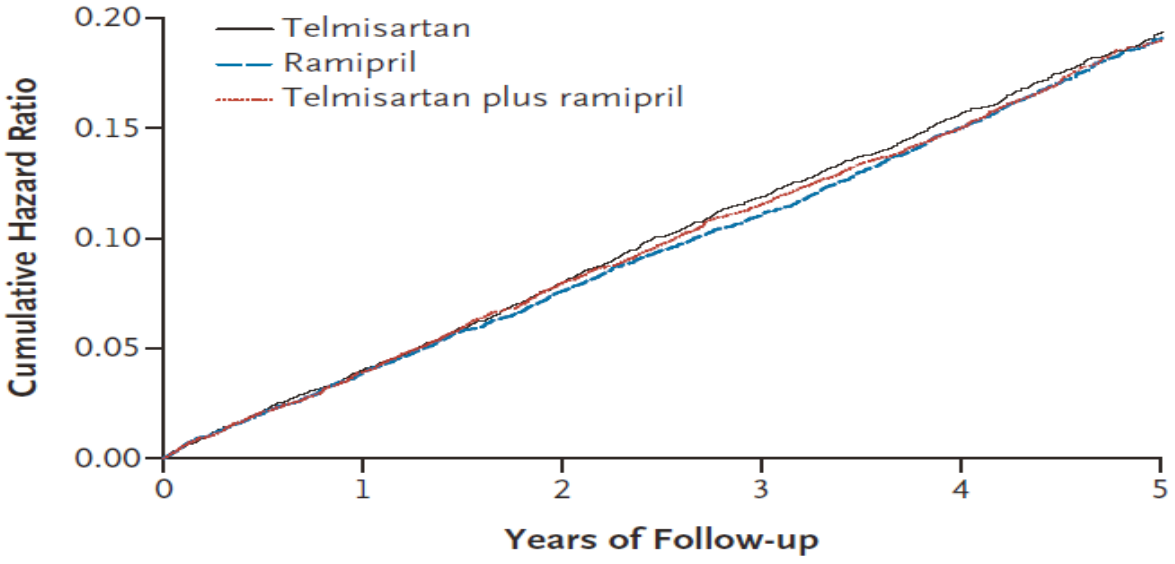
Therapeutic Approaches to Chronic Kidney Disease—Beyond the RAS

- Despite improvements in glycemia and BP control, and the efficacy of RAS blockade, a substantial number of patients will progress to ESRD.
- This finding is consistent that key pathogenetic mechanisms leading to progression of renal disease are not modified or inactivated by current therapeutic approaches.
- Understanding the key mechanisms leading to progressive CKD and developing nephroprotective agents is critical to slowing the progression of this deadly process.

Nat Rev Nephrol 2014;10:325-346

ON-TARGET Trial: Dual RAS Therapy with Ramipril and Telmisartan Failed to Decrease Vascular Events



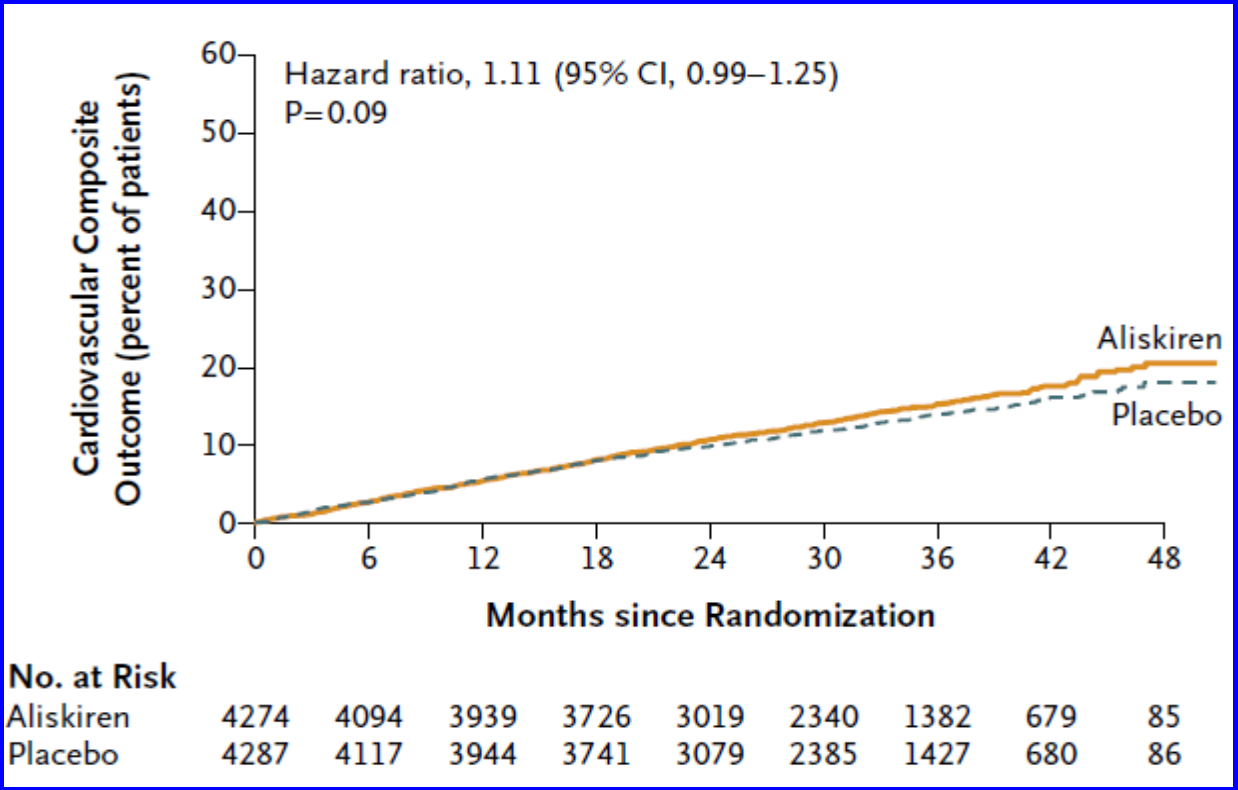
No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

Baseline UACR 929 mg/g CR

FAILED

N Engl J Med 2008;358:1547-1559

ALTITUDE Trial: Dual RAAS Therapy with Aliskiren and ACEi/ARB Failed to Decrease Vascular Events

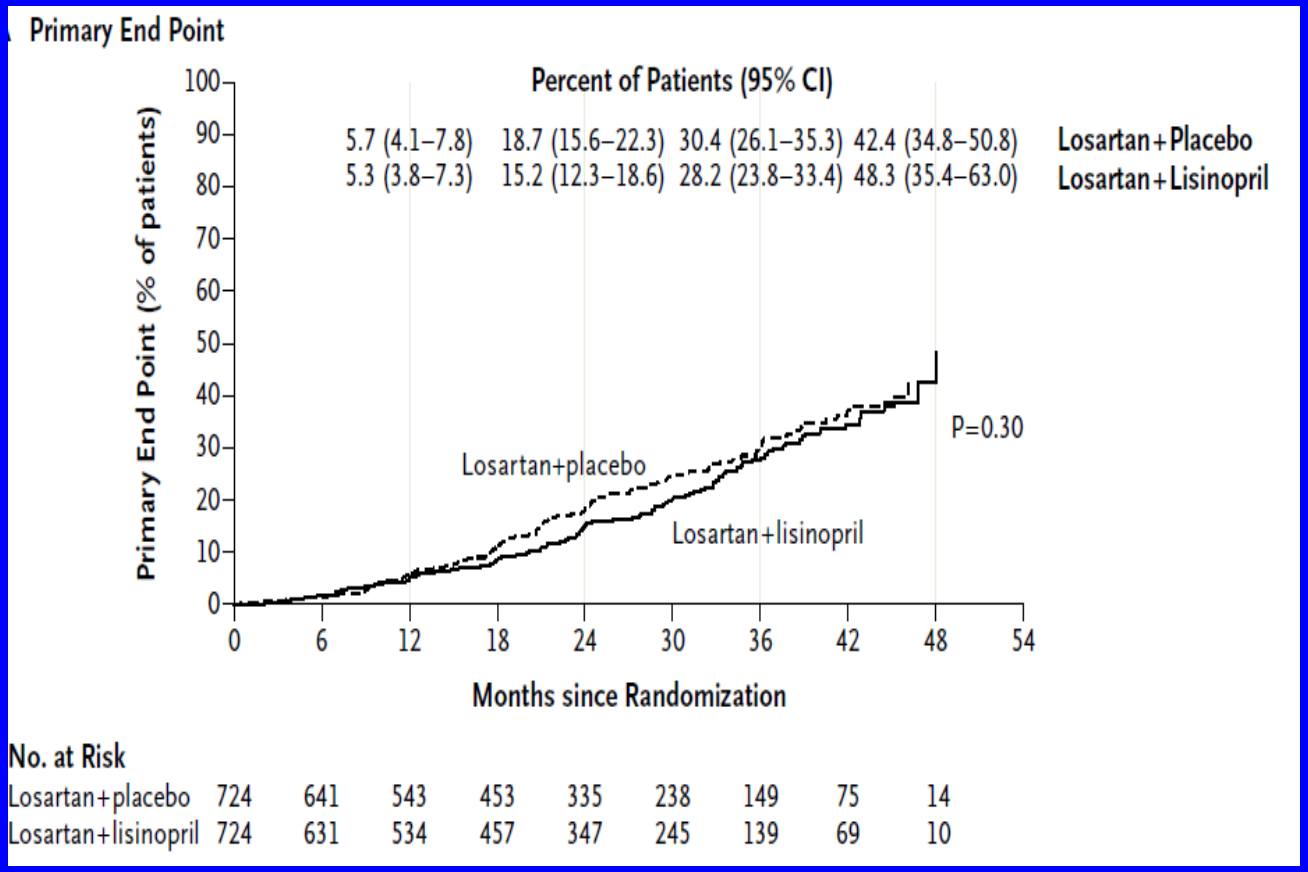


Baseline UACR 206 mg/g CR

FAILED

N Engl J Med 2012;367:2204-2213

VA-NEPHRON-D Trial: Dual RAAS Therapy with Losartan and Lisinopril Did Not Provide an Overall Clinical Benefit

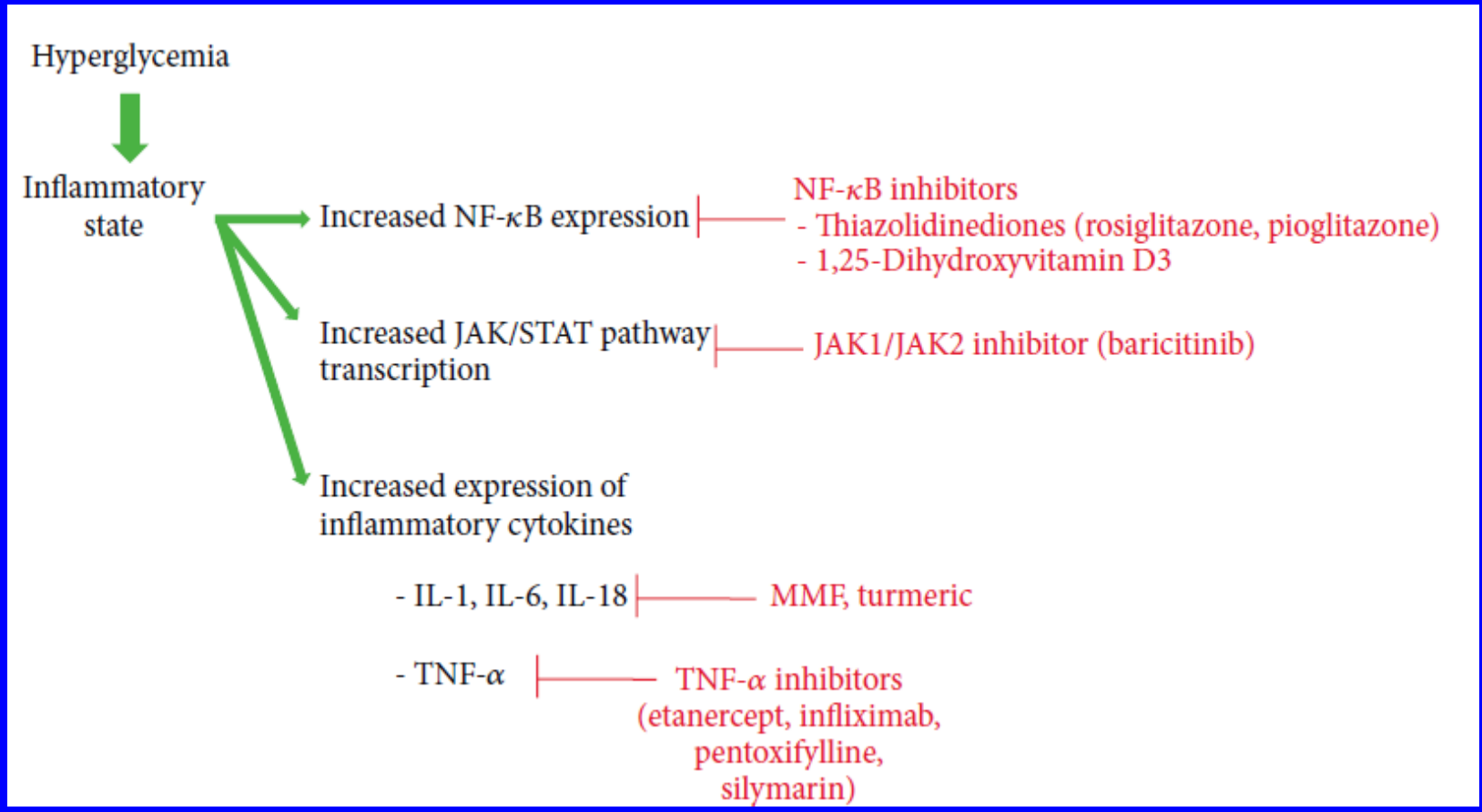


FAILED

Baseline UACR 862 mg/g CR

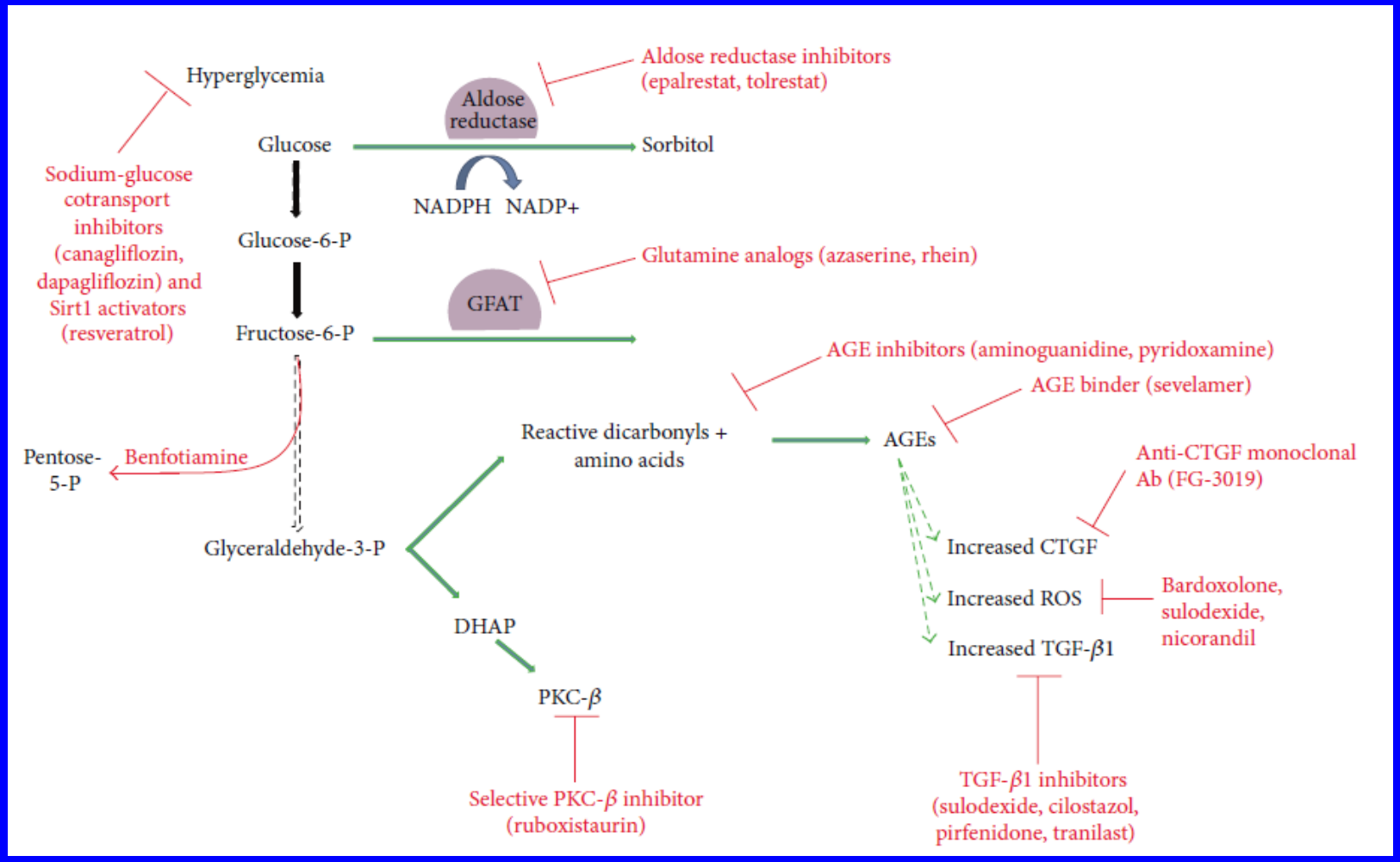
N Engl J Med 2013;369:1892-1903

Therapeutics Identified in the Inflammatory Pathway



Journal of Diabetes Research Volume 2015, Article ID 697010, 16 pages

Therapeutic Agents Identified in the Metabolic and Alternative Pathways



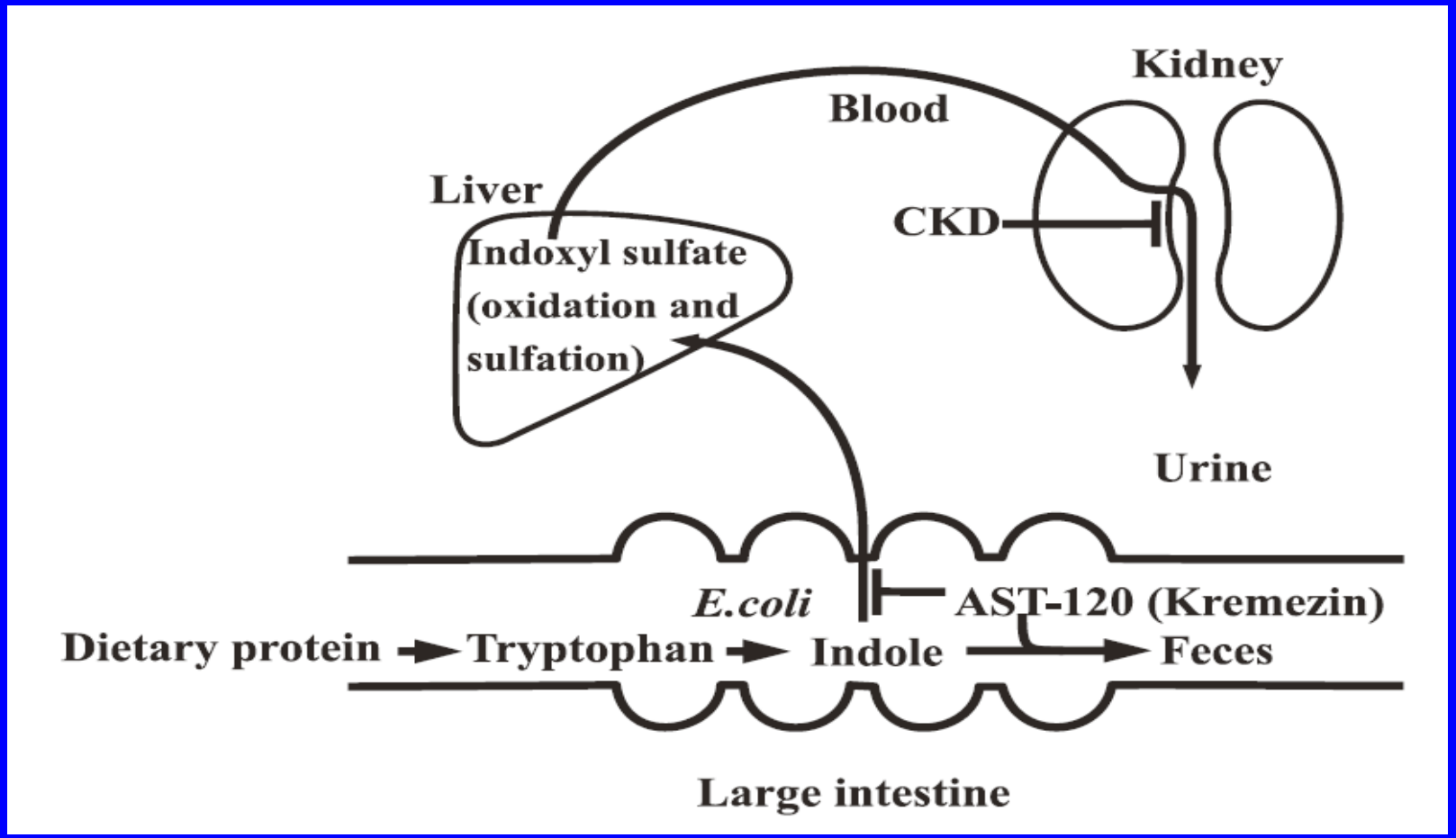
Journal of Diabetes Research Volume 2015, Article ID 697010, 16 pages

Indoxyl Sulfate

- Indoxyl sulfate is derived from dietary proteins
- Uremic toxin which stimulates glomerular sclerosis and interstitial fibrosis
- Increases reactive oxygen species production in tubular cells and increases NAD(P)H oxidase activity in endothelial cells
- Orally administered spherical carbon adsorbent AST-120 reduces “uremic toxins”, like indoxyl sulfate, and is used in patients with CRF

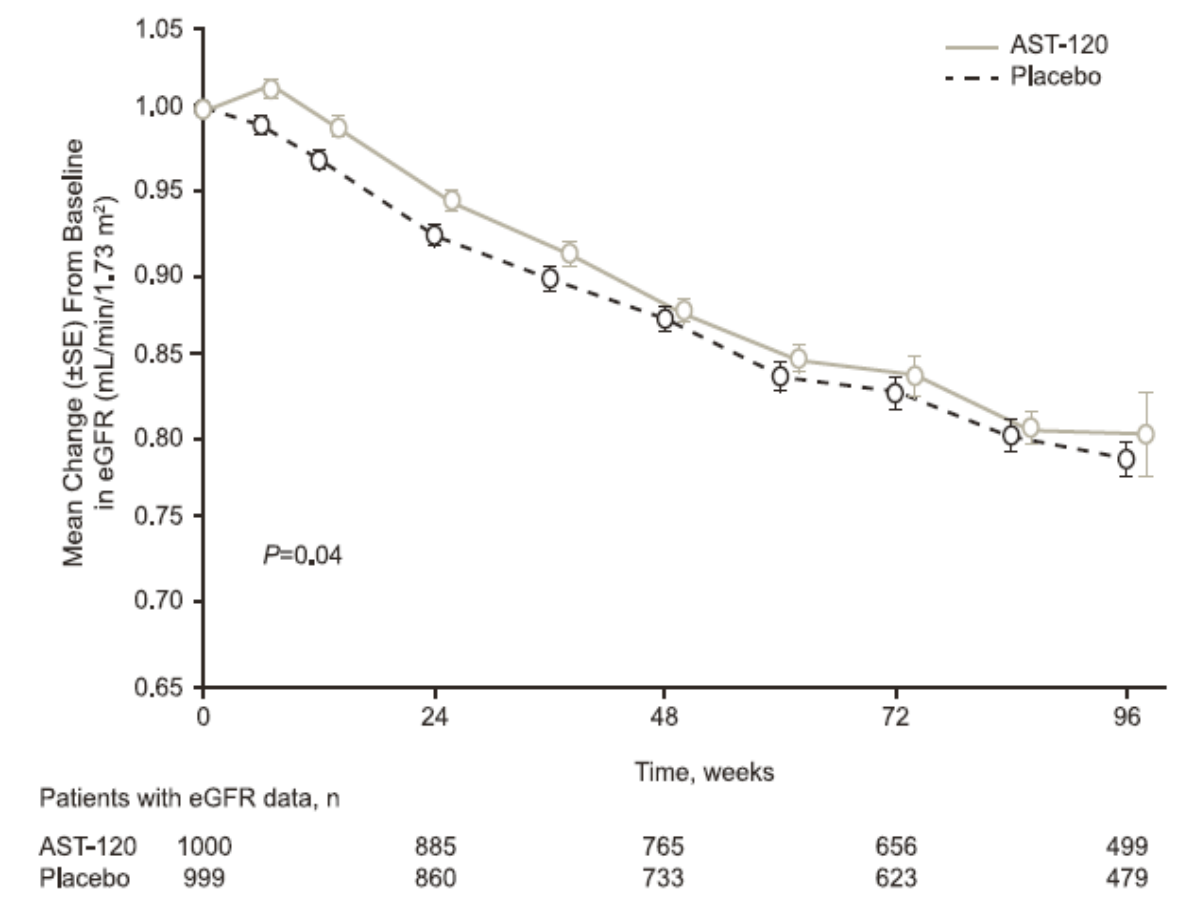
Nagoya J Med Sci 2010;72.1-11

Metabolism of Indoxyl Sulfate and Effect of AST-120



Nagoya J Med Sci 2010;72:1-11

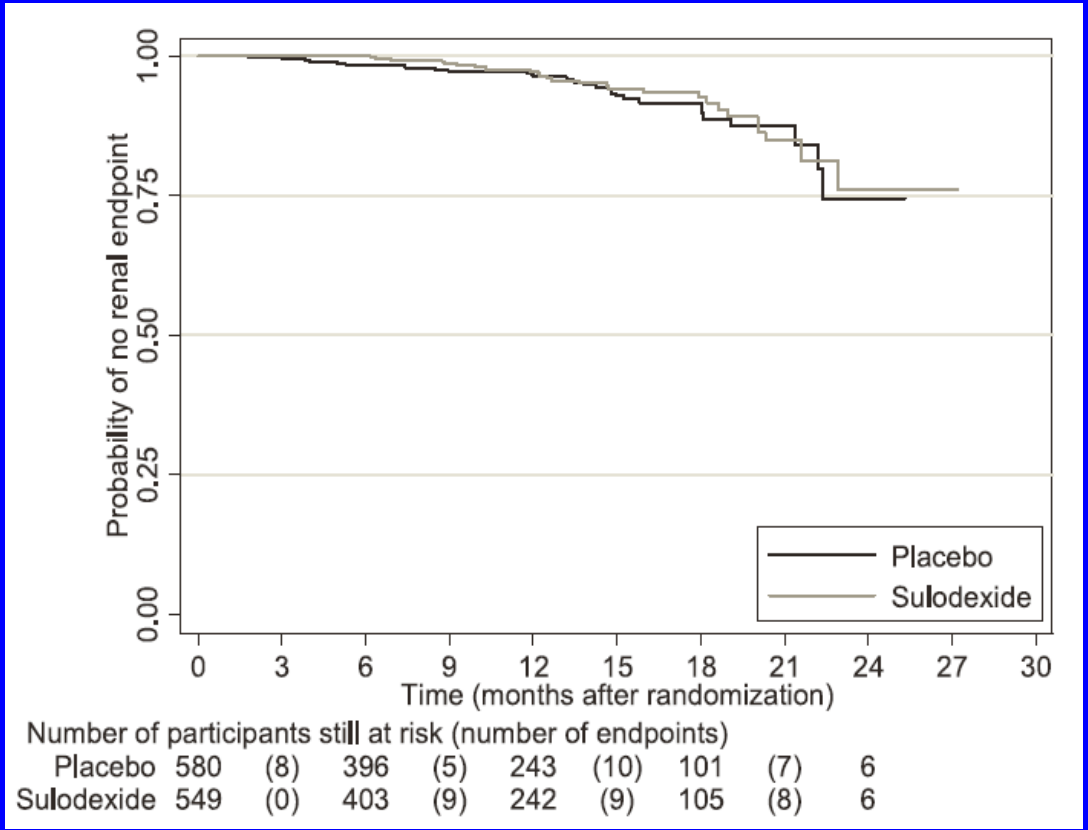
EPPIC Trials of AST-120:
NO Additional Benefit to Standard of Care in CKD



FAILED

J Am Soc Nephrol 2015;26:1732–1746

SUN Trial: Sulodexide (Heparan and Chondroitin Sulfates) Failed to Demonstrate Renoprotection in Overt Type 2 Diabetic Nephropathy

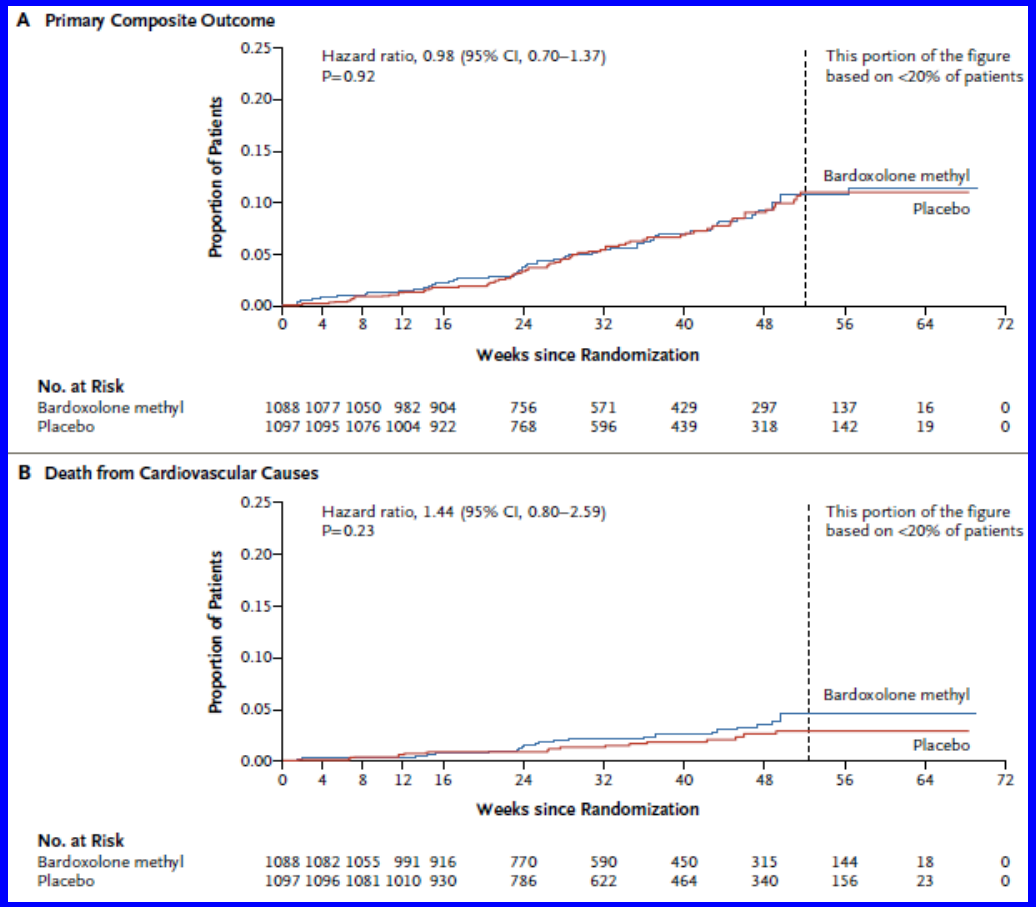


Baseline UACR ~1000 mg/g CR

FAILED

J Am Soc Nephrol 2012;23:123–130

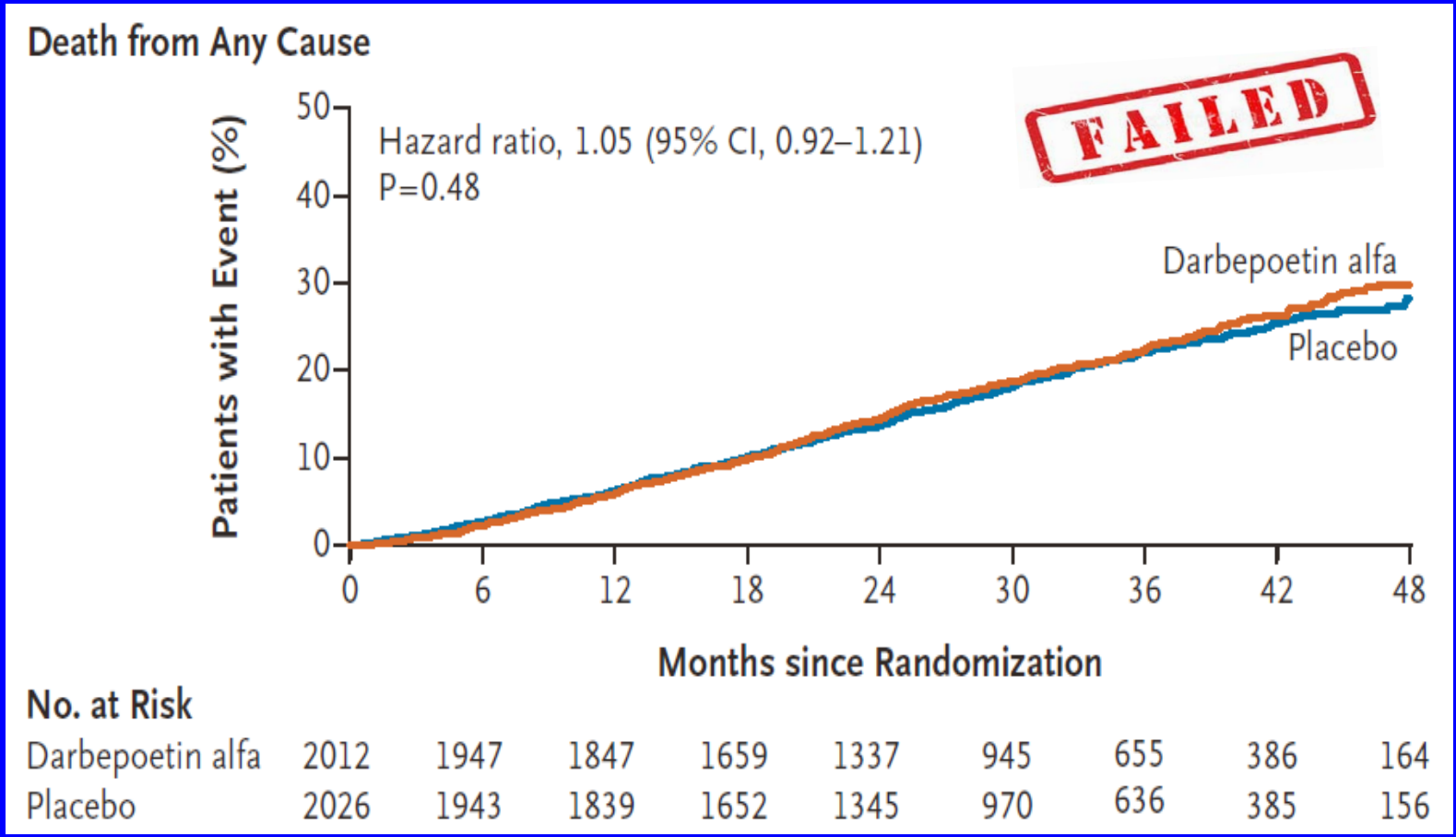
BEACON Study: Bardoxolone Methyl Increased CV Deaths in Type 2 Diabetes and Stage 4 CKD





N Engl J Med 2013;369:2492-2503

TREAT Trial: Darbepoetin Alfa Failed to Demonstrate Renoprotection in Overt Type 2 Diabetic Nephropathy



N Engl J Med 2009;361:2019-2032