# CONGRESSO REGIONALE AMD - SID

## Alleanza strategica nella gestione del paziente diabetico: attori a confronto
## Roma, 5-6 maggio 2017

- Il /la dr./sa Martina Vitale dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Congresso Regionale AMD - SID Lazio
"Alleanza strategica nella gestione del paziente diabetico: attori a confronto"

Roma
5-6 Maggio 2017

# NEFROPATIA DIABETICA

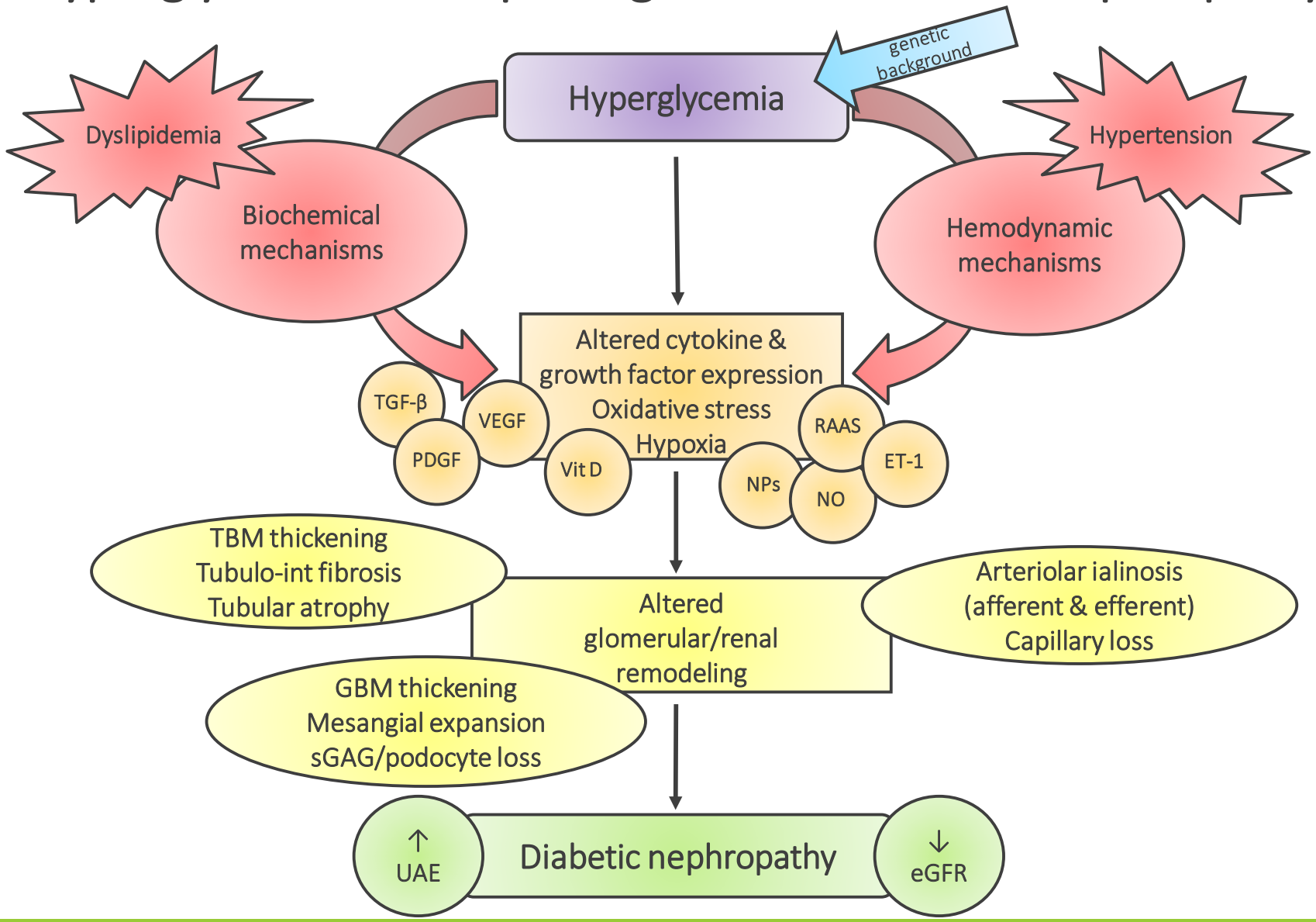
# LO STATO DELLA RICERCA

MARTINA VITALE

*U.O.C. MEDICINA 2 – DIABETOLOGIA*

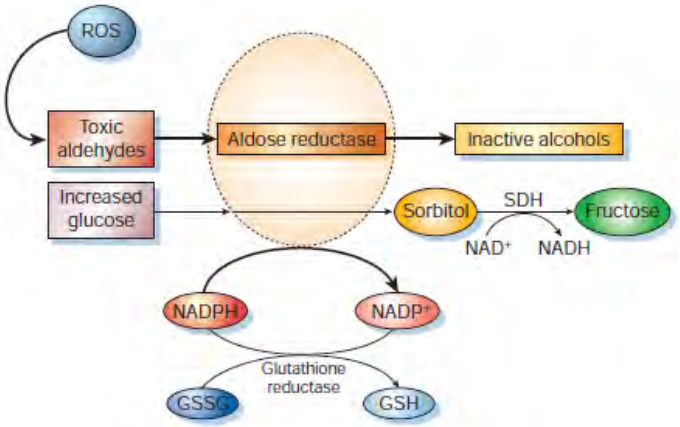
*AZIENDA OSPEDALIERA SANT'ANDREA, ROMA*

# Hyperglycemia in the pathogenesis of diabetic nephropathy

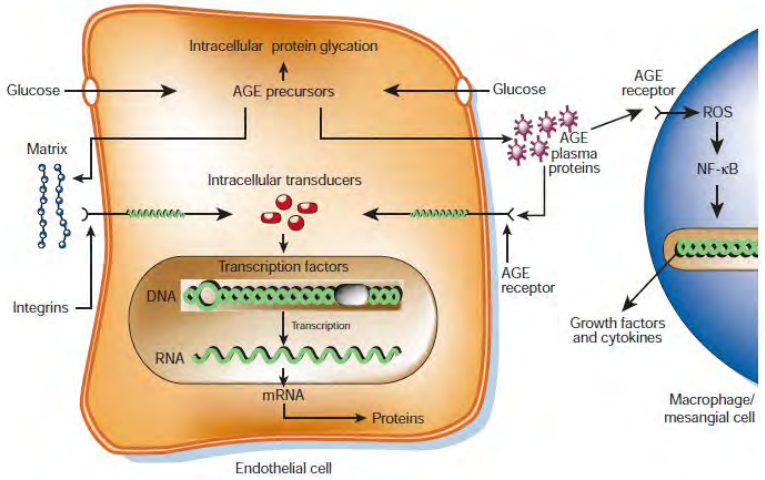


# Biochemical mechanisms

## 1) Polyol pathway

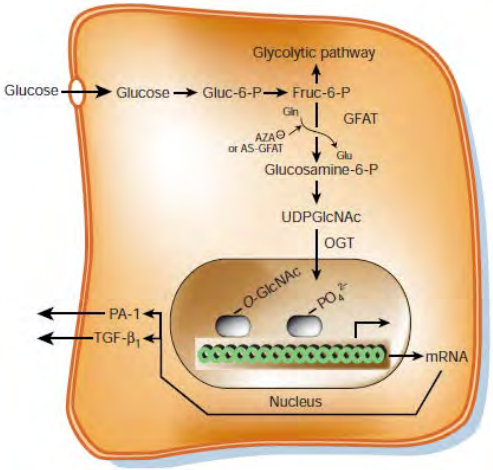



## 2) AGEs pathway

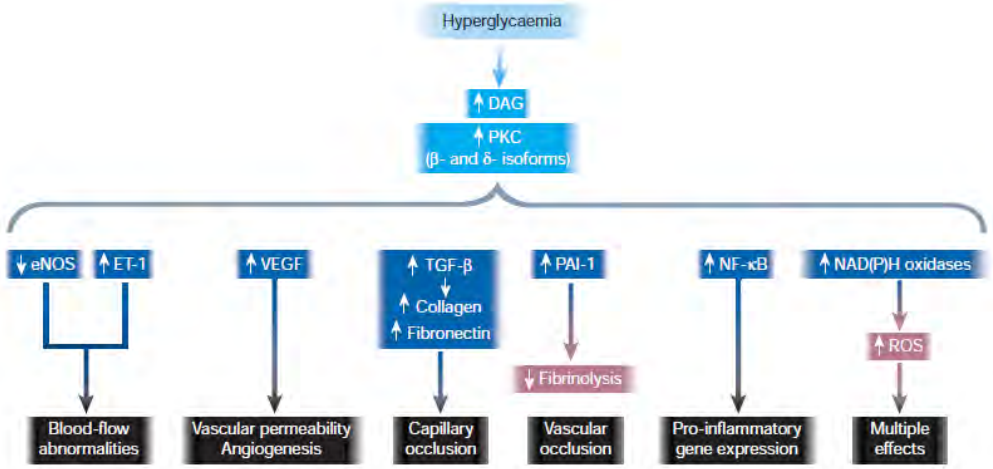



$O_2^-$

## 3) Hexosamine pathway

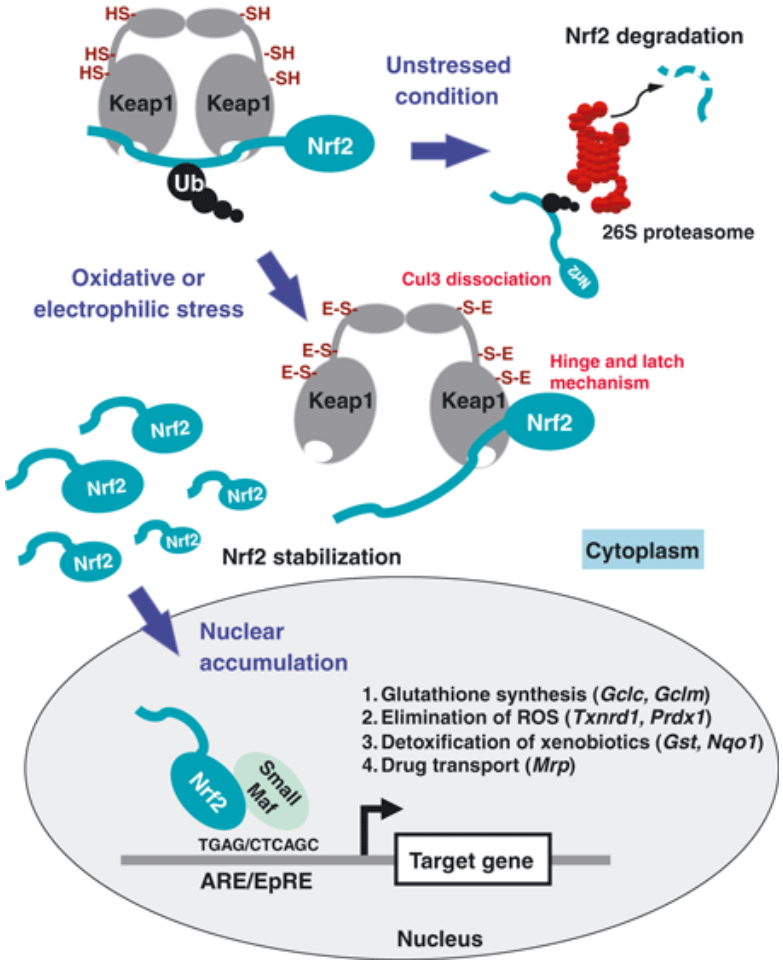



## 4) PKC pathway




Brownlee M et al. Nature. (2001)

# The Keap1-Nrf2 pathway

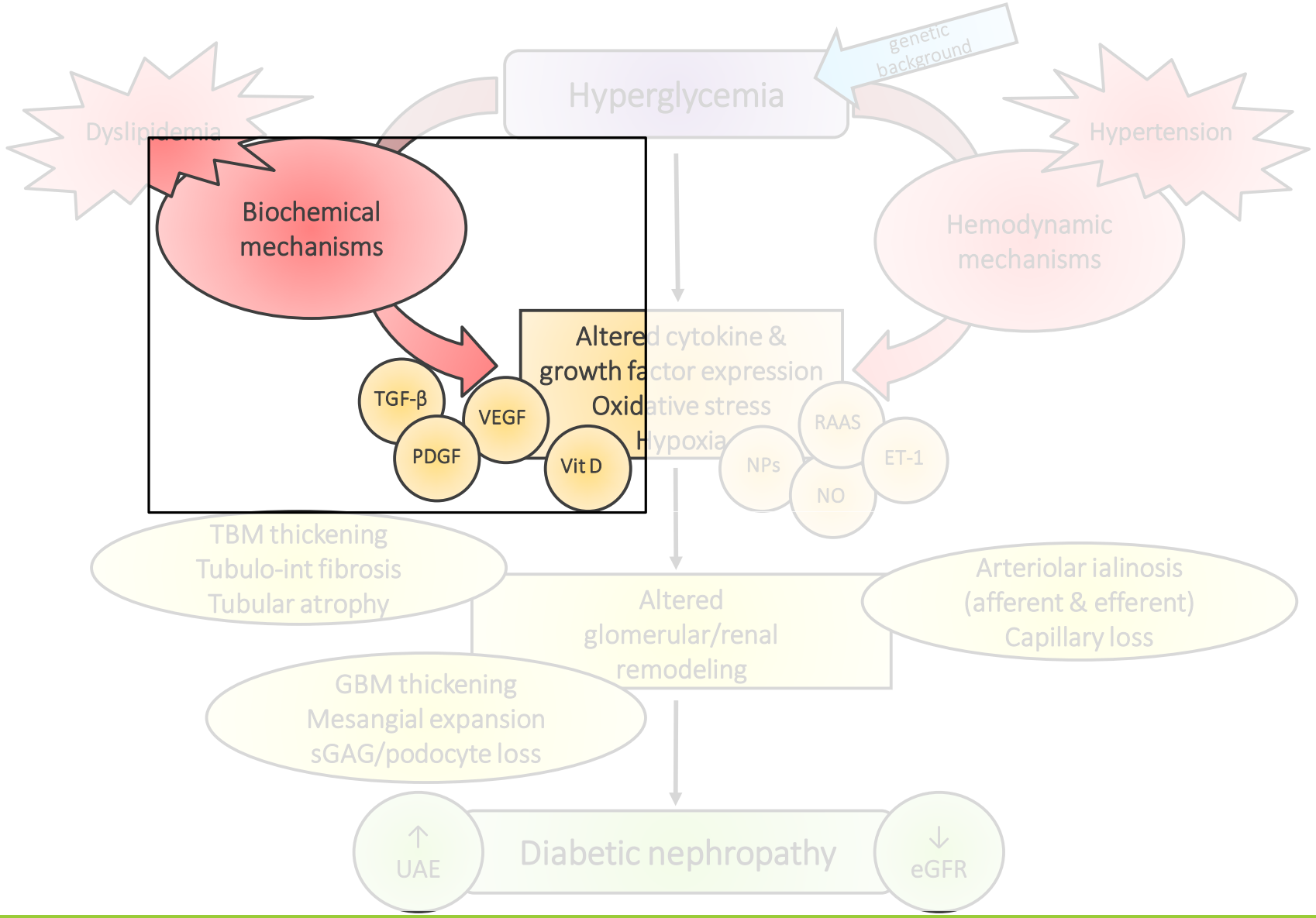



The Keap1–Nrf2 regulatory pathway plays a central role in the protection of cells against oxidative and xenobiotic damage.

- Under unstressed conditions, Nrf2 is constantly ubiquitinated by Keap1 complex and rapidly degraded in proteasomes.
- Upon exposure to oxidative stresses, reactive cysteine residues of Keap1 become modified, leading to a stabilization of Nrf2 and robust induction of a battery of cytoprotective genes.

Taguchi K et al. Genes Cells. 2011 Feb;16(2):123-40.

# Hyperglycemia in the pathogenesis of diabetic nephropathy



# RUBOXISTAURIN

PKC-β inhibitor

## *Kidney Outcomes in Long-Term Studies of Ruboxistaurin for Diabetic Eye Disease*

Three diabetic retinopathy trials (The PKC-Diabetic Retinopathy Study (PKC-DRS), PKC-Diabetic Macular Edema Study (PKC-DMES) and PKC-DRS2)
- 1157 pz
- moderate-severe or mild-moderate non-proliferative retinopathy + macular edema
- normal eGFR
→ randomized to placebo or ruboxistaurin (32 mg/day) for 36-52 weeks

Renal outcomes:
- Doubling of serum creatinine
- Progression to advanced chronic kidney disease (CKD stages 4 to 5)
- Death

| Characteristic | Placebo | RBX 32 mg/d | Total | *P* |
|---|---|---|---|---|
| Doubling of serum creatinine | 6.1% (35/577) | 5.9% (34/580) | 6.0% (69/1157) | 0.88 |
| Progression to advanced CKD | 4.3% (25/577) | 3.8% (22/580) | 4.1% (47/1157) | 0.64 |
| Death | 4.7% (27/577) | 3.6% (21/580) | 4.1% (48/1157) | 0.37 |
| At least one kidney outcome | 11.8% (68/577) | 10.9% (63/580) | 11.3% (131/1157) | 0.62 |

[a]CKD, chronic kidney disease.

Tuttle KR et al. Clin J Am Soc Nephrol. 2007; 2:631-636

# PYRIDOXAMINE

Anti AGEs

## *Pyridorin in Type 2 Diabetic Nephropathy*

Double-blind, randomized, placebo-controlled trial
- 317 pz
- serum creatinine of 1.3–3.3 (women) or 1.5–3.5 mg/dl (men), UACR ≥ 1,200 mg/g
- on ACE-i/ARBs
→ randomized to placebo or pyridorin (150 or 300 mg twice daily) for 52 weeks

**Primary EP:** Change in serum creatinine

**Table 2.** Changes from baseline serum creatinine concentration

| Variable | Placebo Group | PYR 150 Group | PYR 300 Group |
|---|---|---|---|
| All patients (*n*) | 103 | 99 | 105 |
| baseline serum creatinine (mg/dl) | 2.20±0.56 | 2.22±0.55 | 2.17±0.57 |
| change at end point (mg/dl) | 0.36±0.38 | 0.42±0.38 | 0.36±0.37 |
| | | p= 0.48 | p= 0.95 |
| | | vs placebo | |

Lewis EJ et al. J Am Soc Nephrol. 2012; 23: 131–136

# BARDOXOLONE Methyl

Antioxidant
Nrf2 inductor

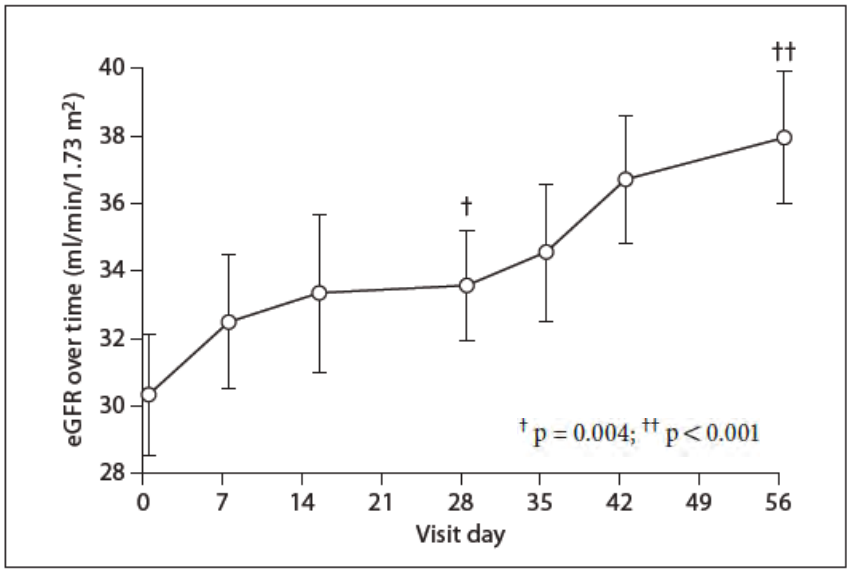
## *Effect of Bardoxolone Methyl on Kidney Function in Patients with T2D and Stage 3b–4 CKD*

Pilot, multi-center, open-label, single arm study
- 20 pz
- eGFR 15-45 ml/min/1.73 $m^2$
- 75% on ACE-i/ARBs

→ bardoxolone methyl 25 mg/day for 28 days, followed by 75 mg/day for another 28 days

**Primary EP:** Change eGFR

**Safety:** no life-threatening adverse events
Muscle spasms (n = 7; 35%)




Pergola PE et al. Am J Nephrol. 2011;33(5):469-76

# BARDOXOLONE Methyl

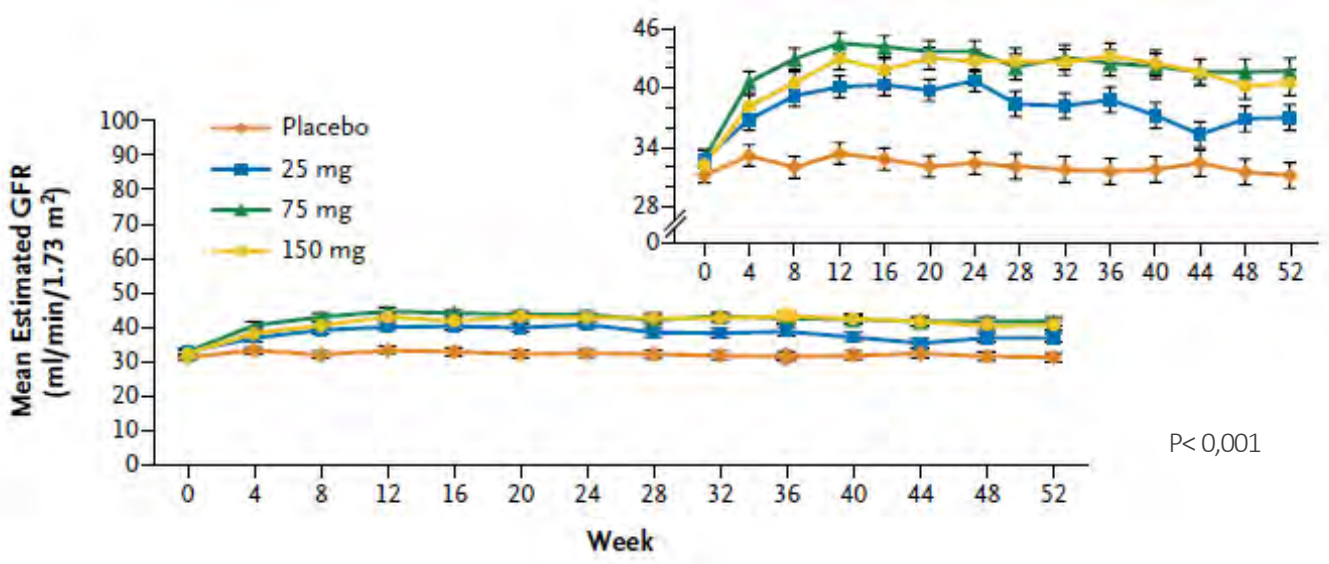
## *Bardoxolone Methyl and Kidney Function in CKD with Type 2 Diabetes (BEAM Study)*

Phase 2, double-blind, randomized, placebo-controlled trial
- 227 pz
- eGFR 20-45 ml/min/1.73 $m^2$
- on ACE-i/ARBs

→ randomized to placebo or bardoxolone methyl (25, 75, or 150 mg/day) for 52 weeks

**Primary EP:** Change eGFR

**Advers Event:** Muscle spasms




P< 0,001

Pergola PE et al. N Engl J Med. 2011; 365:327-336

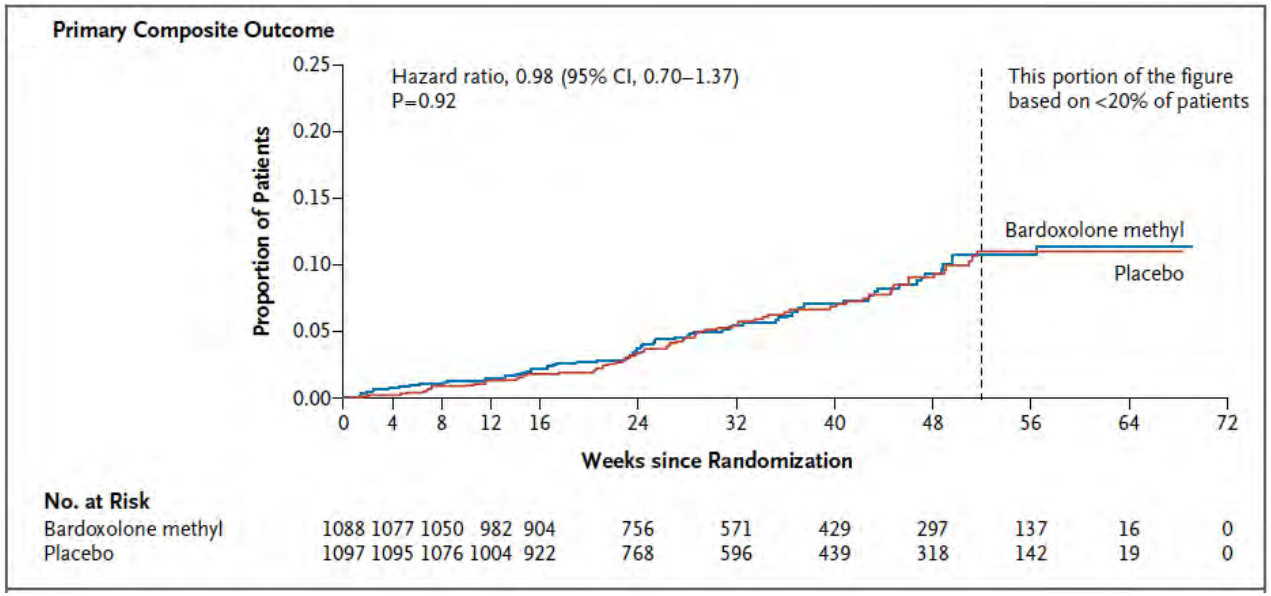
# BARDOXOLONE Methyl

## *Bardoxolone Methyl in Type 2 Diabetes and Stage 4 Chronic Kidney Disease (BEACON Trial)*

Double-blind, randomized, parallel-group trial
- 2185 pz
- eGFR 15-30 ml/min/1.73 $m^2$
- on ACE-i/ARBs

→ randomized to placebo or bardoxolone methyl 20 mg/day

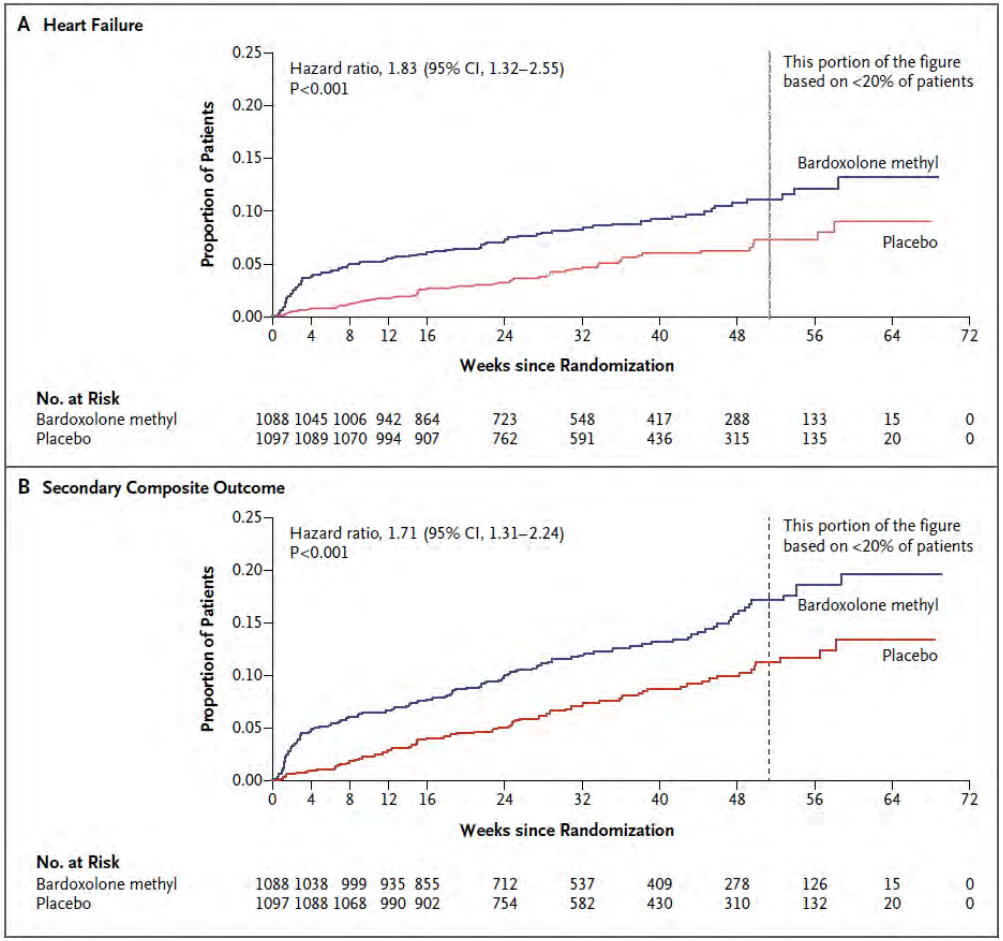
**Primary Composite Outcome:**
ESRD or death from cardiovascular causes




De Zeeuw D et al. N Engl J Med. 2013; 369:2492-2503

# BARDOXOLONE Methyl

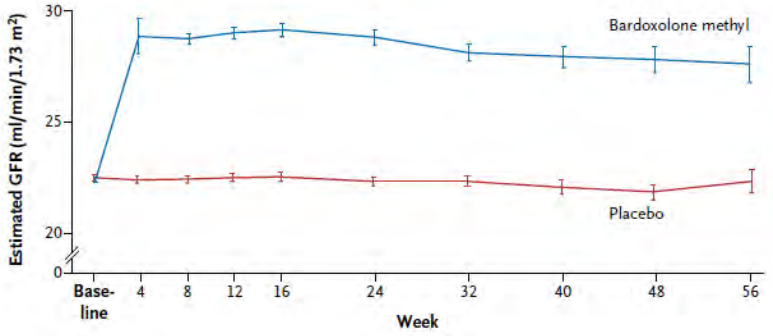
## *Bardoxolone Methyl in Type 2 Diabetes and Stage 4 Chronic Kidney Disease (BEACON Trial)*




Secondary Outcome:

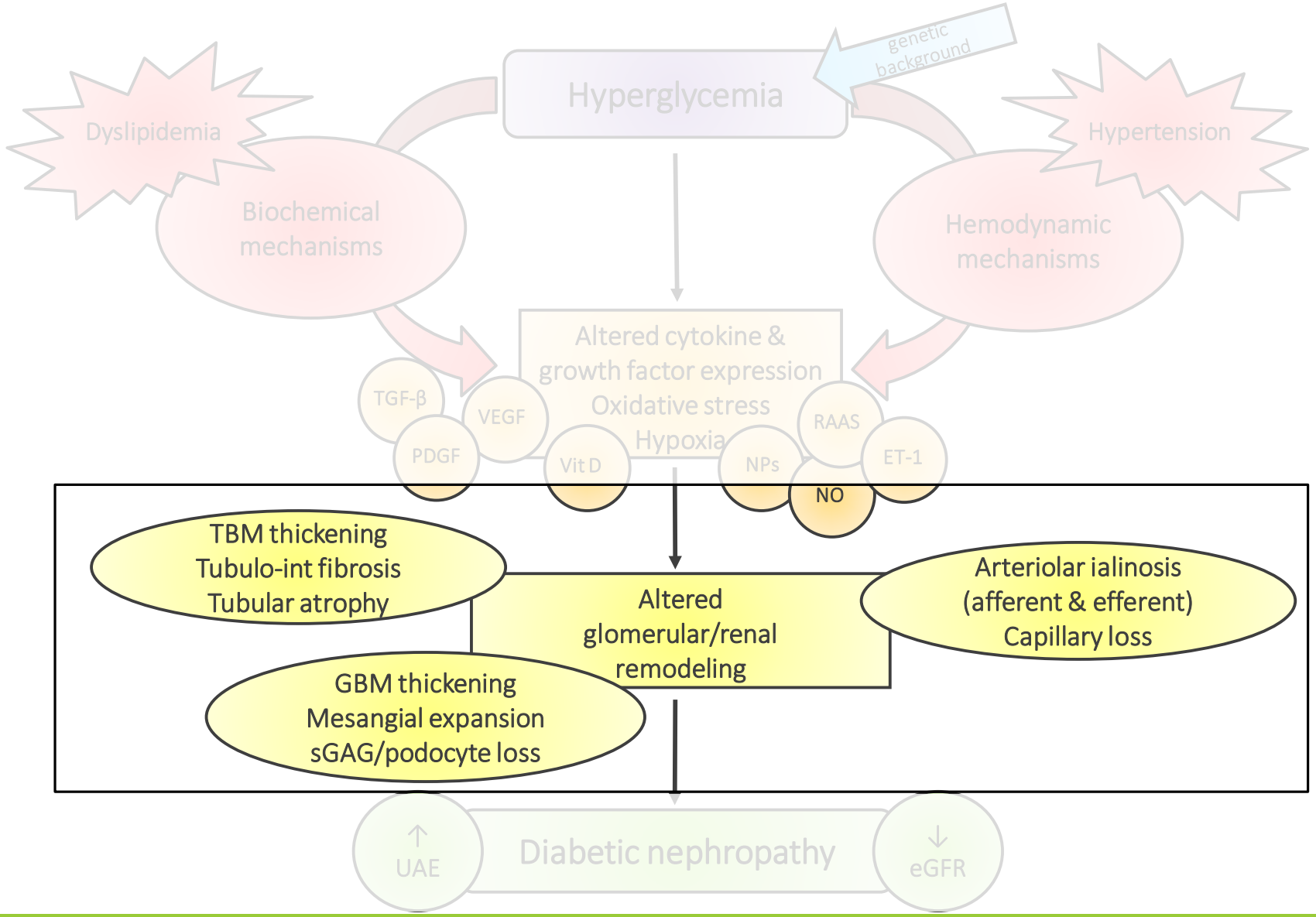
- Change eGFR
- Hospitalization for heart failure
- Composite outcome of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death from cardiovascular causes

Interrupted




De Zeeuw D et al. N Engl J Med. 2013; 369:2492-2503

# Hyperglycemia in the pathogenesis of diabetic nephropathy



# SULODEXIDE

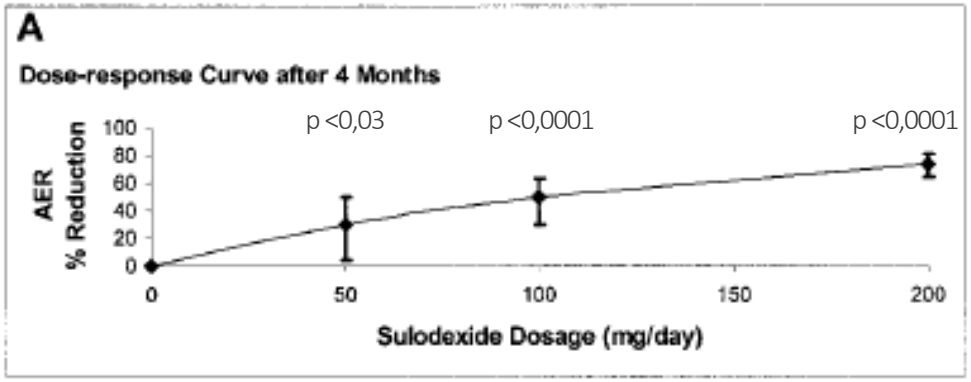
Glycosaminoglycan

## *Oral Sulodexide Reduces Albuminuria in Microalbuminuric and Macroalbuminuric Type 1 and Type 2 Diabetic Patients (Di.N.A.S. Trial)*

Double-blind, randomized, placebo-controlled trial
- 223 pz
- Serum Creatinine <1,7 mg/dl, micro/macro albuminuria
- on ACE-i/ARBs

→ randomized to placebo or sulodexide (50, 100, or 200 mg/day) for 4 months

**Primary EP:** Change UACR




Gambaro G et al. J Am Soc Nephrol. 2002 Jun;13(6):1615-25

# SULODEXIDE

## *Sulodexide for Kidney Protection in Type 2 Diabetes Patients with Microalbuminuria (SunMICRO Trial)*

Double-blind, randomized, placebo-controlled trial
- 1056 pz
- Serum Creatinine <1,5 mg/dl, UACR 35-45/200 mg/g
- on ACE-i/ARBs

→ randomized to placebo or sulodexide 200 mg/day for 26 weeks

**Primary EP:** Change UACR

| Outcome | Sulodexide (n = 492) | Placebo (n = 494) | Total (N = 986) | *P* |
|---|---|---|---|---|
| Therapeutic success | 81 (16.5) | 91 (18.4) | 172 (17.4) | 0.5 |
| Normalization | 39 (7.9) | 30 (6.1) | 69 (7.0) | 0.3 |
| 50% ACR reduction | 76 (15.4) | 87 (17.6) | 163 (16.5) | 0.4 |

Lewis EJ et al. Am J Kidney Dis. 2011; 58:729-736

# SULODEXIDE

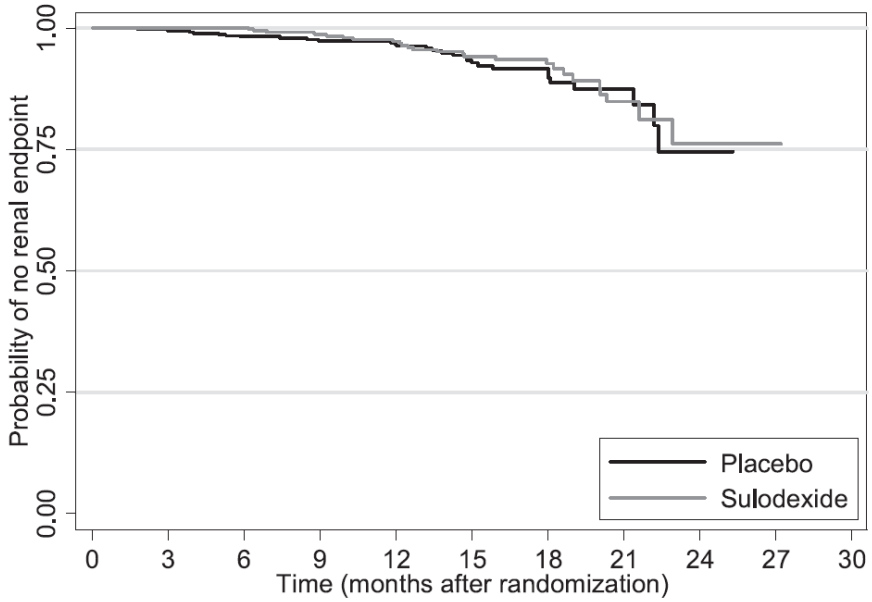
## *Sulodexide Fails to Demonstrate Renoprotection in Overt Type 2 Diabetic Nephropathy (SunMACRO Trial)*

Double-blind, randomized, placebo-controlled trial
- 1248 pz
- eGFR 15-30 ml/min/1.73 $m^2$, proteinuria ≥ 0,9 g/24h
- on ACE-i/ARBs

→ randomized to placebo or sulodexide 200 mg/day for 26 weeks

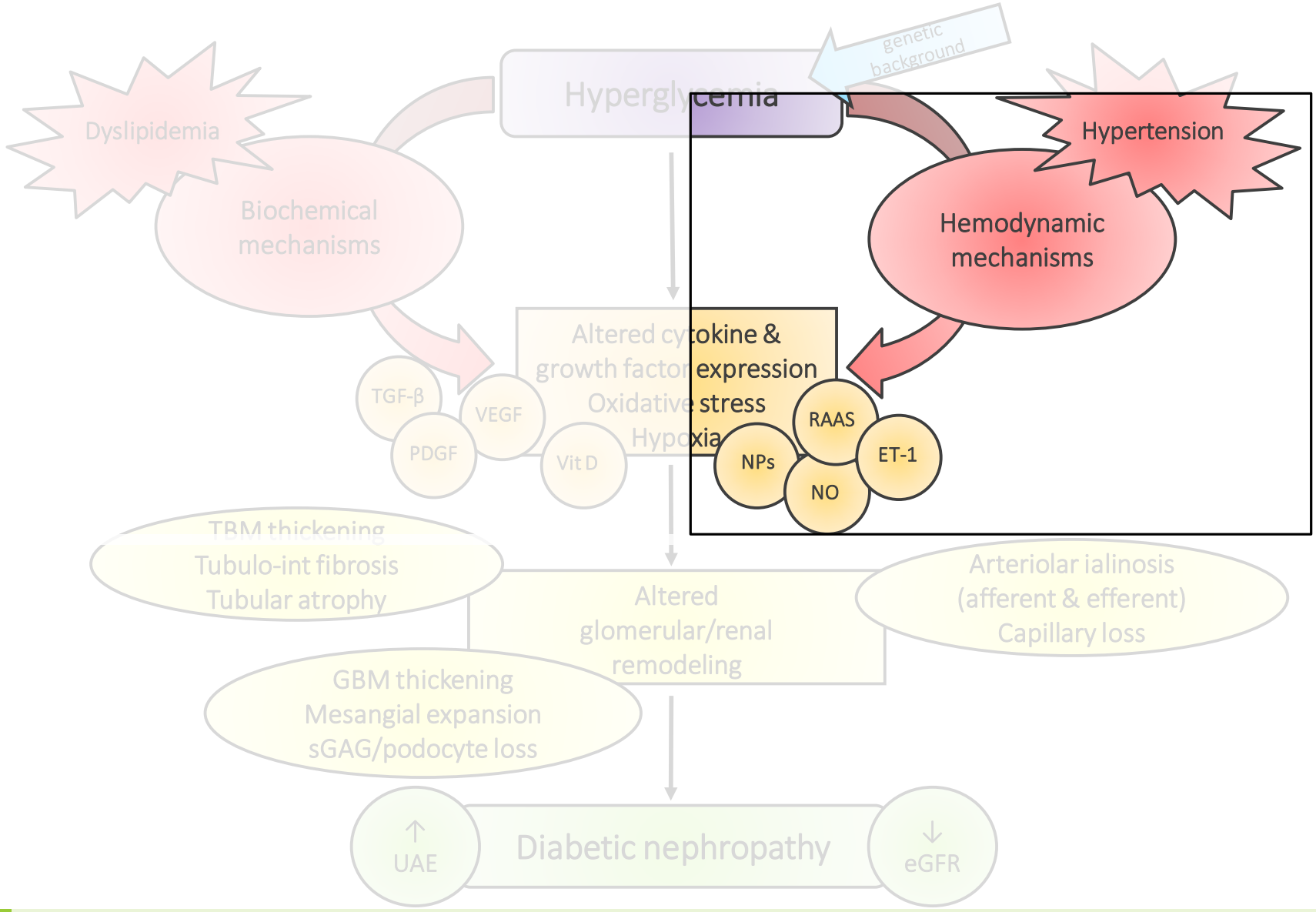
**Primary Composite Outcome:** doubling of baseline serum creatinine, development of ESRD, or serum creatinine ≥ 6.0 mg/dl

Interrupted




Packham DK et al. J Am Soc Nephrol. 2012; 23:123–130

# Hyperglycemia in the pathogenesis of diabetic nephropathy

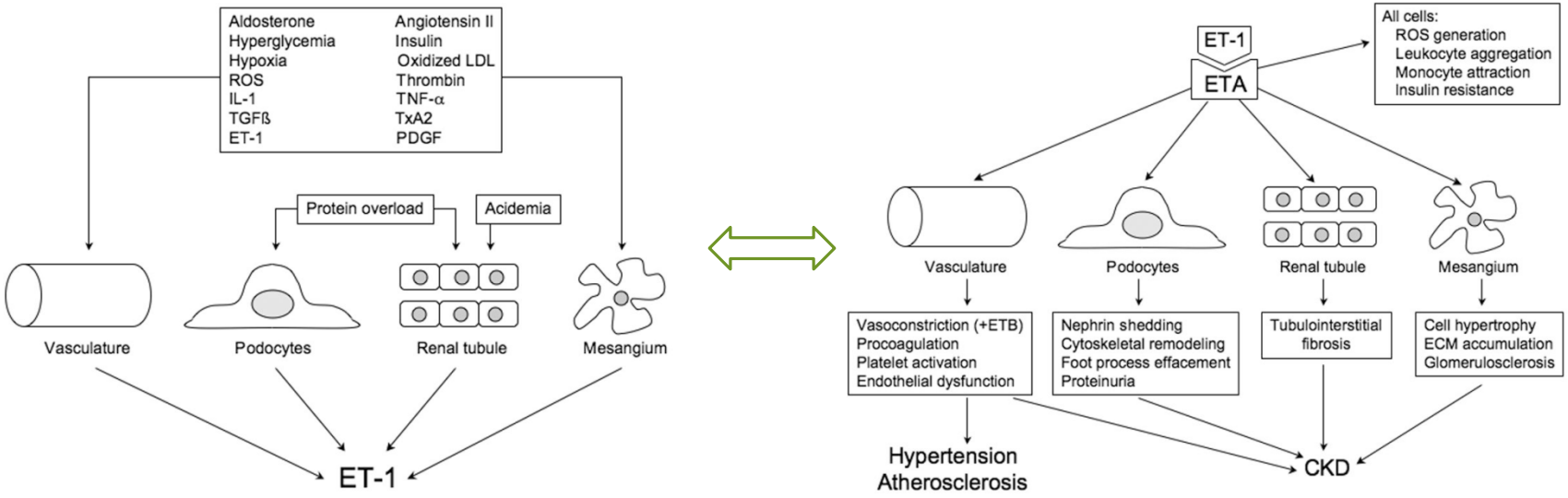


# ENDOTHELIN RECEPTOR ANTAGONIST (ERAs)

Endothelin-1 (ET-1): endothelial cell-derived peptide with high vasoconstrictor potency
Two receptor subtypes:

- **ETA** (in vascular smooth muscle): causes extremely potent vasoconstriction
- **ETB** (in vascular endothelium): induces vasorelaxation via nitric oxide and prostaglandin release. Also promotes natriuresis and diuresis through direct inhibition of nephron sodium and water reabsorption

Renal ET-1 production is increased in virtually every form of CKD




Kohan DE Curr Opin Nephrol Hypertens. 2010 Mar;19(2):134-9.
Kohan DE, Pollock DM. Br J Clin Pharmacol. 2013 Oct;76(4):573-9

# ENDOTHELIN RECEPTOR ANTAGONIST (ERAs)

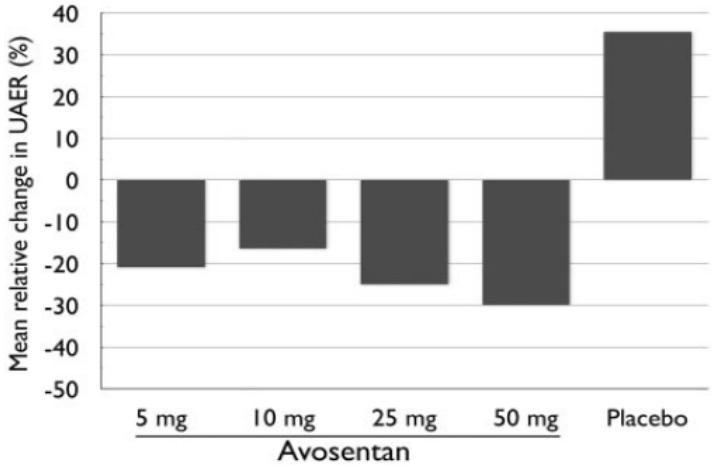
## *Avosentan Reduces Albumin Excretion in Diabetics with Macroalbuminuria*

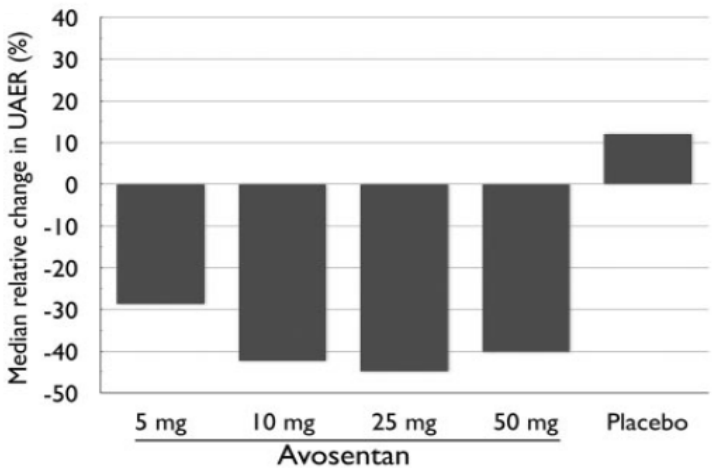
Double-blind, randomized, placebo-controlled trial
- 286 pz
- eGFR > 30 ml/min/1.73 $m^2$, macroalbuminuria
- on ACE-i/ARBs

→ randomized to placebo or avosentan (5, 10, 25, or 50 mg/day) for 12 weeks

**Primary EP:** Change UACR

**Advers Event:**
- Edema (p = 0.01)
- Abnormal electrocardiogram (p = 0.52)
- Anemia (p = 0.71)
- Headache (p = 0.28)




Wenzel RR et al. J Am Soc Nephrol. 2009; 20: 655–664

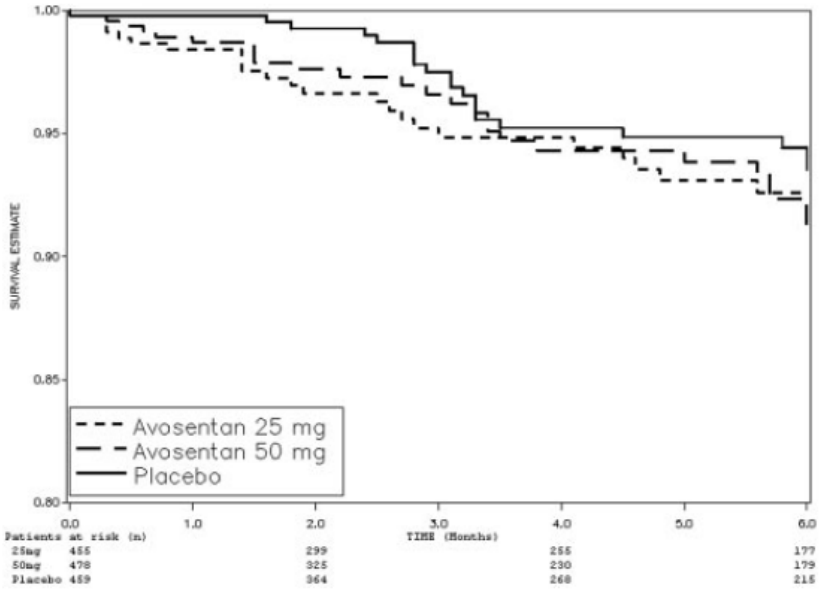
# ENDOTHELIN RECEPTOR ANTAGONIST (ERAs)

## *Avosentan for Overt Diabetic Nephropathy (ASCEND study)*

Double-blind, randomized, placebo-controlled trial
- 1392 pz
- Serum creatinine 1.2-3 mg/dl, UACR ≥ 309 mg/g
- on ACE-i/ARBs

→ randomized to placebo or avosentan (25 or 50 mg/day) for a median follow-up of 4 months

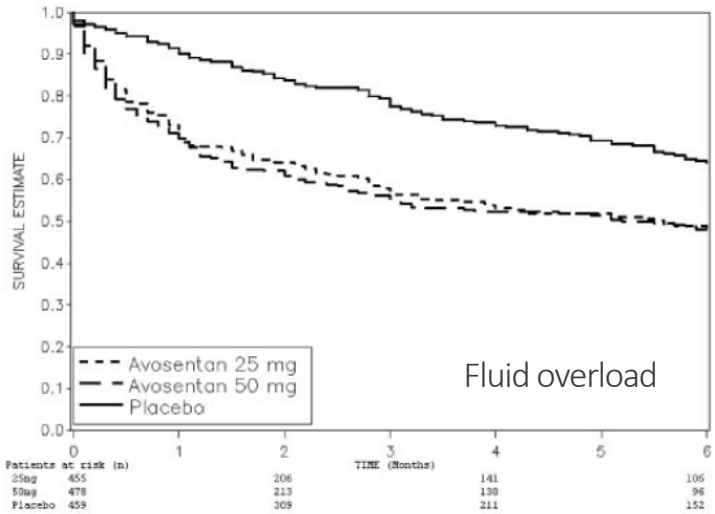
**Primary Composite Outcome:** doubling of serum creatinine, ESRD or death




Mann JFE et al. J Am Soc Nephrol. 2010; 21:527–535

# ENDOTHELIN RECEPTOR ANTAGONIST (ERAs)

## *Avosentan for Overt Diabetic Nephropathy (ASCEND study)*

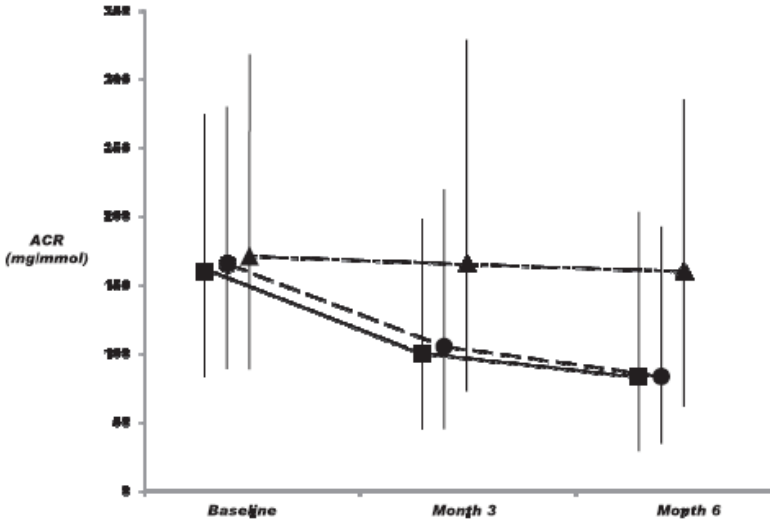



Fluid overload

Interrupted

Secondary EP:

- Change UACR
- Composite cardiovascular outcome (coronary or peripheral vascular revascularization, amputations, non fatal acute myocardial infarction, stroke and CHF)




Mann JFE et al. J Am Soc Nephrol. 2010; 21:527–535

# ENDOTHELIN RECEPTOR ANTAGONIST (ERAs)

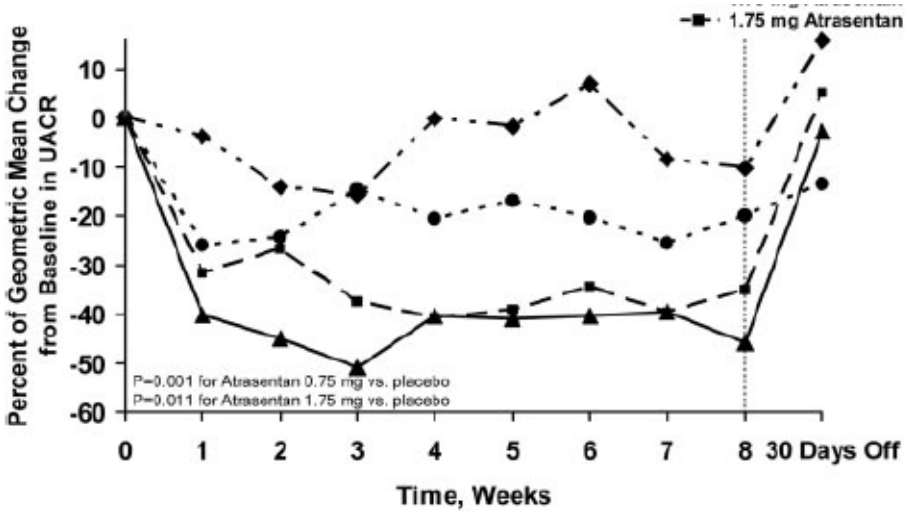
## *Addition of Atrasentan to Renin-Angiotensin System Blockade Reduces Albuminuria in Diabetic Nephropathy*

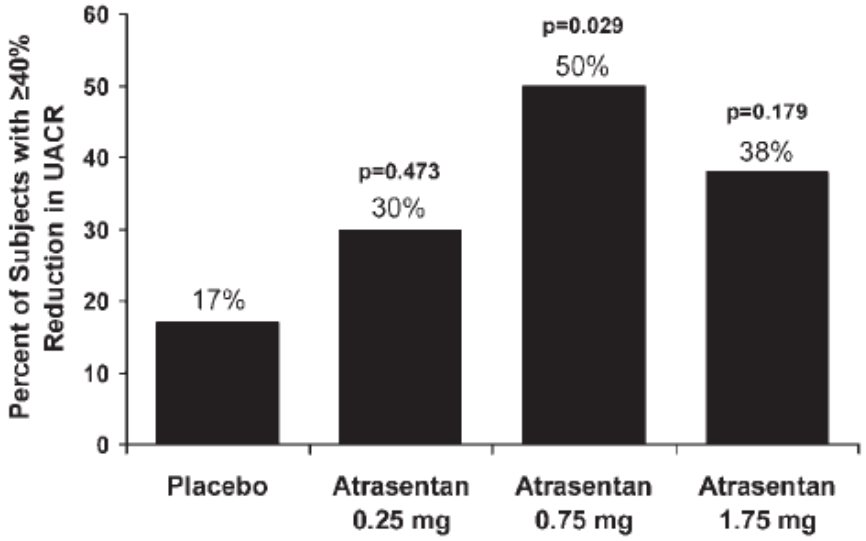
Double-blind, randomized, placebo-controlled trial
- 89 pz
- eGFR >20 ml/min/1.73 $m^2$, UACR 100 - 3000 mg/g
- on ACE-i/ARBs

→ randomized to placebo or atresentan (0.25, 0.75, or 1.75 mg/day) for 8 weeks

**Primary EP:** Change UACR

**Advers Event:**
- Edema (p = 0.007 for 1.75 mg)
- Anemia (p < 0.001 for 1.75 mg)




Kohan DE et al. J Am Soc Nephrol. 2011; 22:763–772

# ENDOTHELIN RECEPTOR ANTAGONIST (ERAs)

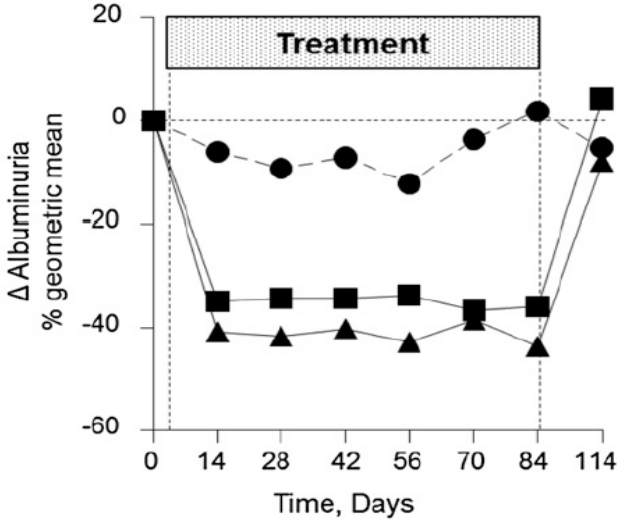
## *The Endothelin Antagonist Atrasentan Lowers Residual Albuminuria in Patients with Type 2 Diabetic Nephropathy*

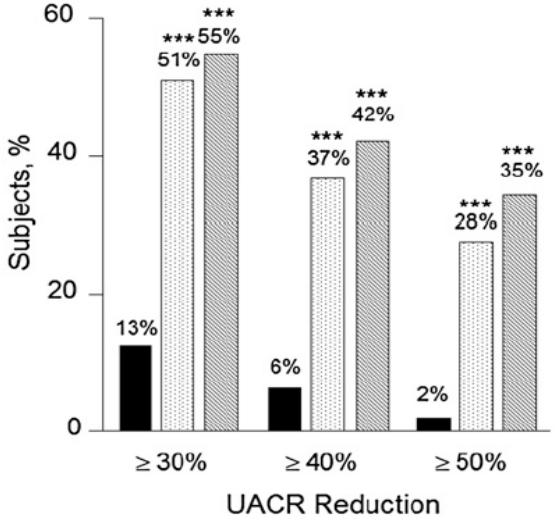
Double-blind, randomized, placebo-controlled trial
- 211 pz
- eGFR 30-75 ml/min/1.73 $m^2$, UACR 300-3500 mg/g
- on ACE-i/ARBs

→ randomized to placebo or atresentan (0.75 or 1.25 mg/day) for 12 weeks

**Primary EP:** Change UACR

**Advers Event:**
- Weight gain ($p < 0.001$ for 1.75 mg)
- Anemia
- Edema (ns)




De Zeeuw D et al. J Am Soc Nephrol. 2014; 25:1083–1093

# ENDOTHELIN RECEPTOR ANTAGONIST (ERAs)

FLUID RETENTION → driven by the endothelin B (ETB) receptor blocking

Avosentan:
- 50:1 selectivity for ETA to ETB
- High dose (25 - 50 mg/die)

} partial block of ETB → fluid retention +++

Atrasentan:
- 1800:1 selectivity for ETA to ETB
- Low dose (0,75 - 1,25 mg/die)

} no block of ETB → fluid retention +

*(vasodilatation?)*

an *optimal dose* is critical to achieve
**maximal albuminuria-lowering effect** with
**minimal fluid retention**

0.75 mg/die dose has been selected for future studies

De Zeeuw D et al. J Am Soc Nephrol. 2014; 25:1083–1093

# ENDOTHELIN RECEPTOR ANTAGONIST (ERAs)

## Study Of Diabetic Nephropathy With Atrasentan (SONAR)

Double-blind, randomized, placebo-controlled trial
- Estimated Enrollment 4148 pz
- eGFR 25-75 ml/min/1.73 $m^2$, UACR 300 - 5000 mg/g
- on ACE-i/ARBs

→ randomized to placebo or atresentan 0.75 mg/day

**Primary Composite Outcome:** doubling of serum creatinine or ESRD

**Secondary EP:**
- 50% eGFR reduction
- Cardiovascular composite endpoint: cardiovascular death, nonfatal myocardial infarction and nonfatal stroke
- Cardio-renal composite endpoint

**Estimated Completion Date: April 8, 2020**

ClinicalTrials.gov Identifier: NCT01858532

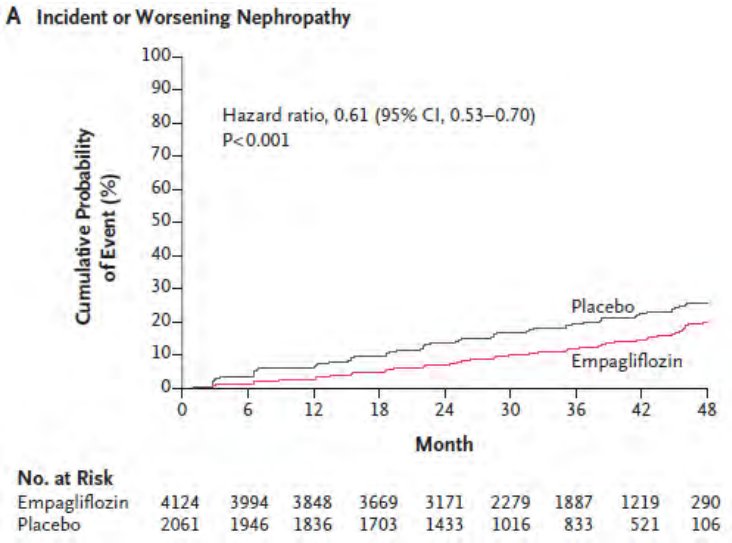
# SGLT2 INHIBITORS

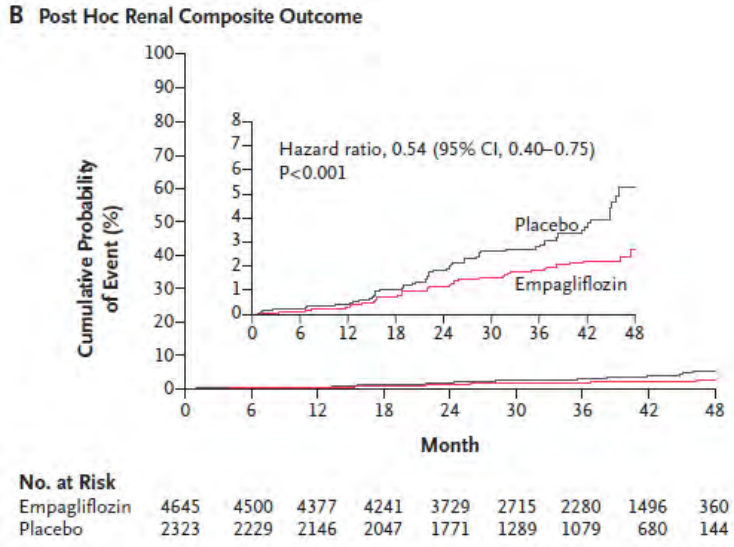
## *Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes (EMPA-REG OUTCOME CKD)*

Data from EMPA-REG OUTCOME Trial
- 7020 pz
- eGFR > 30 ml/min/1.73 $m^2$ (17.8% 45-59; 7.7% 30-44)
- 28.7% microalbuminuria, 11% macroalbuminuria
- 80.7% on ACE-i/ARBs

→ randomized to placebo or empagliflozin (10 or 25 mg/day) for 48 months

Renal outcome:
- Incident or worsening nephropathy (defined as progression to macroalbuminuria)
- Post hoc composite outcome: doubling of the serum creatinine level, initiation of renal-replacement therapy or death from renal disease




Wanner C et al. N Engl J Med. 2016; 375:323-334

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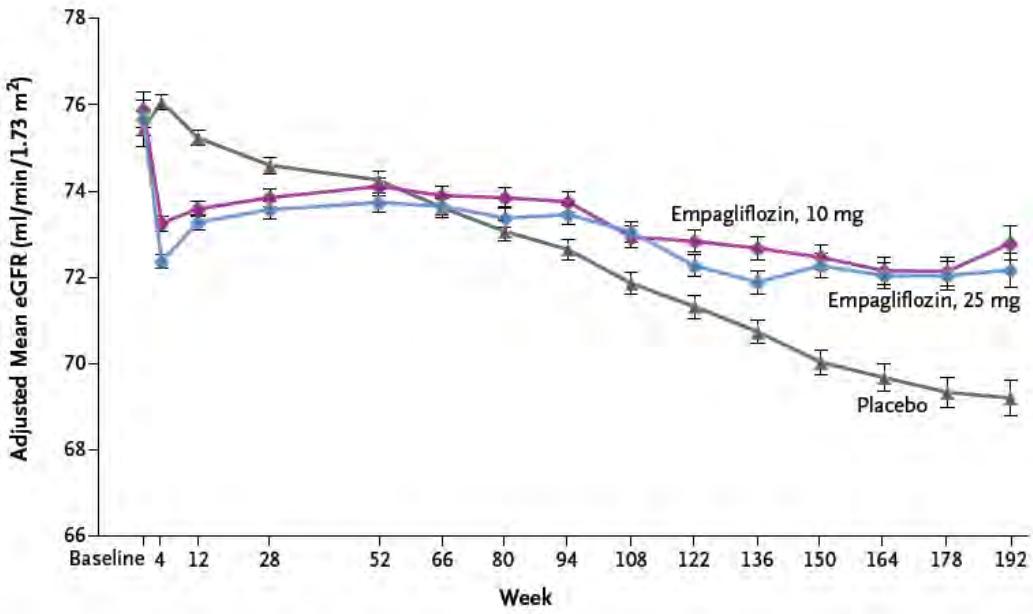



| No. at Risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2323 | 2295 | 2267 | 2205 | 2121 | 2064 | 1927 | 1981 | 1763 | 1479 | 1262 | 1123 | 977 | 731 | 448 |
| Empagliflozin, 10 mg | 2322 | 2290 | 2264 | 2235 | 2162 | 2114 | 2012 | 2064 | 1839 | 1540 | 1314 | 1180 | 1024 | 785 | 513 |
| Empagliflozin, 25 mg | 2322 | 2288 | 2269 | 2216 | 2156 | 2111 | 2006 | 2067 | 1871 | 1563 | 1340 | 1207 | 1063 | 838 | 524 |
| **No. in Follow-up Analysis** | | | | | | | | | | | | | | | |
| Total | 7020 | 7020 | 6996 | 6931 | 6864 | 6765 | 6696 | 6651 | 6068 | 5114 | 4443 | 3961 | 3488 | 2707 | 1703 |

Wanner C et al. N Engl J Med. 2016; 375:323-334

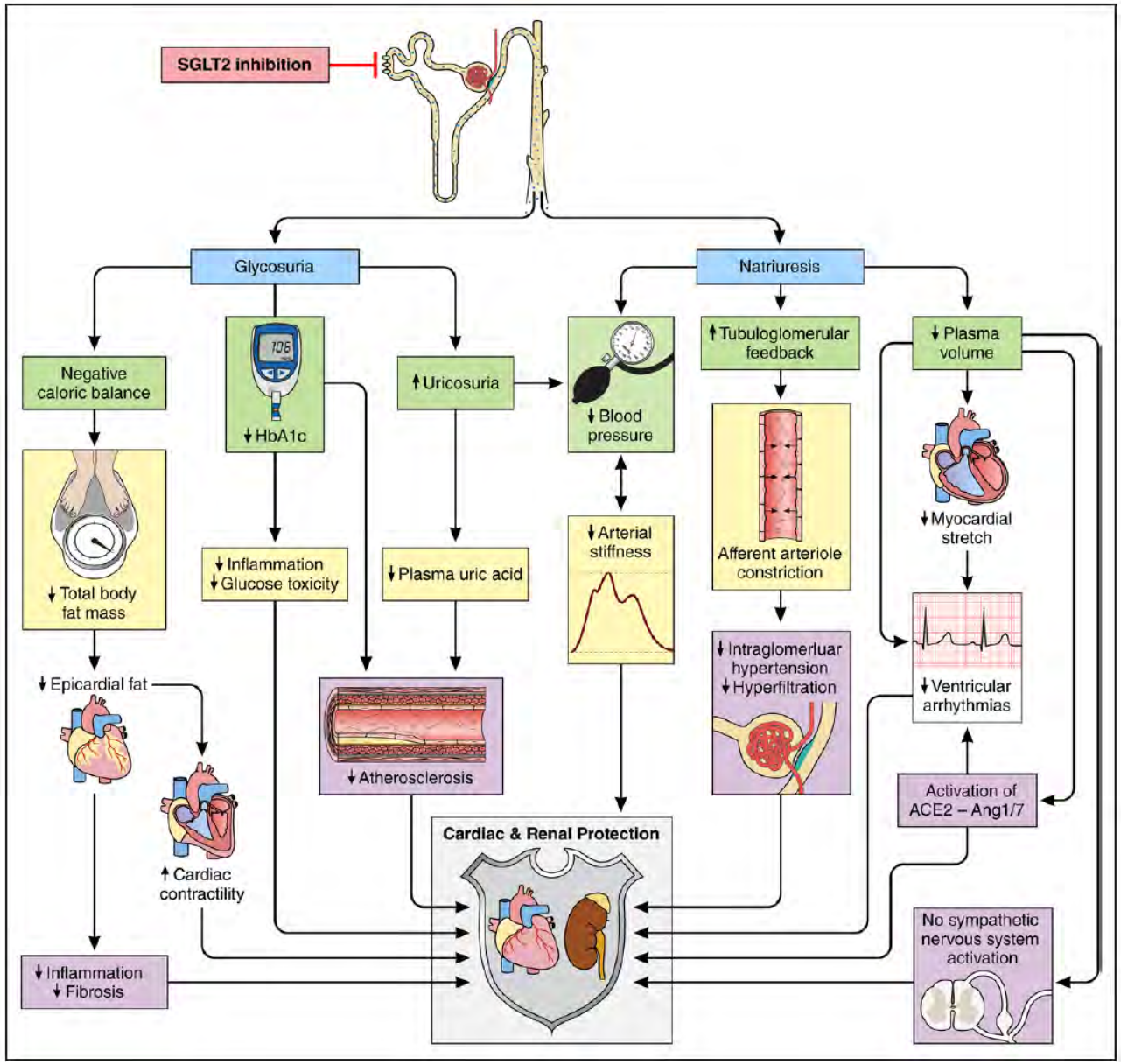
# SGLT2 INHIBITORS

## *Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes (EMPA-REG OUTCOME CKD)*

- ✓ 1,819 patients with an eGFR < 60 ml/min/1.73 $m^2$

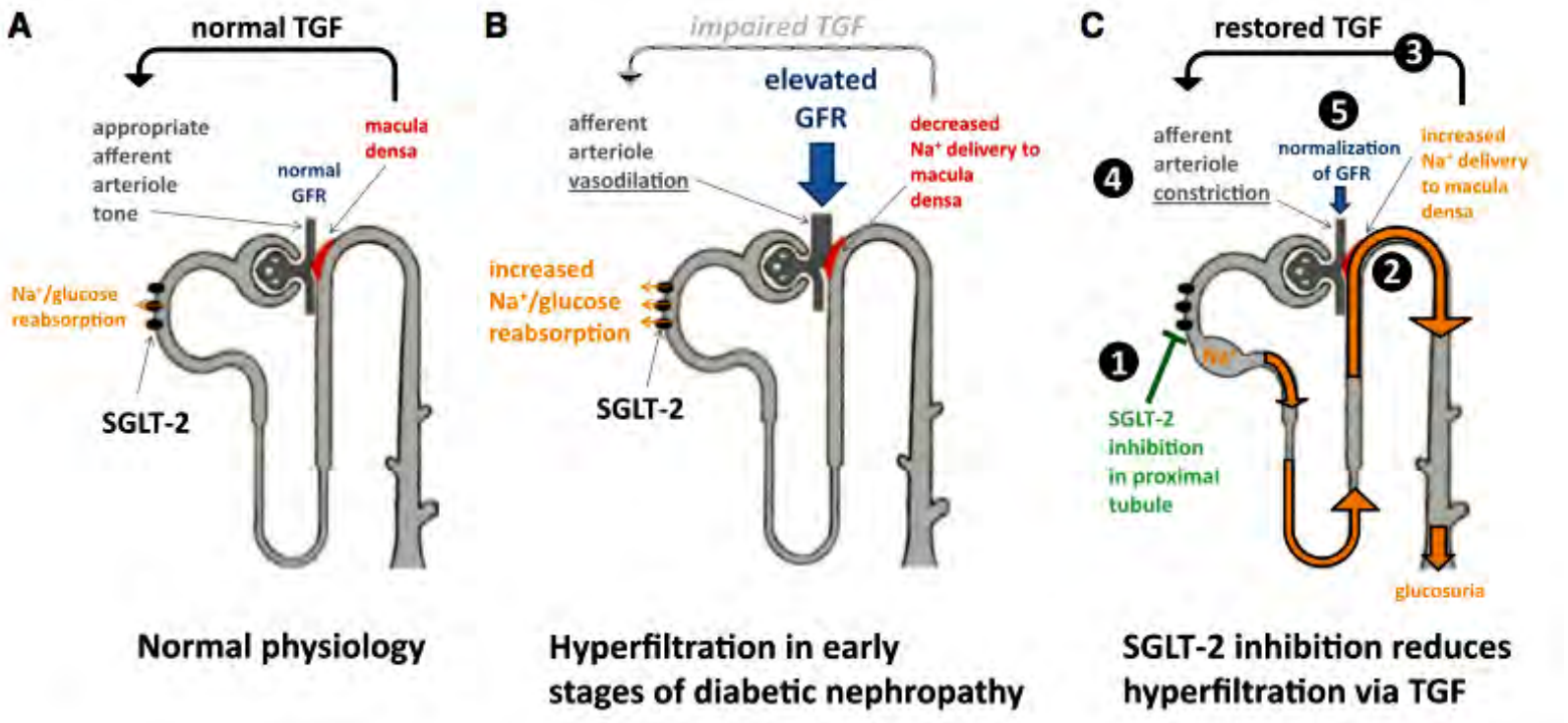
- ✓ Similar impact of Empagliflozin on the primary end-point in patients with CKD compared to those without it:
  - MACE — HR 0.88 (**12%** vs. 14% reduction)
  - CV death — HR 0.78 (**22%** vs. 38% reduction)
  - HF — HR 0.59 (**41%** vs. 35% reduction)

Zinman B at al. N Engl J Med. 2015 Nov 26;373(22):2117-28
Fitchett D et al. Eur Heart J. 2016 May 14;37(19):1526-34



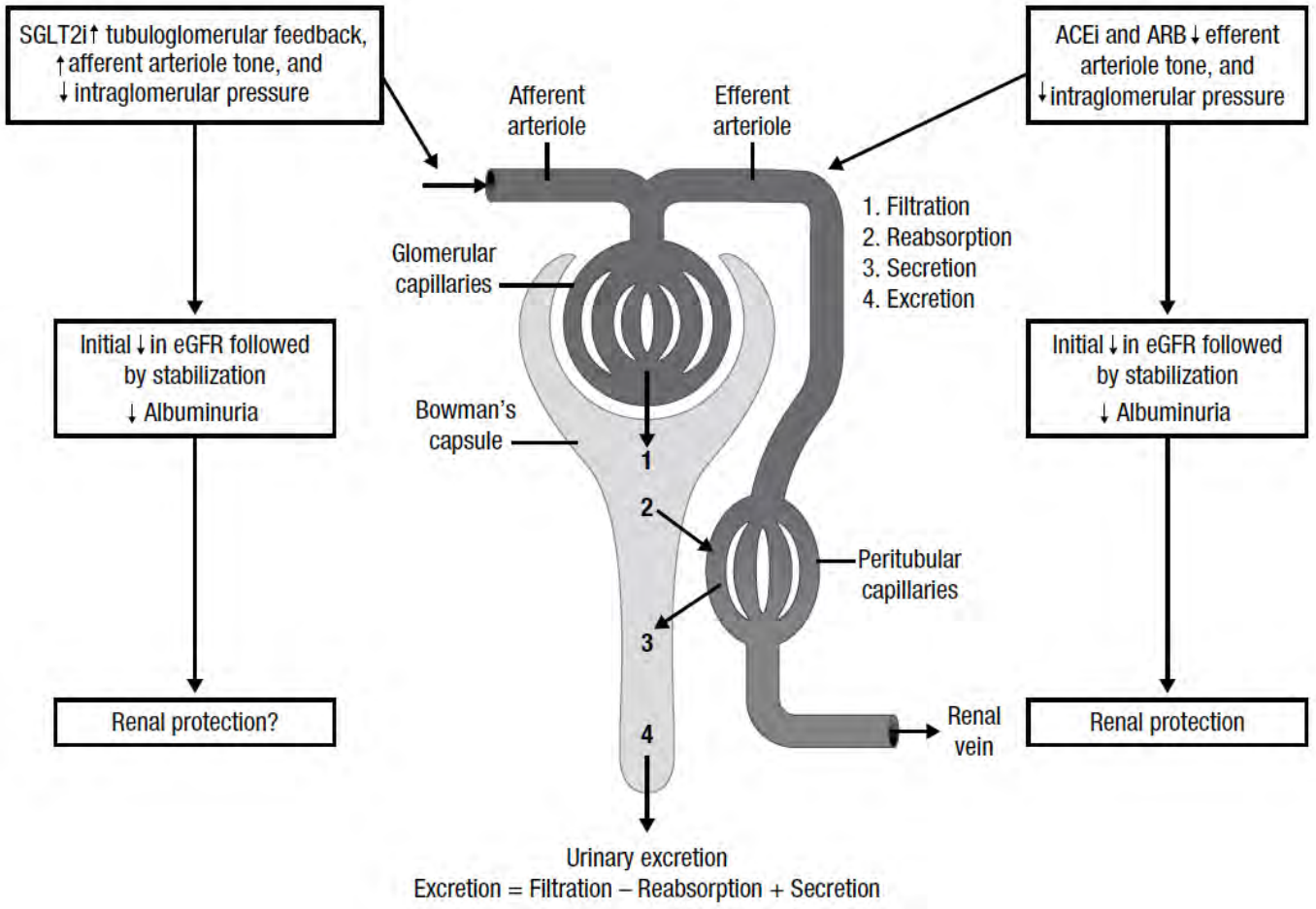

Heerspink IJL et al. Circulation. 2016; 134:752–772

# TUBULOGLOMERULAR FEEDBACK (TGF)




Cherney D et al. Circulation. 2014; 129:587-597

# TUBULOGLOMERULAR FEEDBACK (TGF)



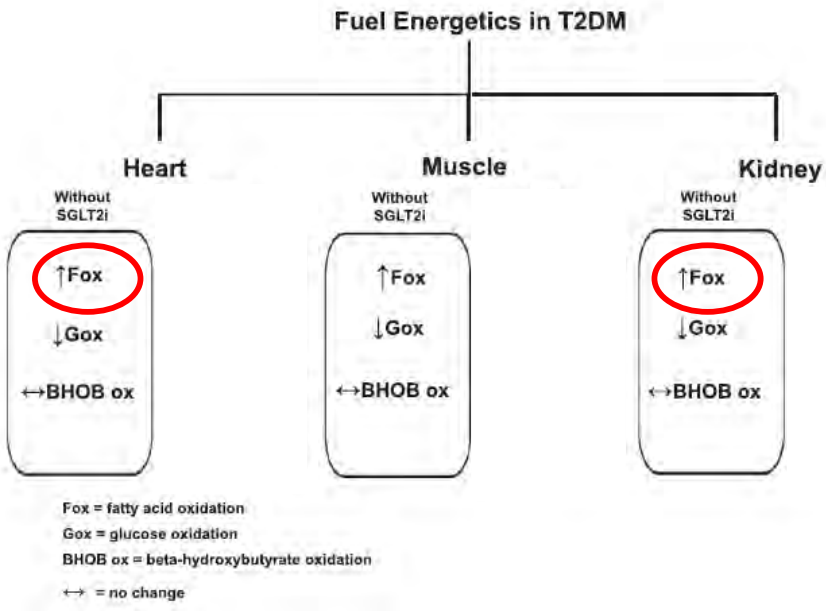

Perkovic V et al. Curr Med Res Opin. 2015; 12:2219-2231

# A new Hypothesis: "Thrifty Substrate"

## Fuel Energetics in Healthy Heart and Kidney

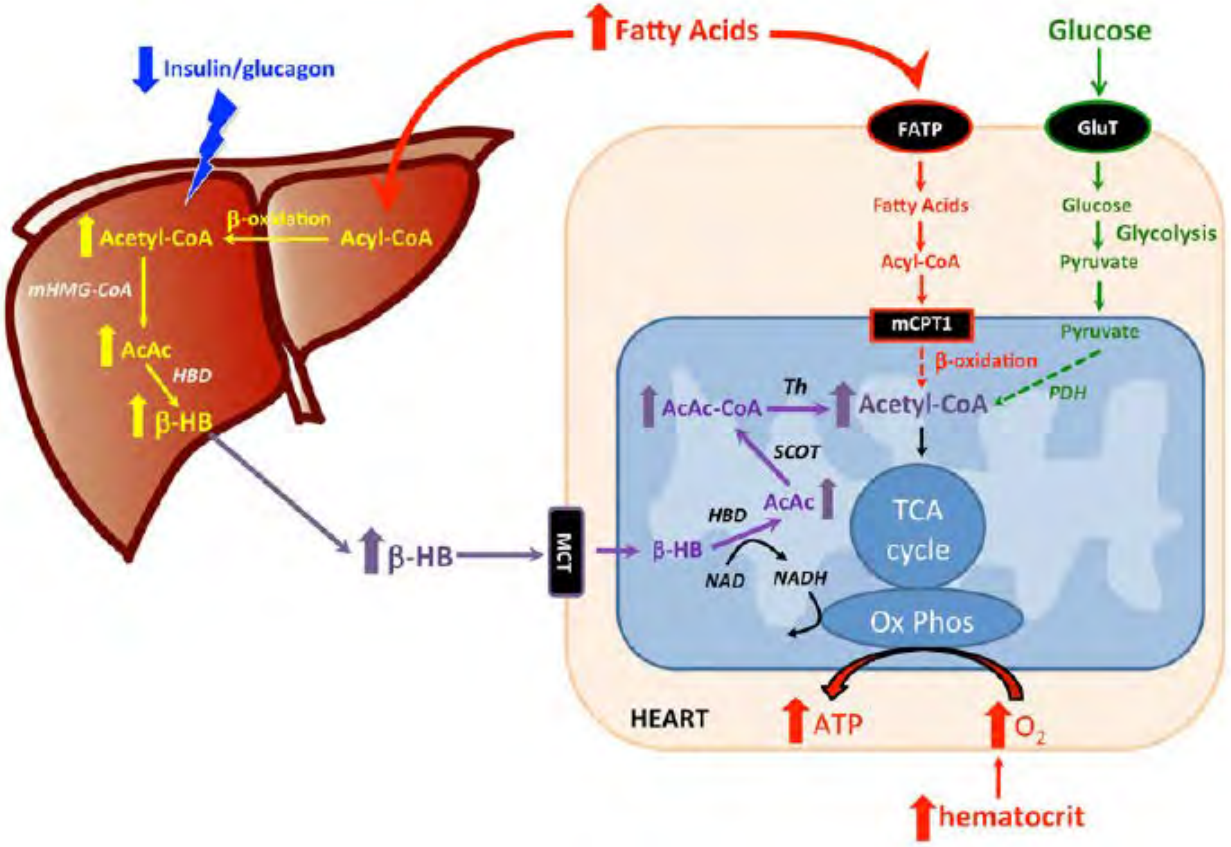
- ➢ Mitochondrial oxidative metabolism
- 60% FFAs → fasting state
- 30% glucose → fed state
- <10% lactate → exercise, hypoxic condition
- ketones, amino acids

} METABOLIC FLEXIBILITY




Ferrannini E et al. Diabetes Care. 2016; 39:1108–1114
Mudaliar S et al. Diabetes Care. 2016; 39:1115–1122

# A new Hypothesis: “Thrifty Substrate”




Ferrannini E et al. Diabetes Care. 2016; 39:1108–1114

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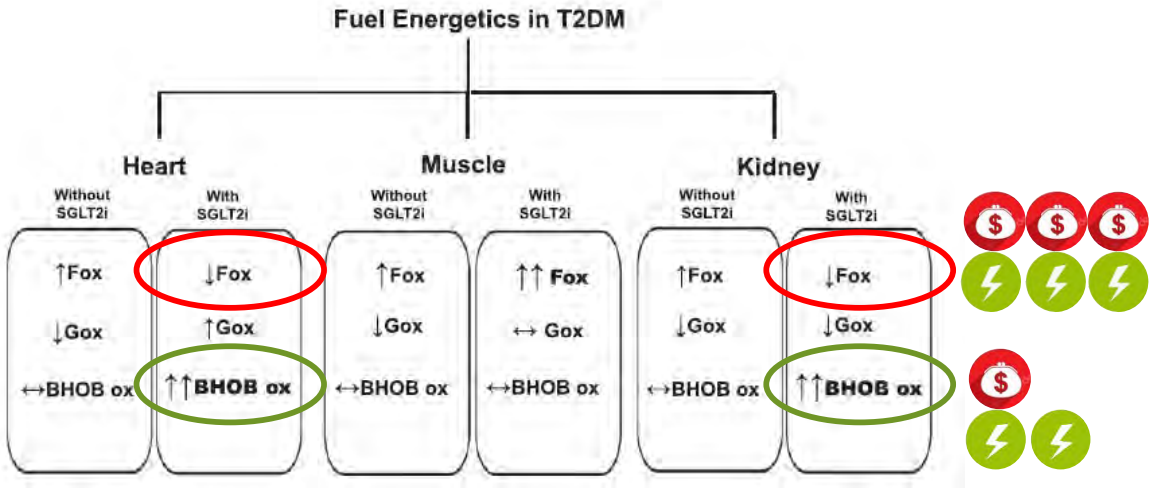
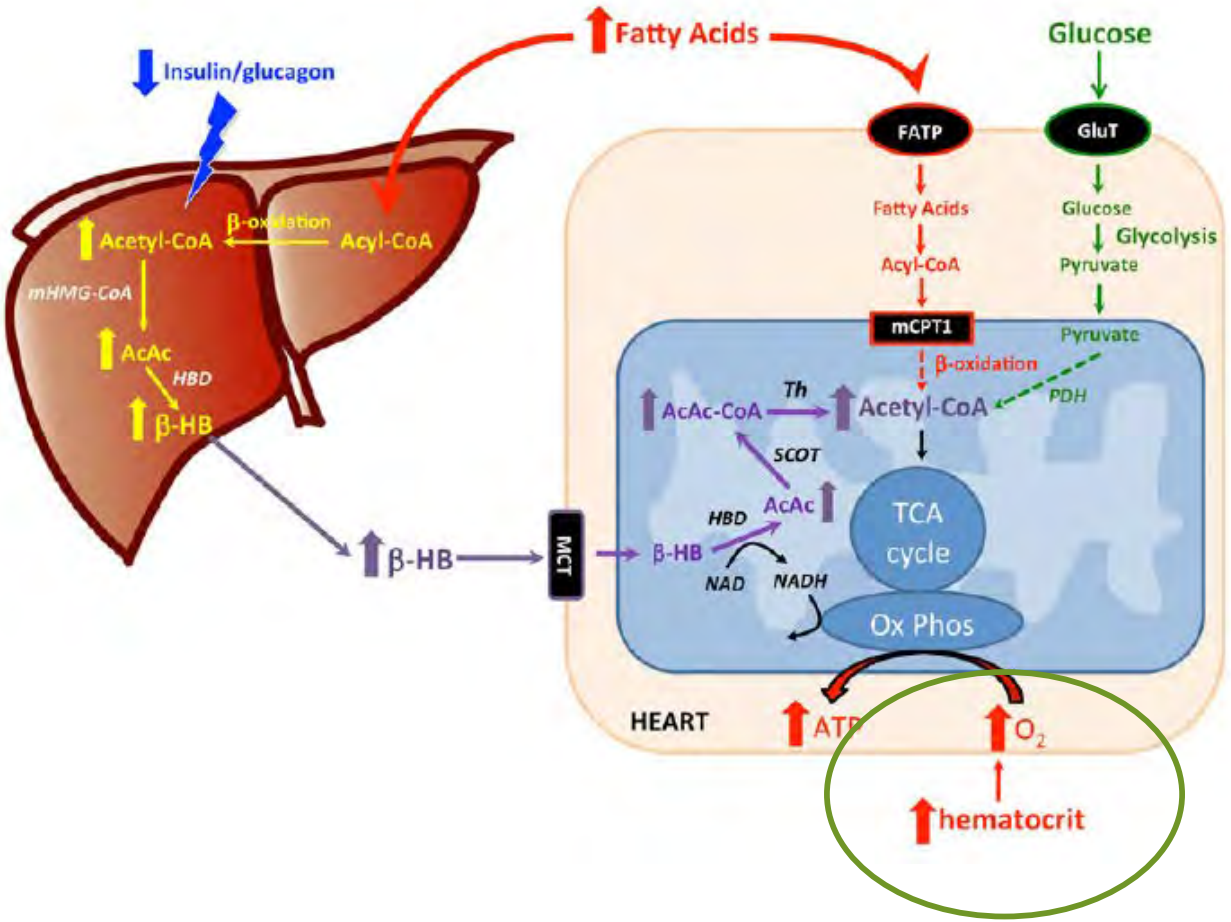



**Table 3—Fuel energetics of various substrates**

| Substrate | P/O ratio*** | Energy liberated, kcal/mol of 2-carbon units |
|---|---|---|
| Glucose | 2.58 | 223.6 |
| Pyruvate | 2.50* | 185.7* |
| Palmitate | 2.33** | 298** |
| BHOB | 2.50* | 243.6* |


Ferrannini E et al. Diabetes Care. 2016; 39:1108–1114
Mudaliar S et al. Diabetes Care. 2016; 39:1115–1122

# A new Hypothesis: “Thrifty Substrate”




Ferrannini E et al. Diabetes Care. 2016; 39:1108–1114

# CONCLUSIONS

**Pathogenic therapies → controversial results**

- New target
- New molecules

**Anti-hyperglycemic treatments → promising results**

- Mechanism(s)?