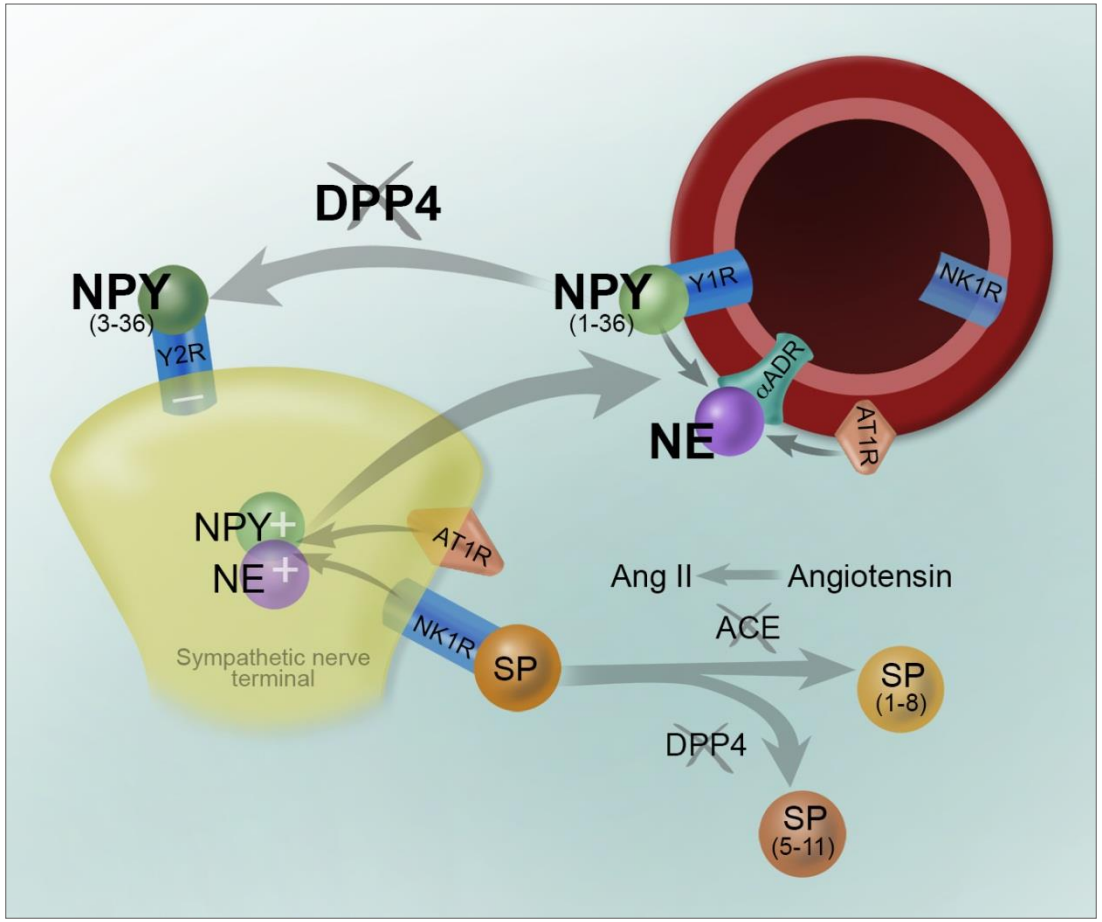
Potential mechanism for decreased t-PA release during combined ACE and DPP4 inhibition

During ACEi+DPP4i substance P accumulates and stimulates SNS

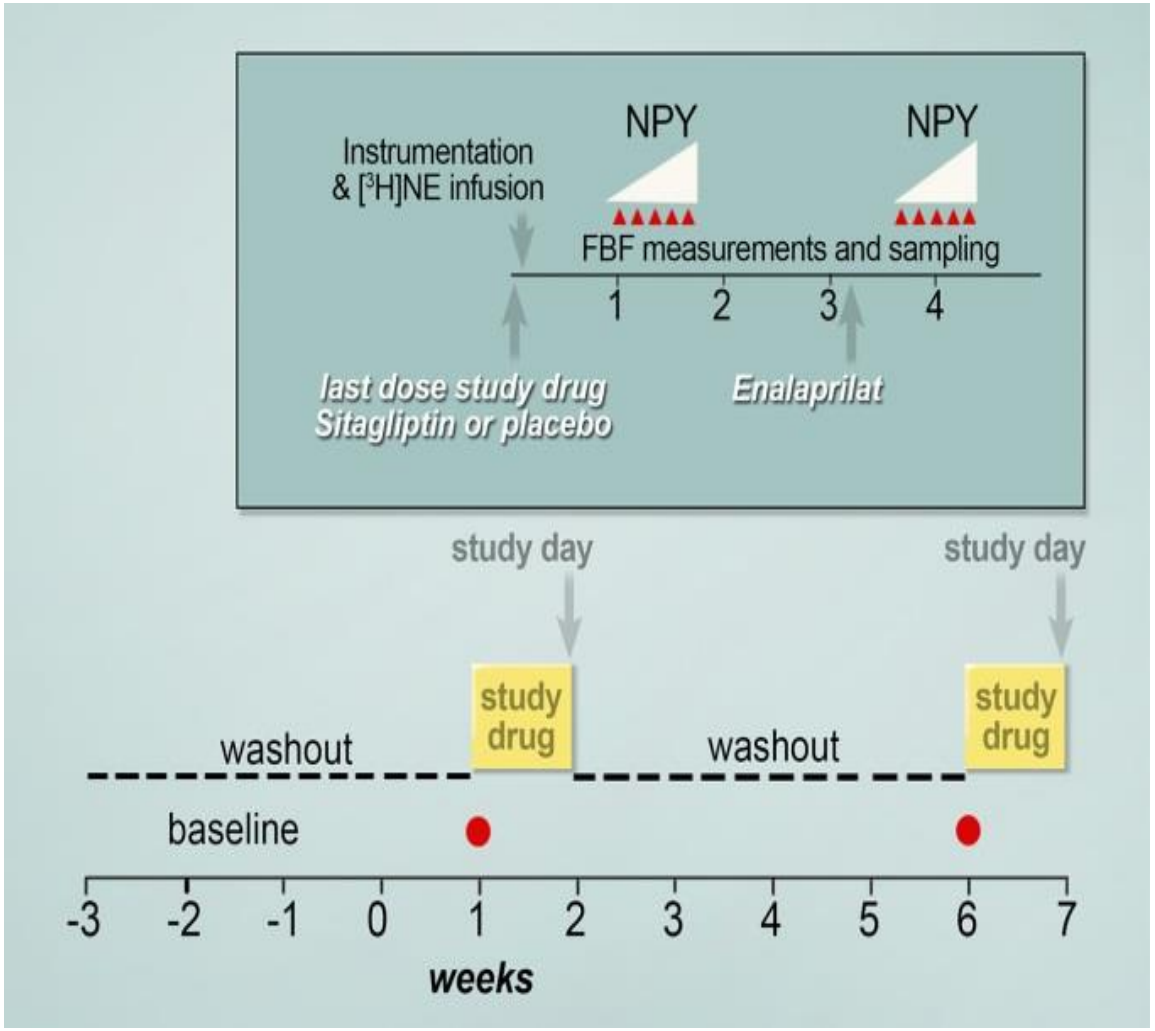
Stimulation of the SNS results in depletion of t-PA



Working Hypothesis

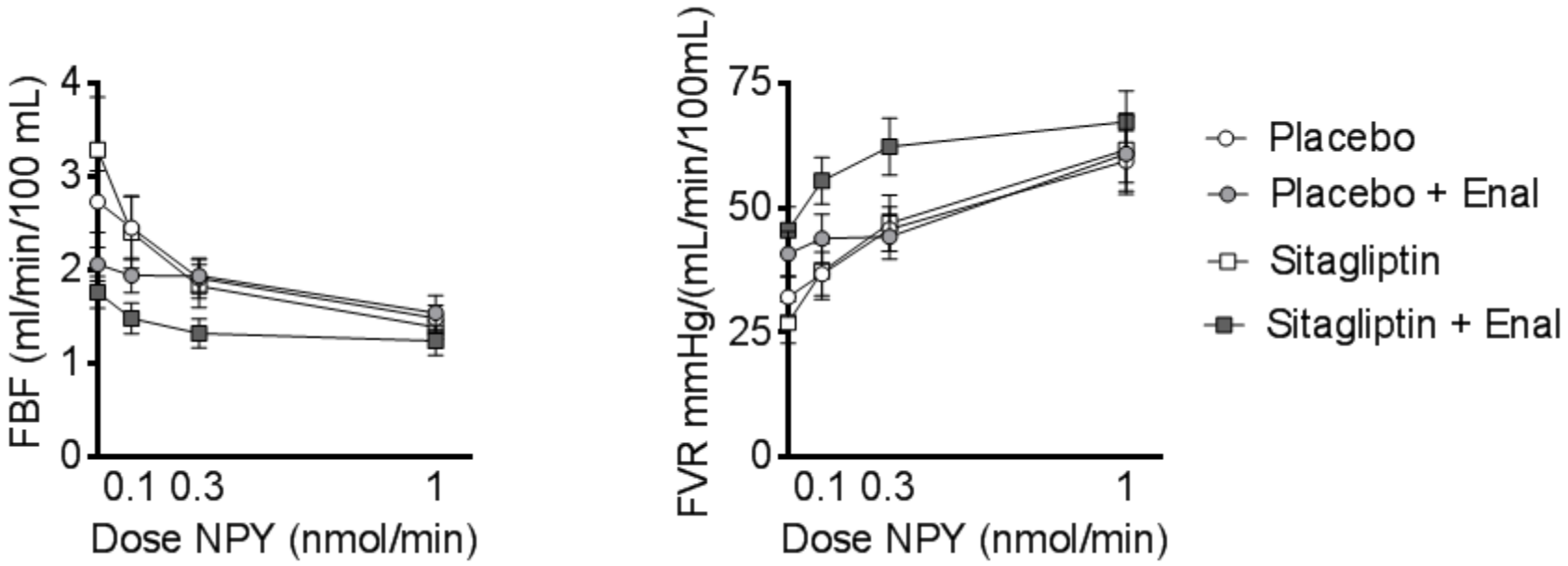


Study Protocol: Effect of DPP4 inhibition on neuropeptide Y (NPY)-mediated vasoconstriction



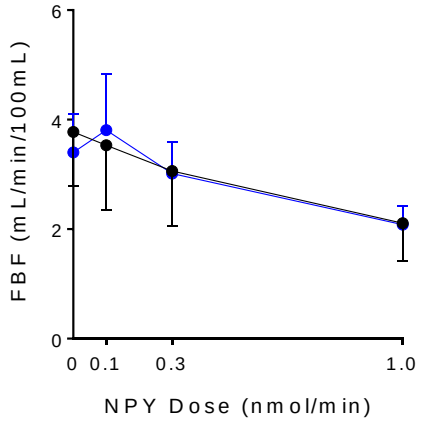
VANDERBILT HEALTH

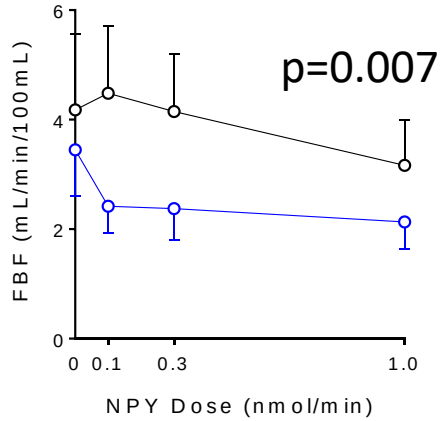
DPP4 increases vasoconstrictor response to NPY during ACEi in healthy subjects

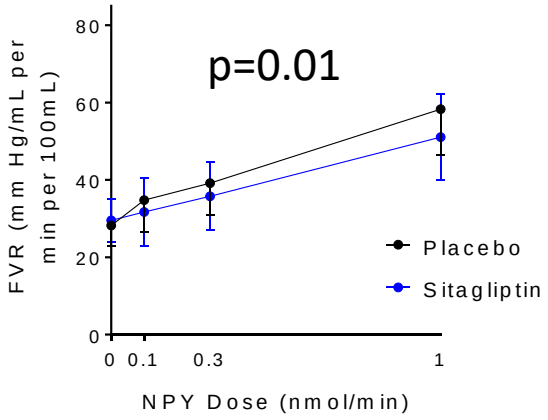


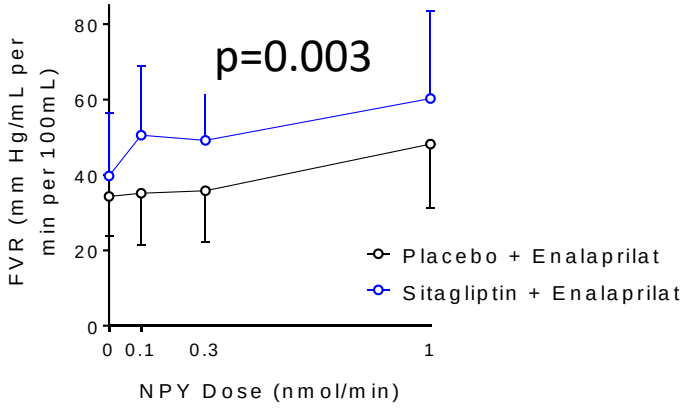
Hubers et al *Hypertension* 2018

DPP4 inhibition increases vasoconstrictor response to NPY during ACEi in T2DM



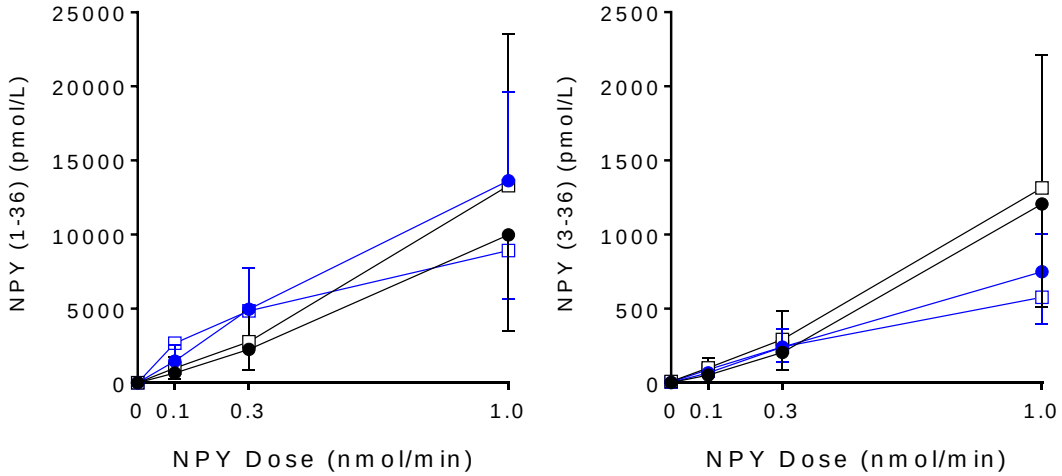


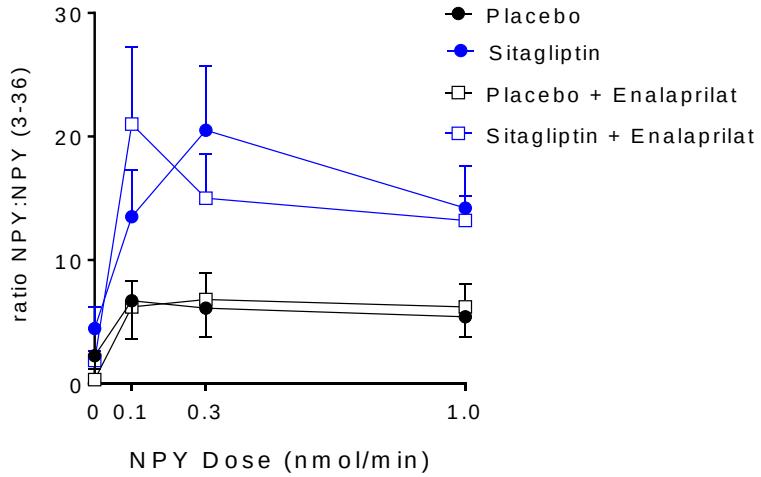




Hubers et al *Hypertension* 2018

Sitagliptin decreases degradation of NPY

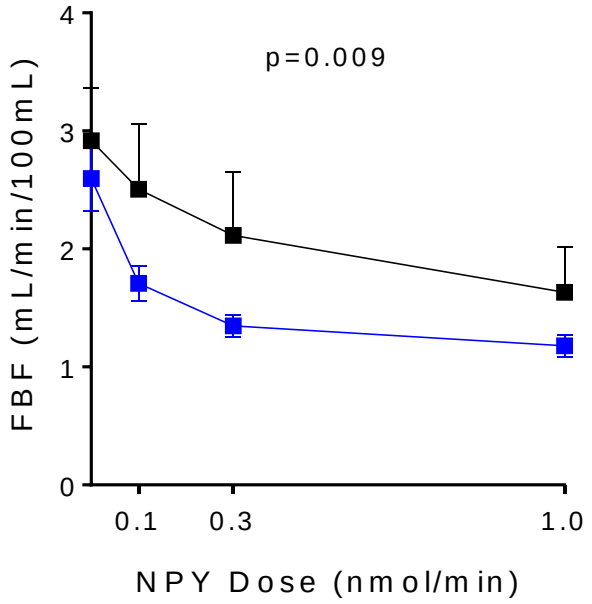


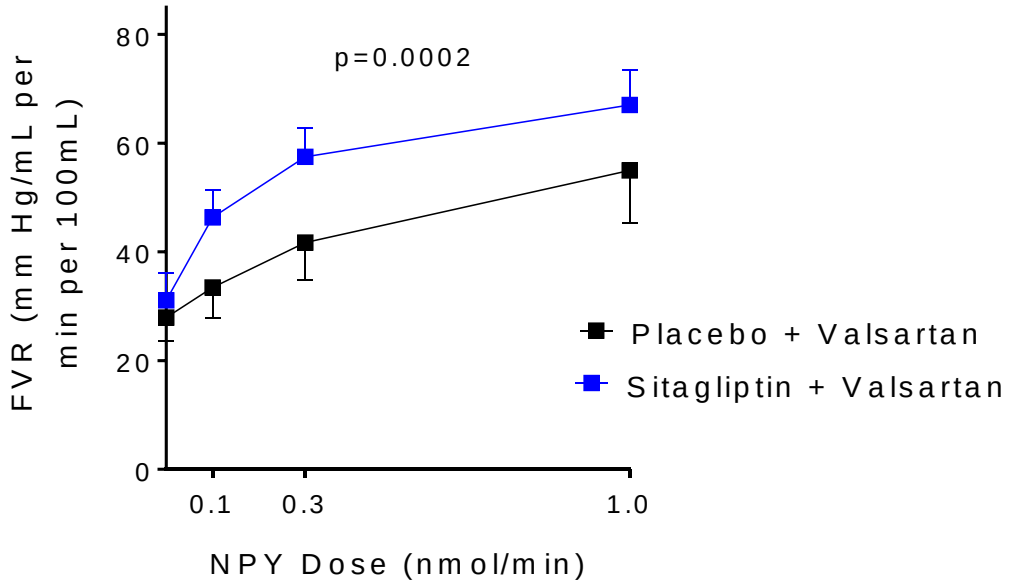


VANDERBILT HEALTH

Hubers et al *Hypertension* 2018

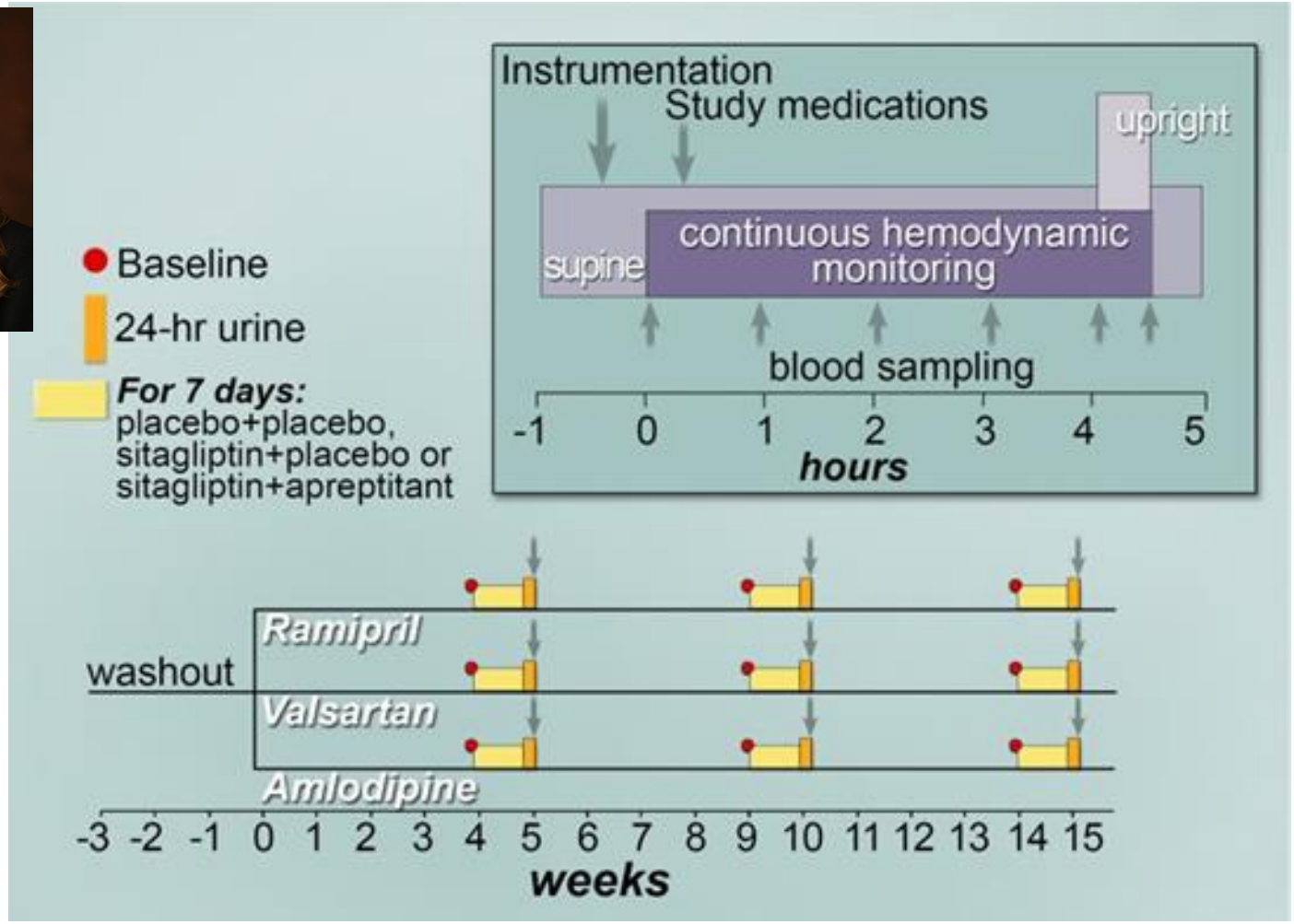
DPP4 inhibition increases vasoconstrictor response to NPY during ARB



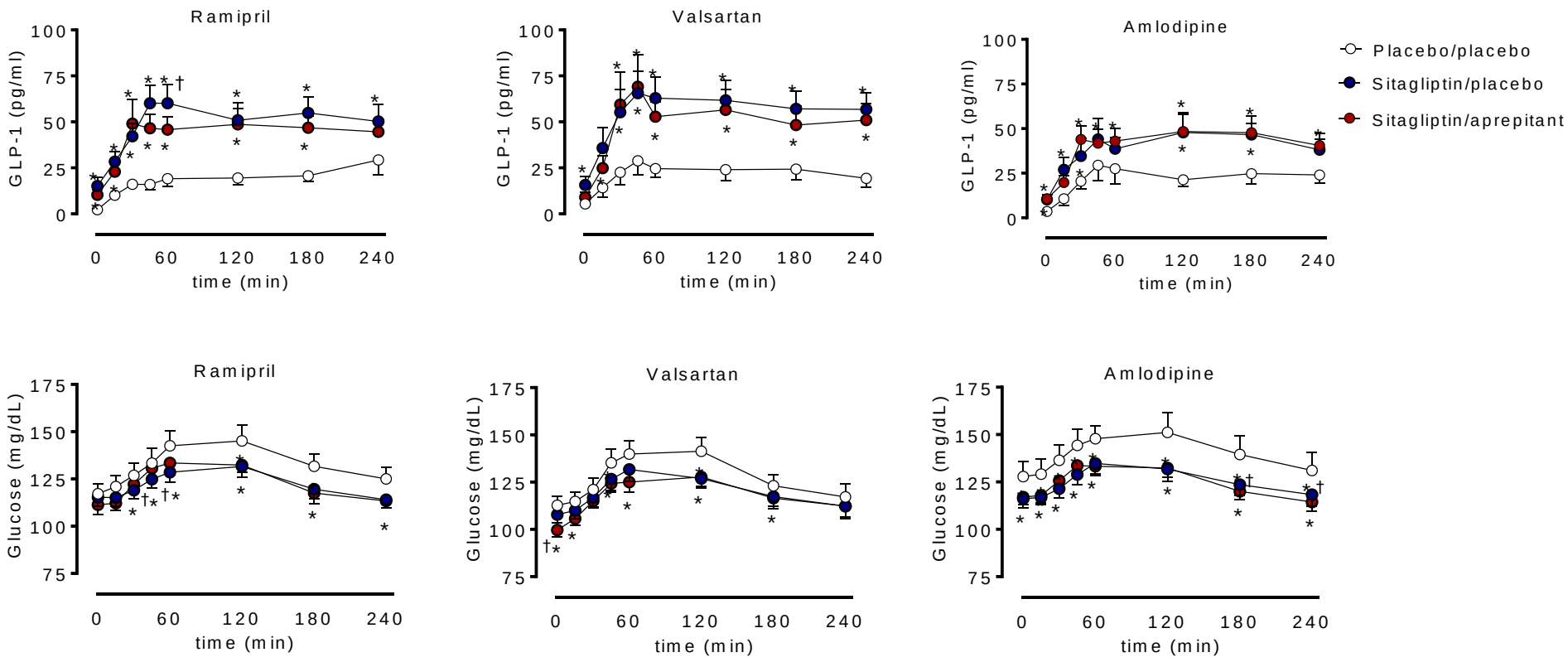


Hubers et al *Hypertension* 2018

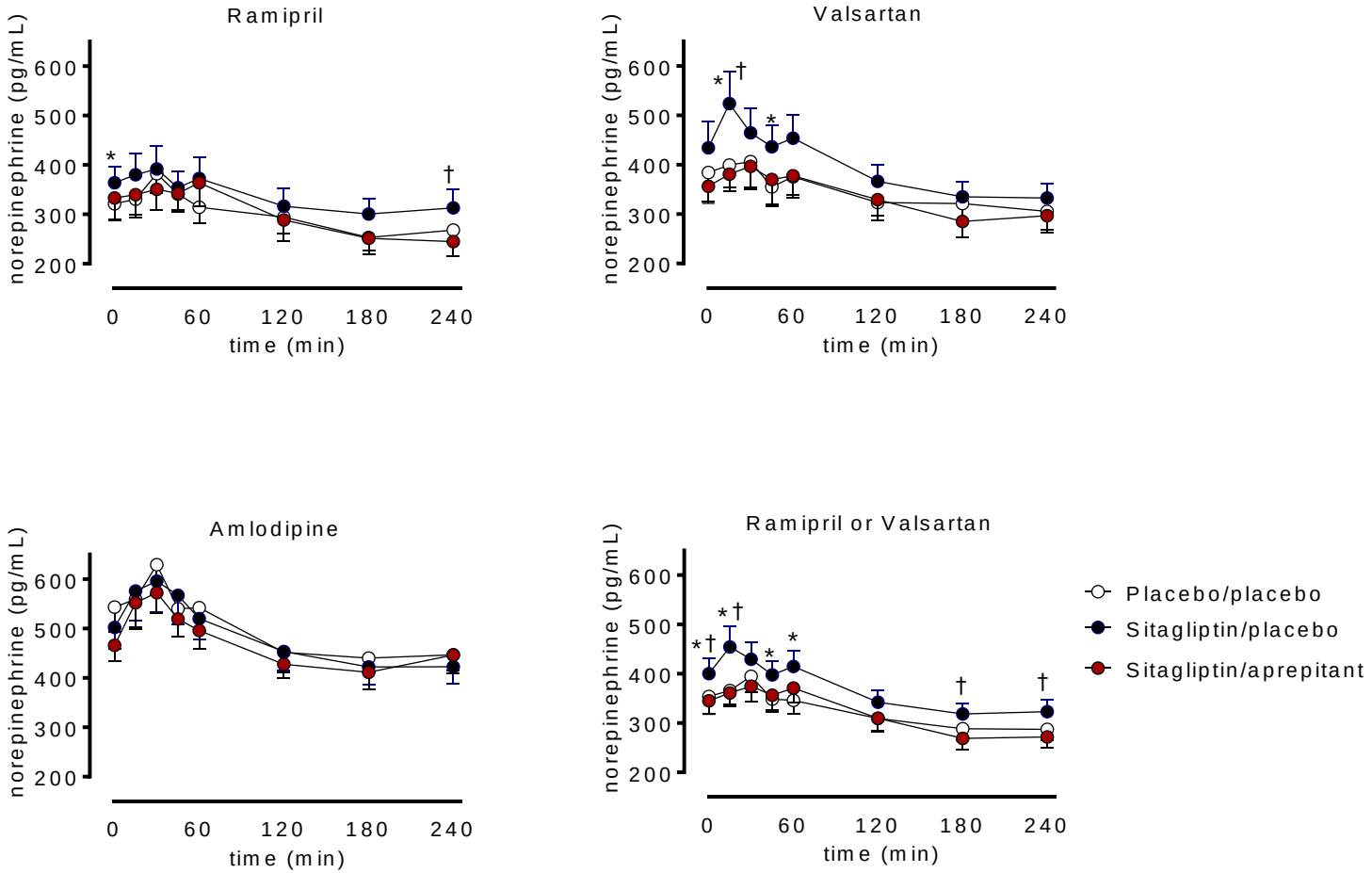
Protocol: Contribution to endogenous substance P to effects of combined DPP4 and chronic ACE inhibition



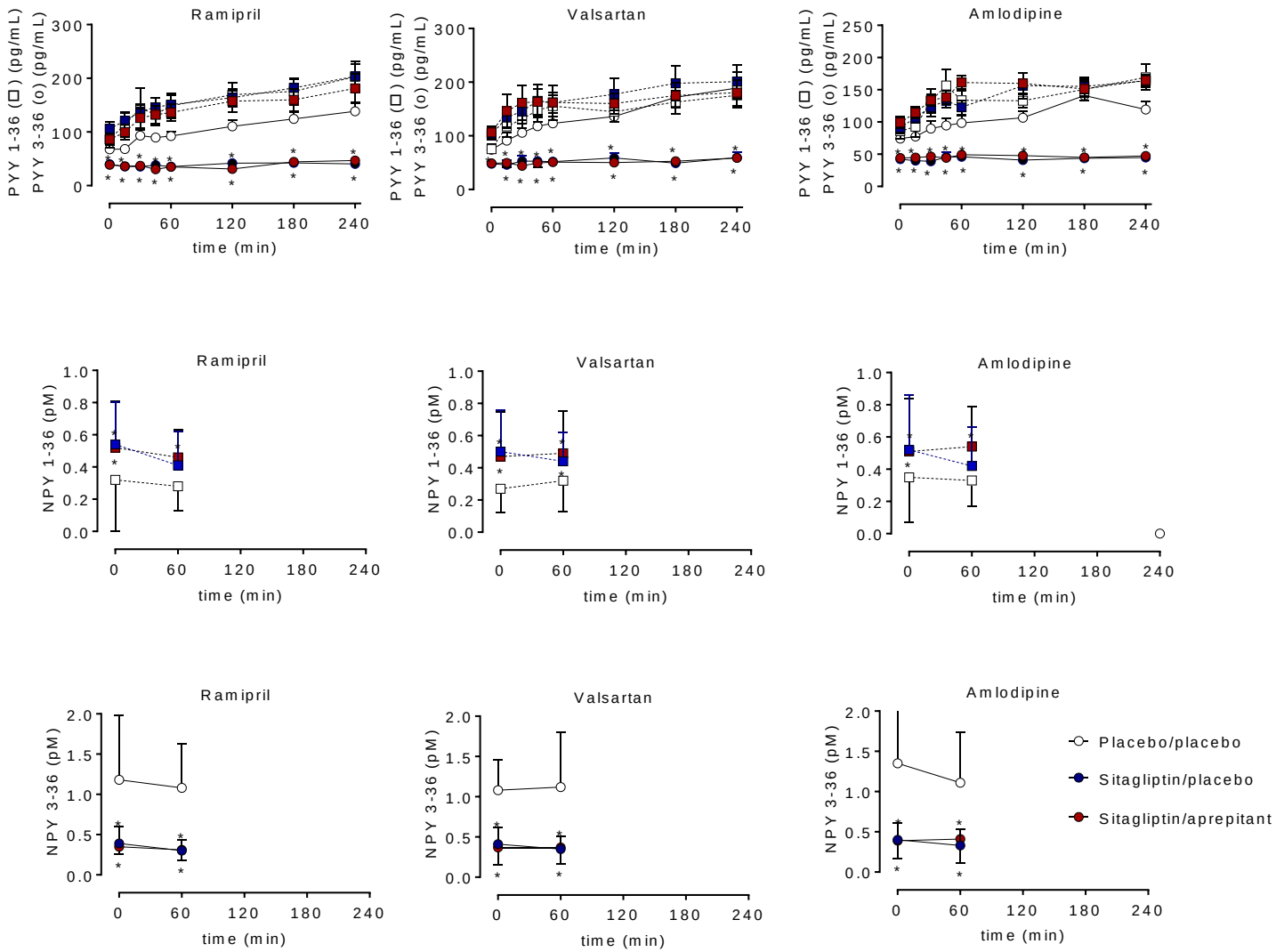
Metabolic effects of sitagliptin similar during ACEi, ARB and CCB



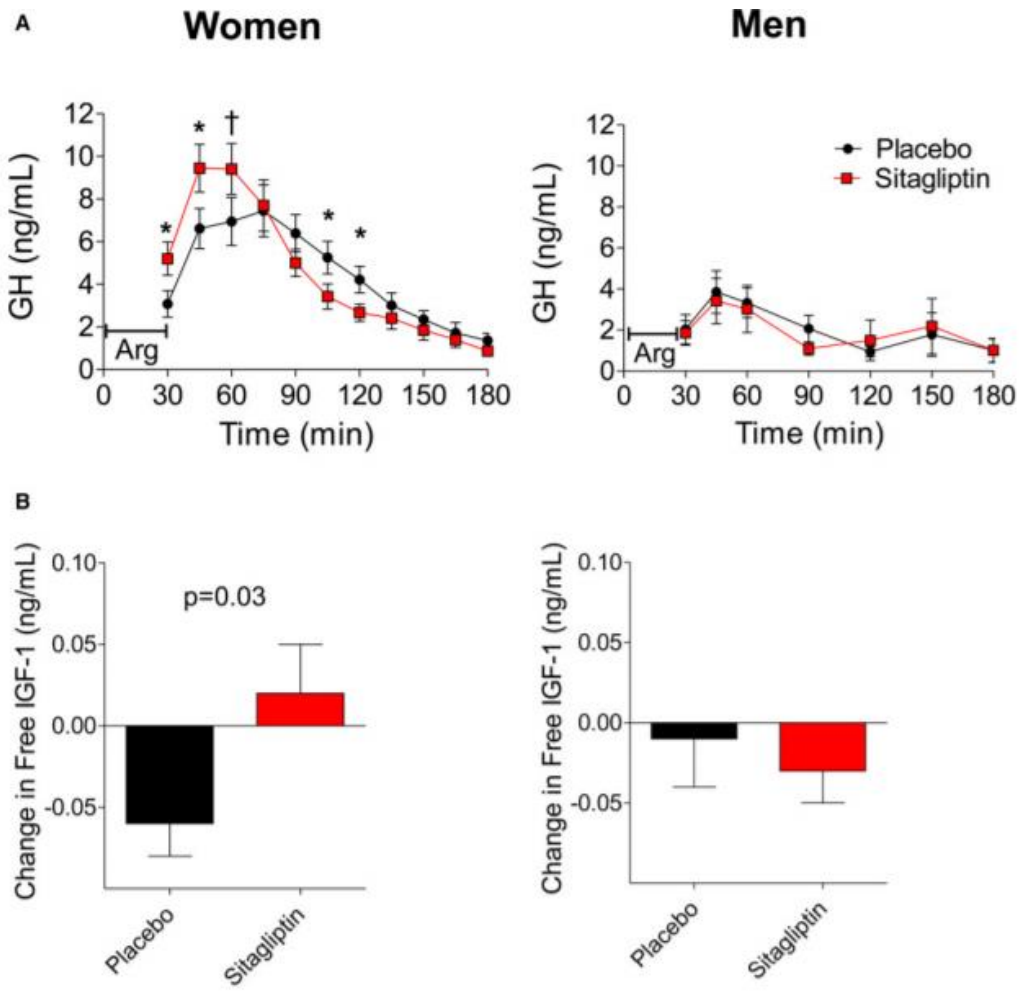
Sitagliptin increases post-prandial norepinephrine during inhibition of the renin-angiotensin-aldosterone system



Sitagliptin decreases the conversion of Y1 to Y2 agonists

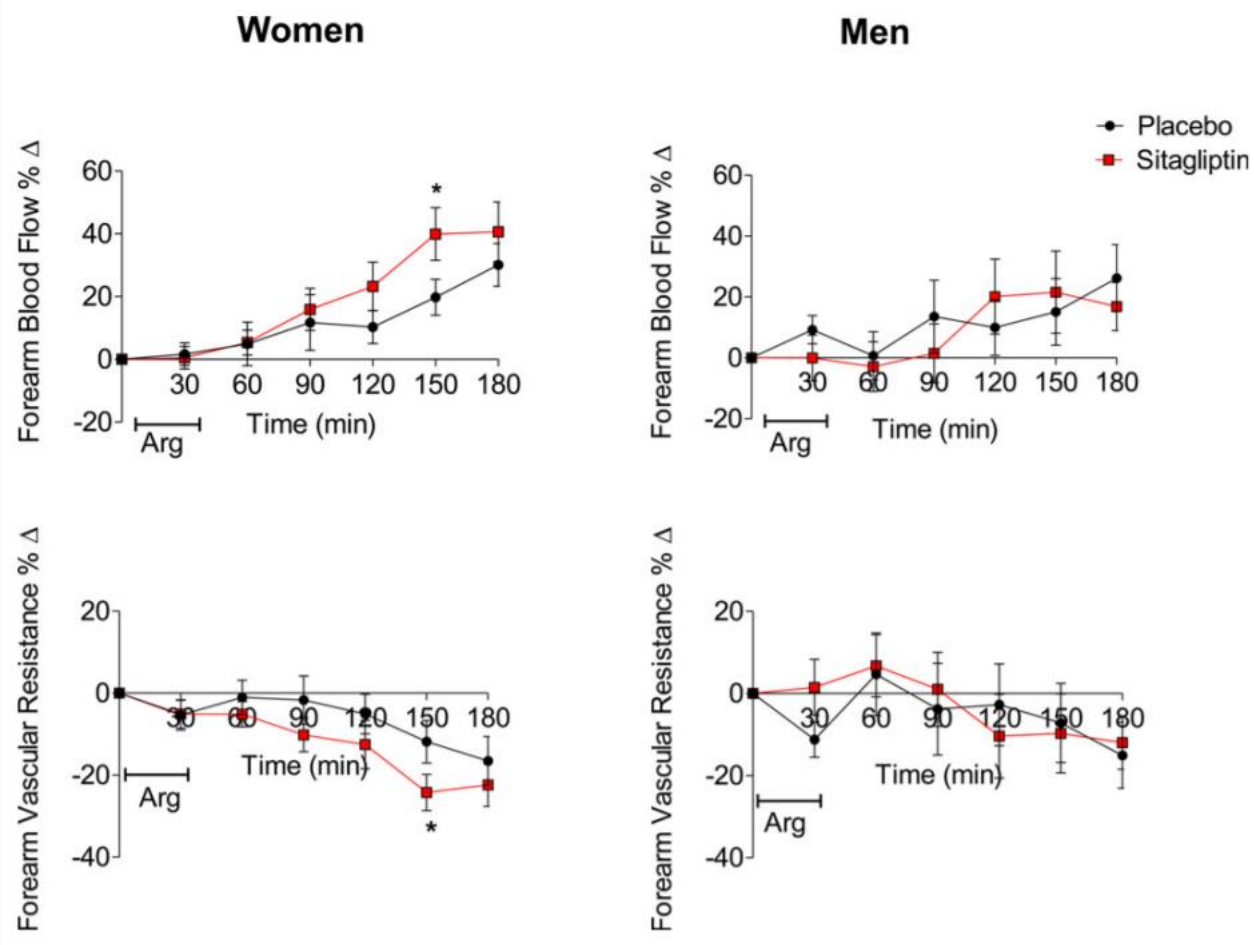


DPP4 inhibition increases GHRH-stimulated growth hormone secretion in women



Wilson et al *JAHA* 2018

DPP4 inhibition increases GH-stimulated forearm vasodilation in women



Wilson et al *JAHA* 2018

Interim Summary

- DPP4 inhibition attenuates the blood pressure response to acute ACE inhibition and increases catecholamines
- During concurrent DPP4 and ACE inhibition substance P increases forearm release of catecholamines
- DPP4 inhibition potentiates the effect of NPY during either ACE inhibition or ARB treatment
- During interruption of the renin-angiotensin-system, DPP4 inhibition increases circulating catecholamines through an NK1 receptor-dependent mechanism
- These findings have implications for mechanism of increased risk of heart failure with DPP4 inhibition

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

ORIGINAL ARTICLE

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

N Engl J Med 2013

Saxagliptin use associated with increased risk of heart failure

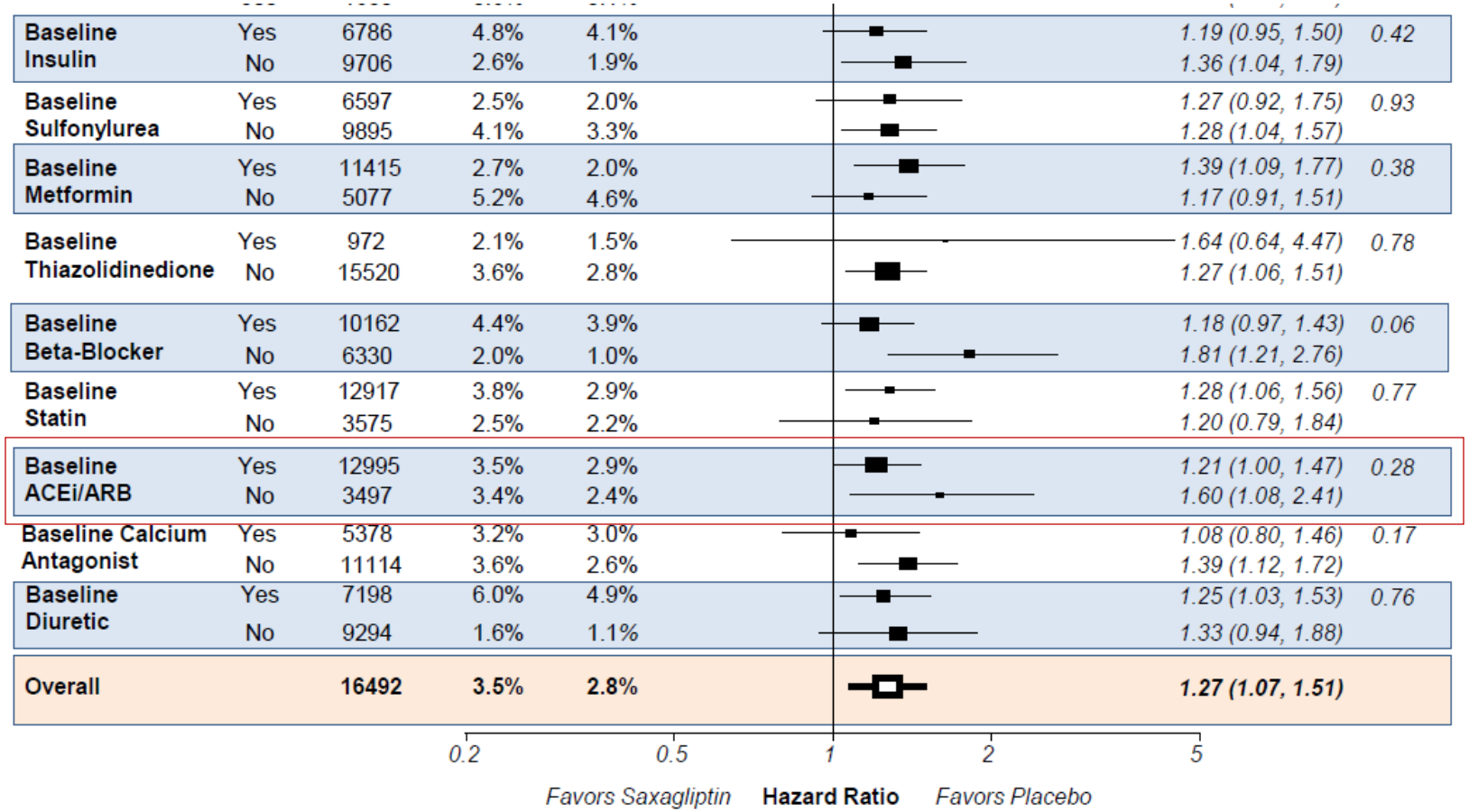
Table 2. Prespecified Clinical End Points.*

End Point	Saxagliptin (N=8280)	Placebo (N=8212)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.89–1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94–1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96–1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87–1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80–1.12)	0.52
Ischemic stroke	157 (1.9)	141 (1.7)	1.11 (0.88–1.39)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89–1.60)	0.24
Hospitalization for heart failure	289 (3.5)	228 (2.8)	1.27 (1.07–1.51)	0.007
Hospitalization for coronary revascularization	423 (5.2)	459 (5.6)	0.91 (0.80–1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 μmol/liter)	194 (2.2)	178 (2.0)	1.08 (0.88–1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	43 (0.5)	1.22 (0.82–1.83)	0.33

* Event rates and percentages are 2-year Kaplan–Meier estimates.

Scirica BM et al. *N Engl J Med* 2013;369:1317-1326

Concomitant medications and risk of heart failure with saxagliptin



Scirica et al *Circulation* 2014

Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial

Faiez Zannad, Christopher P Cannon, William C Cushman, George L Bakris, Venu Menon, Alfonso T Perez, Penny R Fleck, Cyrus R Mehta, Stuart Kupfer, Craig Wilson, Hung Lam, William B White, for the EXAMINE Investigators

	All patients		History of heart failure at baseline		No history of heart failure at baseline	
	Alogliptin (n=2701)	Placebo (n=2679)	Alogliptin (n=771)	Placebo (n=762)	Alogliptin (n=1930)	Placebo (n=1917)
Cardiovascular death and hospital admission for heart failure	201 (7·4)	201 (7·5)	107 (13·9)	120 (15·7)	94 (4·9)	81 (4·2)
Hazard ratio (95% CI)	1·00 (0·82–1·21)		0·90 (0·70–1·17)		1·14 (0·85–1·54)	
p value	0·976		0·446		0·337	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·221	..	..	..
Cardiovascular death*	112 (4·1)	130 (4·9)	55 (7·1)	69 (9·1)	57 (3·0)	61 (3·2)
Hazard ratio (95% CI)	0·85 (0·66–1·10)		0·77 (0·54–1·09)		0·92 (0·64–1·32)	
p value	0·212		0·141		0·643	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·508	..	..	..
Hospital admission for heart failure	106 (3·9)	89 (3·3)	63 (8·2)	65 (8·5)	43 (2·2)	24 (1·3)
Hazard ratio (95% CI)	1·19 (0·90–1·58)		1·00 (0·71–1·42)		1·76 (1·07–2·90)	
p value	0·220		0·996		0·026	
$p_{interaction}$ for treatment and history of heart failure	..	..	0·068	..	..	..

*Analysis includes all cardiovascular deaths, including those that followed heart failure that were not counted in the analysis of the composite endpoint.

Table 4: **Risk of events assessed in the post-hoc analysis, by history of heart failure**

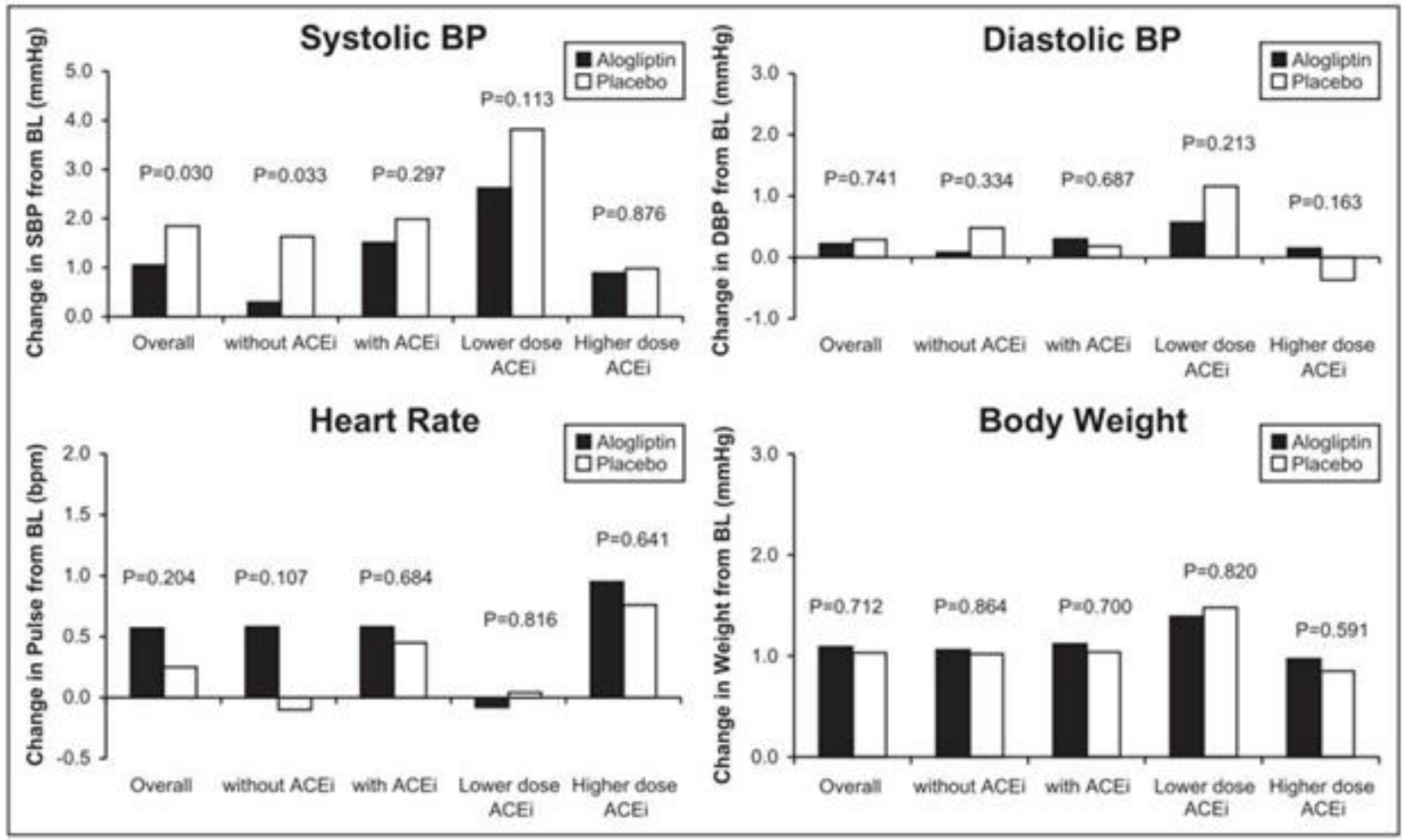


Figure 1. Changes from baseline in blood pressure, heart rate, and body weight at the final visit according to angiotensin-converting enzyme inhibitor (ACEi) use. BP indicates blood pressure.

White et al *Hypertension* 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

Jennifer B. Green, M.D., M. Angelyn Bethel, M.D., Paul W. Armstrong, M.D.,
John B. Buse, M.D., Ph.D., Samuel S. Engel, M.D.,
Robert Josse, M.B., B.S., Keith D. Kaufman, M.D.,
Scott Korn, M.D., John M. Lachin, Sc.D., Darren K.
Michael J. Pencina, Ph.D., Eberhard Standl, M.D., Ph.
Shailaja Suryawanshi, Ph.D., Frans Van de W
Eric D. Peterson, M.D., M.P.H., and Rury R. H
for the TECOS Study Group

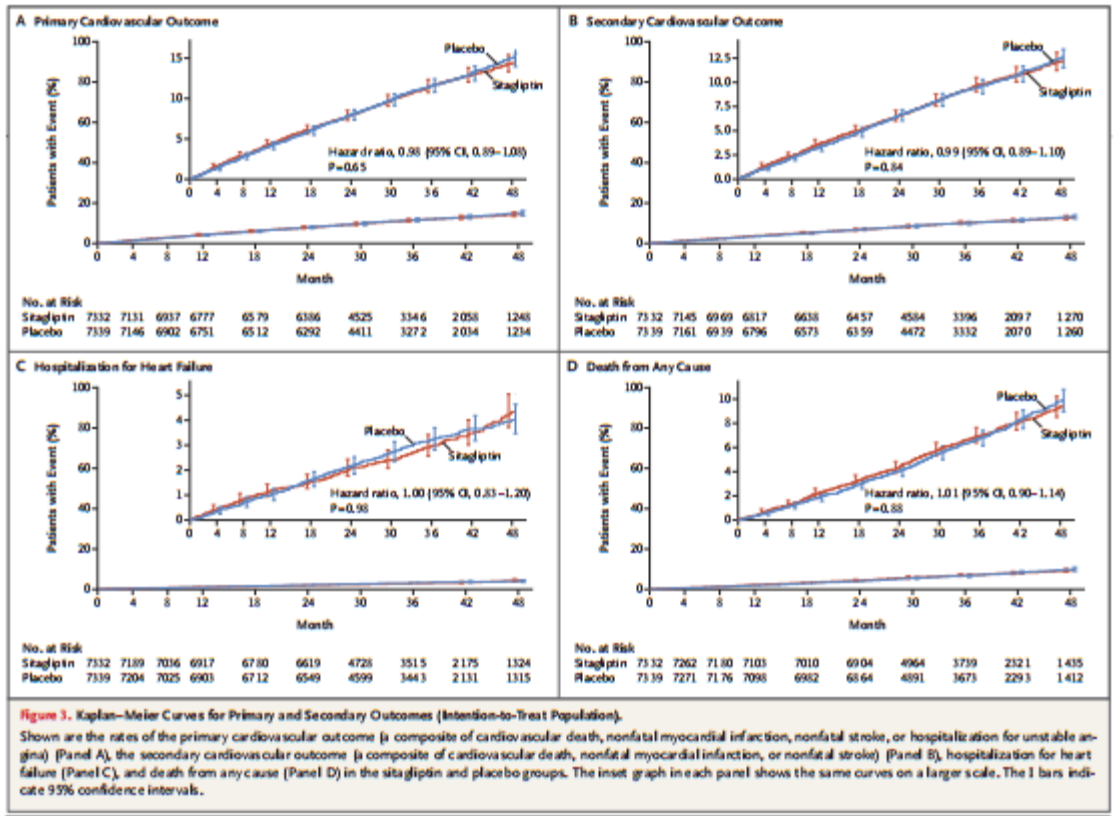


Figure 3. Kaplan–Meier Curves for Primary and Secondary Outcomes (Intention-to-Treat Population).

Shown are the rates of the primary cardiovascular outcome (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) (Panel A), the secondary cardiovascular outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel B), hospitalization for heart failure (Panel C), and death from any cause (Panel D) in the sitagliptin and placebo groups. The inset graph in each panel shows the same curves on a larger scale. The I bars indicate 95% confidence intervals.

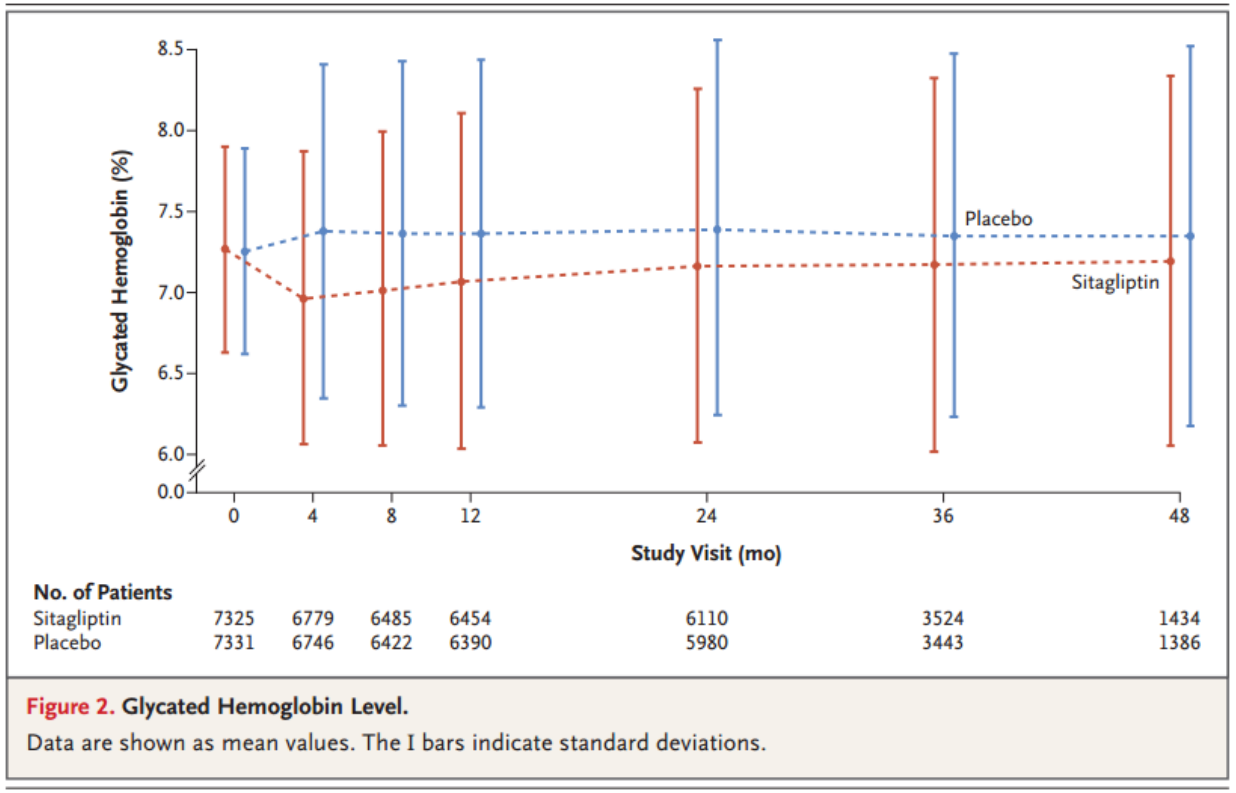
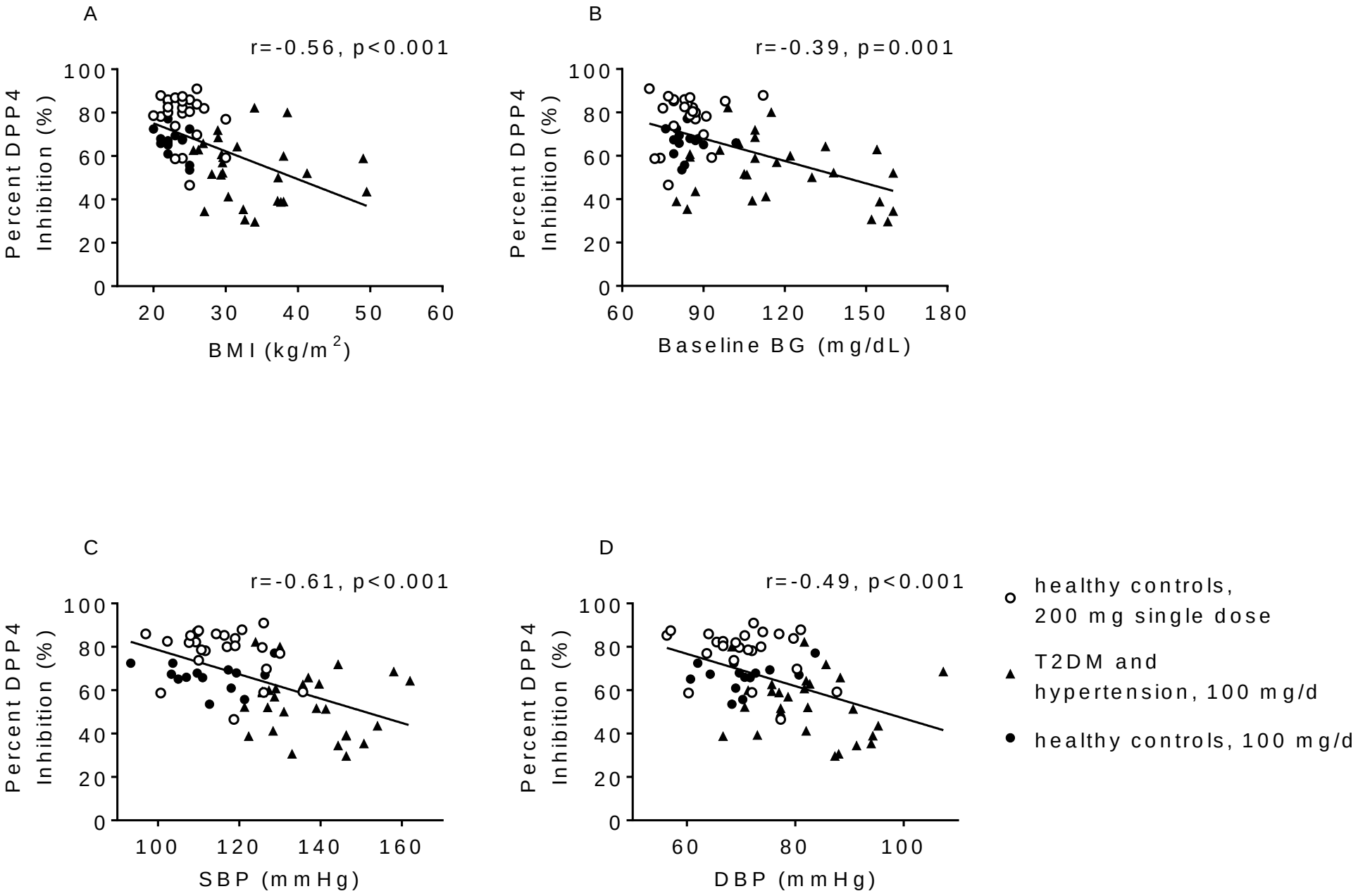


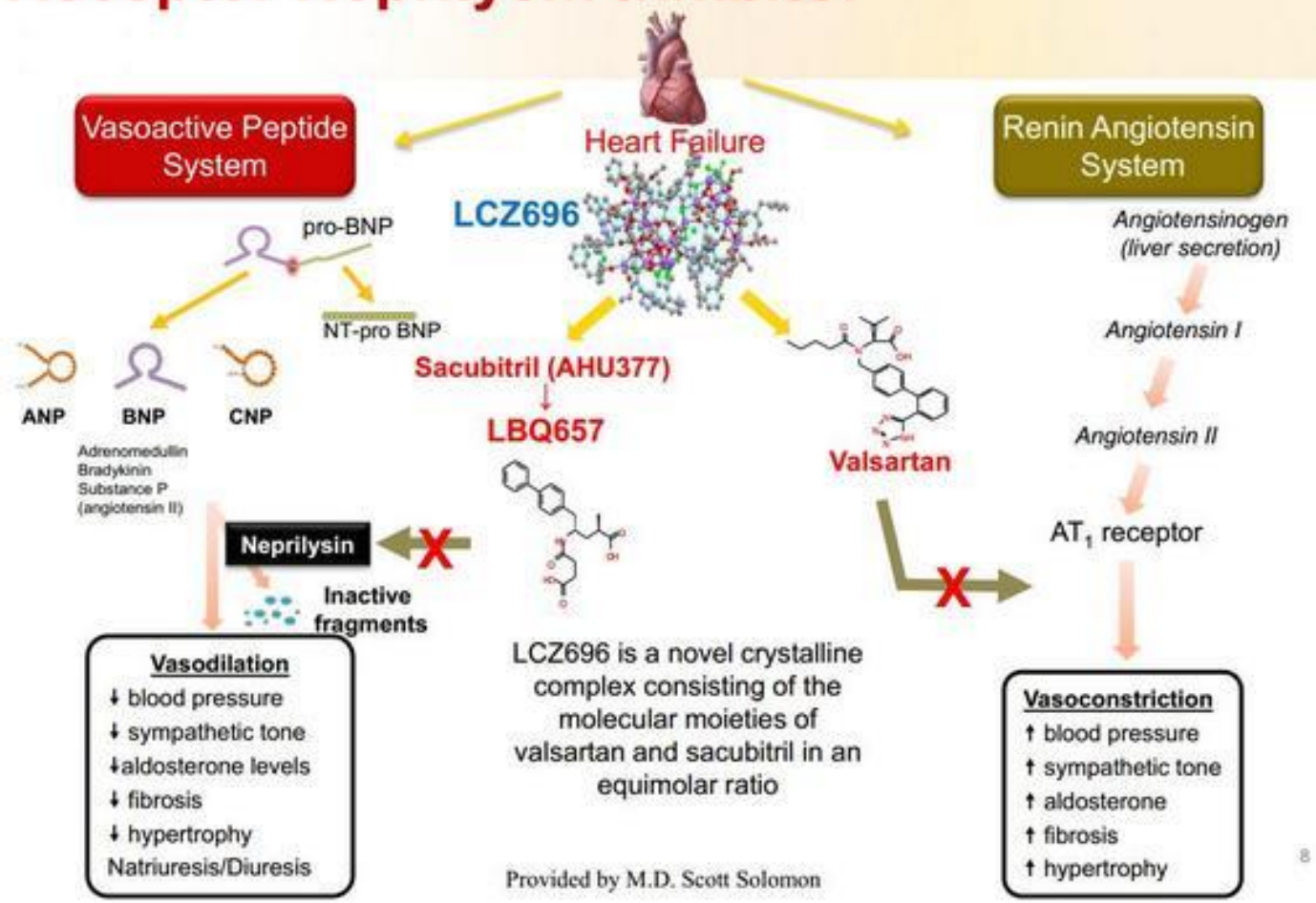
Figure 2. Glycated Hemoglobin Level.
Data are shown as mean values. The I bars indicate standard deviations.

	Sitagliptin	Placebo	HR (95% CI)	P Value
Number initiating chronic insulin therapy	542/5608 (9.7%)	744/5655 (13.2%)	0.7 (0.63-0.79)	<0.001
Number initiating additional hypoglycemic agents	1591/7332 (21.7%)	2046/7332 (27.9%)	0.72 (0.68-0.77)	<0.001



Wilson JR et al *J Endocr Soc* 2017

LCZ696 – A first-in-class Angiotensin Receptor Neprilysin Inhibitor



Provided by M.D. Scott Solomon

PARADIGM: ARB/NEP inhibitor superior to ACE inhibition in heart failure

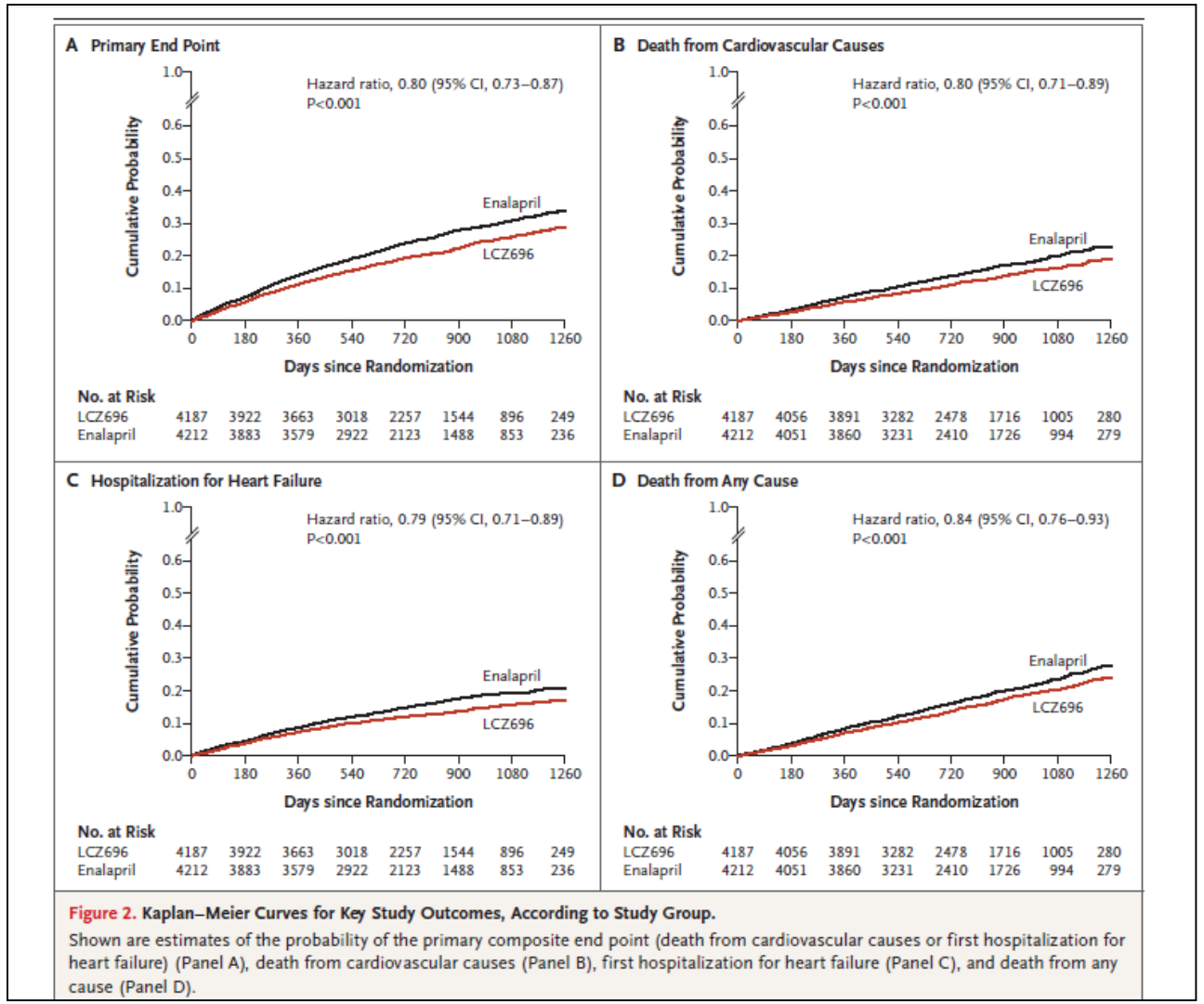


Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.
Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any cause (Panel D).

McMurray et al *N Eng J Med* 2014

PIONEER: ARB/NEP inhibitor reduces readmissions after acute heart failure decompensation

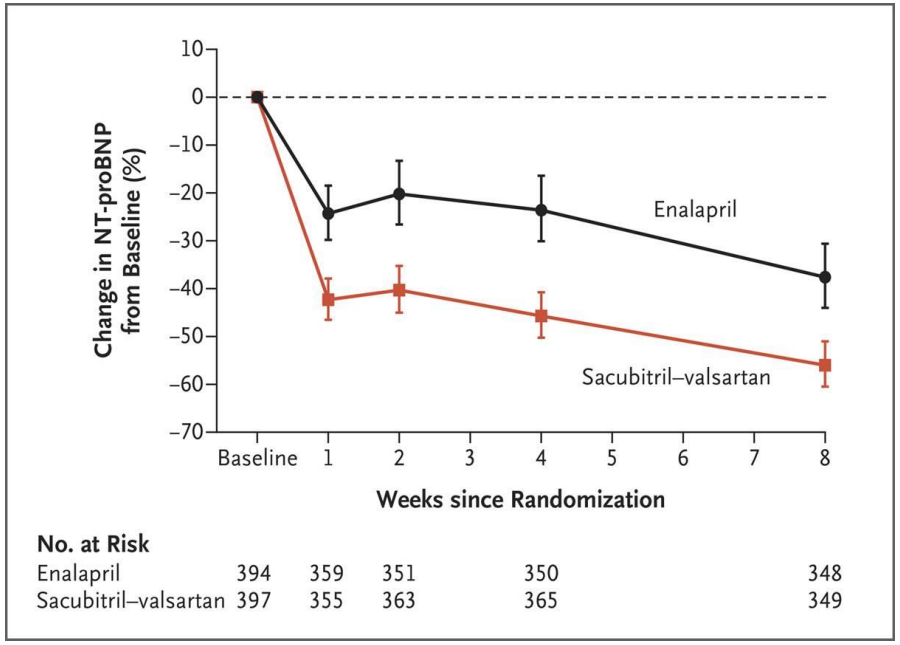
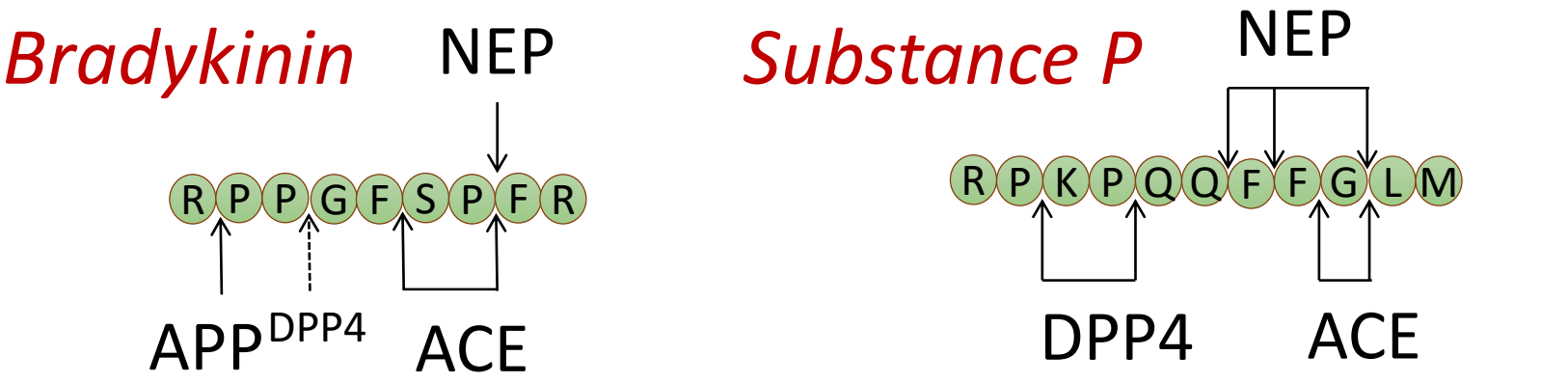


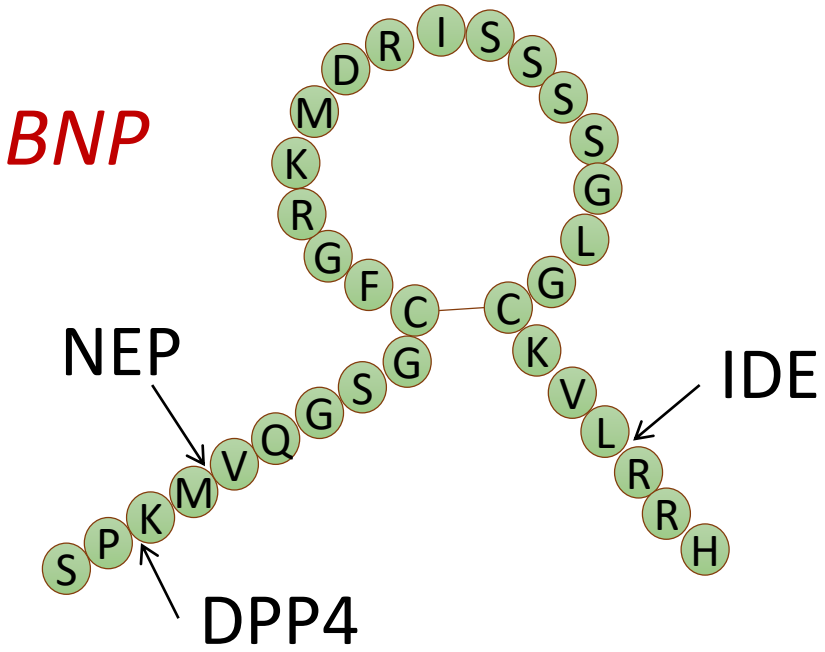
Table 2. Secondary Efficacy and Safety Outcomes.*

Outcome	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Sacubitril–Valsartan vs. Enalapril
Key safety outcomes — no. (%)			**Relative risk (95% CI)**
Worsening renal function†	60 (13.6)	65 (14.7)	0.93 (0.67 to 1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84 to 1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85 to 1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02 to 1.38)
Secondary biomarker outcomes — % (95% CI)‡			**Ratio of change (95% CI)**
Change in high-sensitivity troponin T concentration	−36.6 (−40.8 to −32.0)	−25.2 (−30.2 to −19.9)	0.85 (0.77 to 0.94)
Change in B-type natriuretic peptide concentration	−28.7 (−35.5 to −21.3)	−33.1 (−39.5 to −25.9)	1.07 (0.92 to 1.23)
Change in ratio of B-type natriuretic peptide to NT-proBNP	35.2 (28.8 to 42.0)	−8.3 (−3.6 to −12.7)	1.48 (1.38 to 1.58)
Exploratory clinical outcomes — no. (%)			**Hazard ratio (95% CI)§**
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)
Composite of serious clinical events¶	41 (9.3)	74 (16.8)	0.54 (0.37 to 0.79)

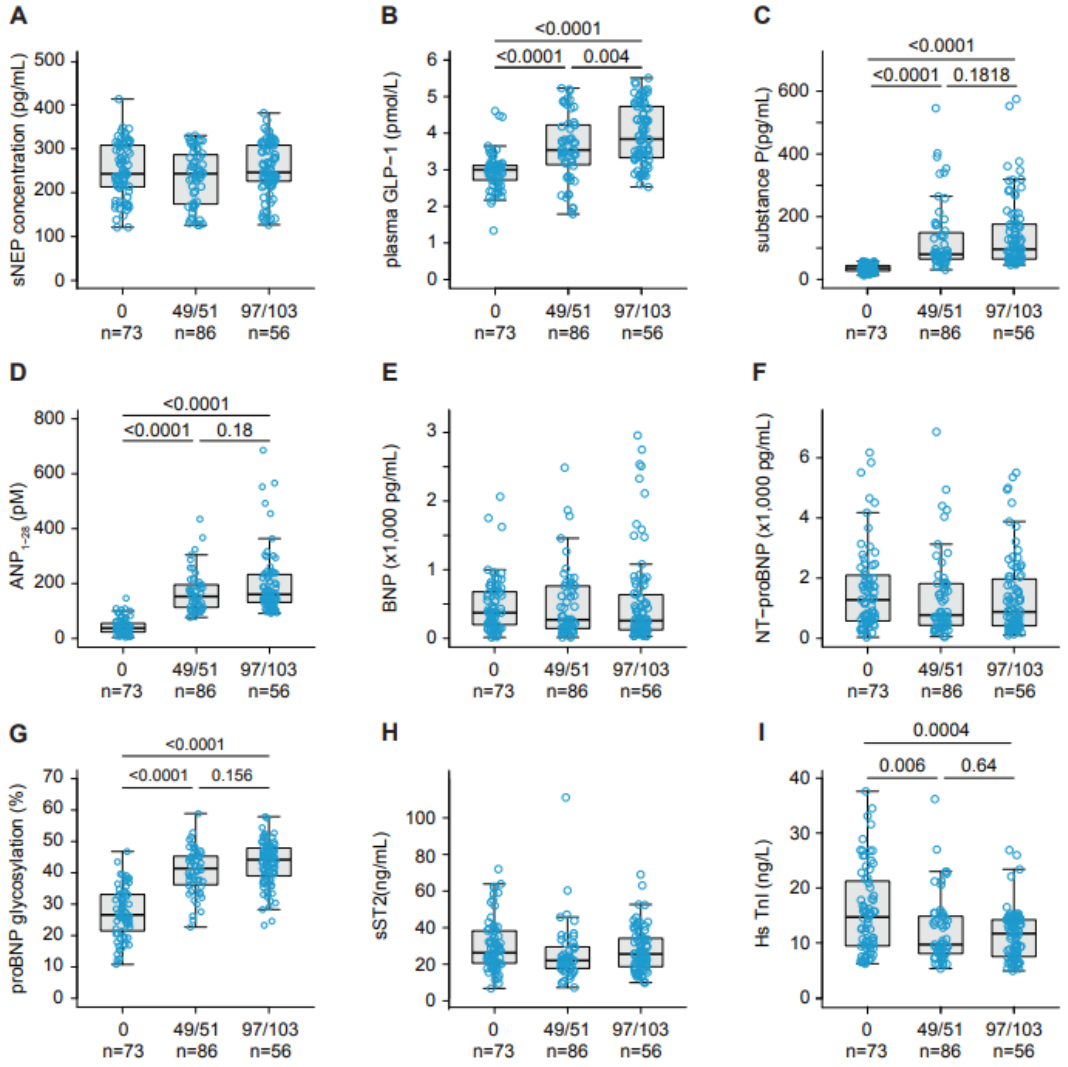
* NA denotes not available.
† Worsening renal function was defined by an increase in the serum creatinine concentration of 0.5 mg per deciliter or more (≥44 μmol per liter) and a decrease in the estimated glomerular filtration rate of 25% or more.
‡ Shown are data on the time-averaged proportional change, from the baseline value to the geometric mean of values obtained at weeks 4 and 8.
§ Hazard ratios and associated 95% confidence intervals were calculated with a Cox proportional-hazards model. Confidence intervals have not been adjusted for multiple comparisons, and therefore, inferences drawn from these intervals may not be reproducible.
¶ The outcome of a composite of serious clinical events was added to the list of exploratory clinical outcomes in May 2018, before the database was locked and unblinding occurred. This end point included death, rehospitalization for heart failure, implantation of a left ventricular device, and inclusion on the list of patients eligible for heart transplantation.

ACE and neprilysin share substrates





Peptide concentrations in patients treated with sacubitril/valsartan



"Venous blood samples were collected in tubes containing EDTA."

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Closing Thoughts

Understanding how a drug works matters.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers have different efficacy in preventing thrombotic events in part because ACE inhibitors alter the degradation of bradykinin as well as the formation of angiotensin II.

Similarly, DPP4 inhibitors have effects distinct from GLP-1 analogues due to effects on the degradation of vasoactive peptide substrates.

Understanding the contribution of decreased degradation of peptides such as bradykinin and substance P, as well as the natriuretic peptides, would enhance the use of sacubitril/valsartan in patients with heart failure.

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