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ICDM

Review of the Clinical Trials on Vascular Complications of Diabetes

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Disclosures

- No conflicts of interest

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- Diabetic Nephropathy
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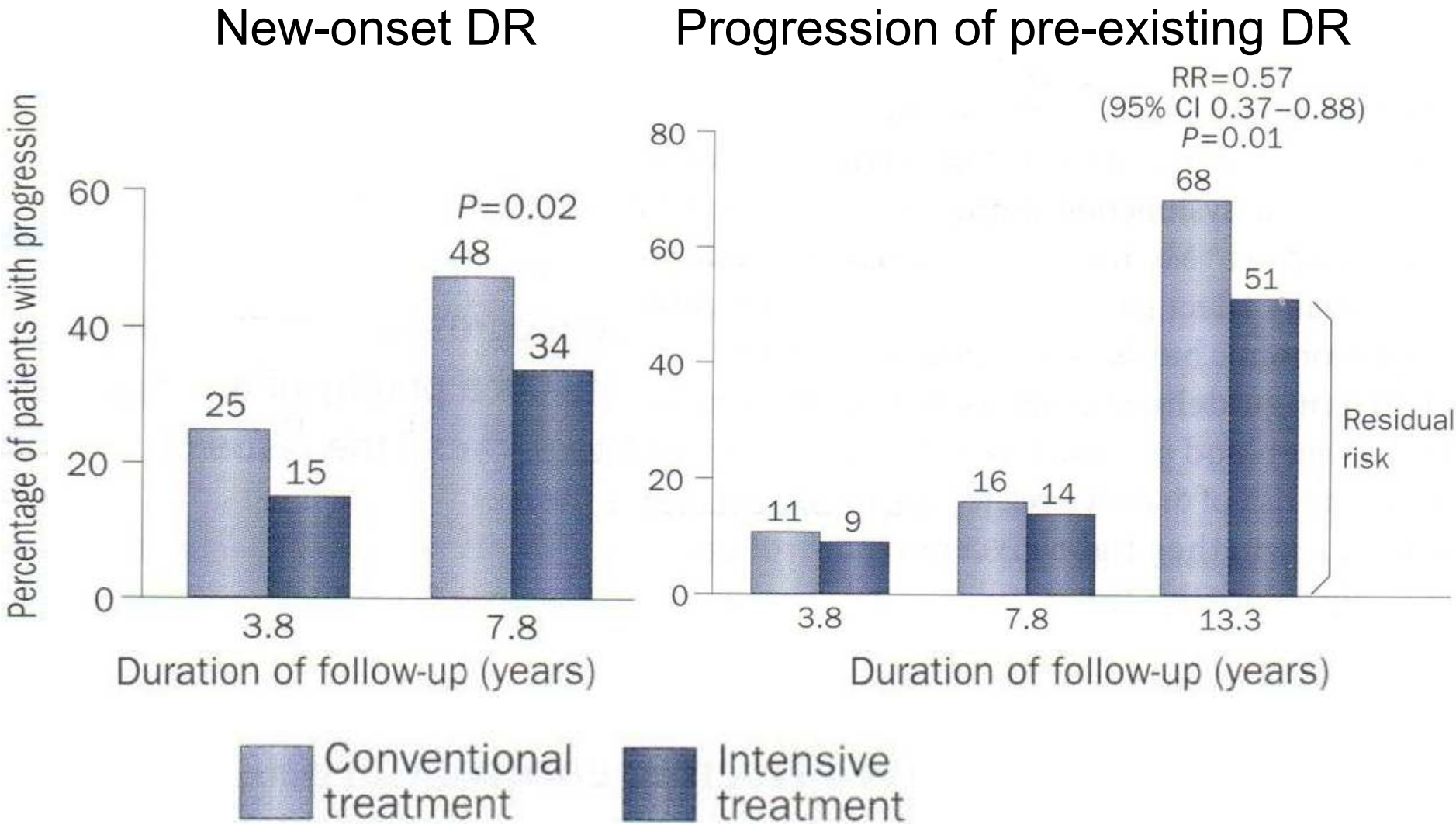
Introduction

- The vascular complications of diabetes are among the most serious manifestations of diabetes mellitus

- Well-established clinical advances in preventing vascular complications of diabetes include intensive blood glucose lowering, antihypertensive medicine, panretinal photocoagulation, and statin therapy

- Despite these advances, diabetes complications remain a serious public health problem

Steno-2 : Risk of Diabetic Retinopathy



N Engl J Med, 2008
Nat Rev Endocrinol, 2010

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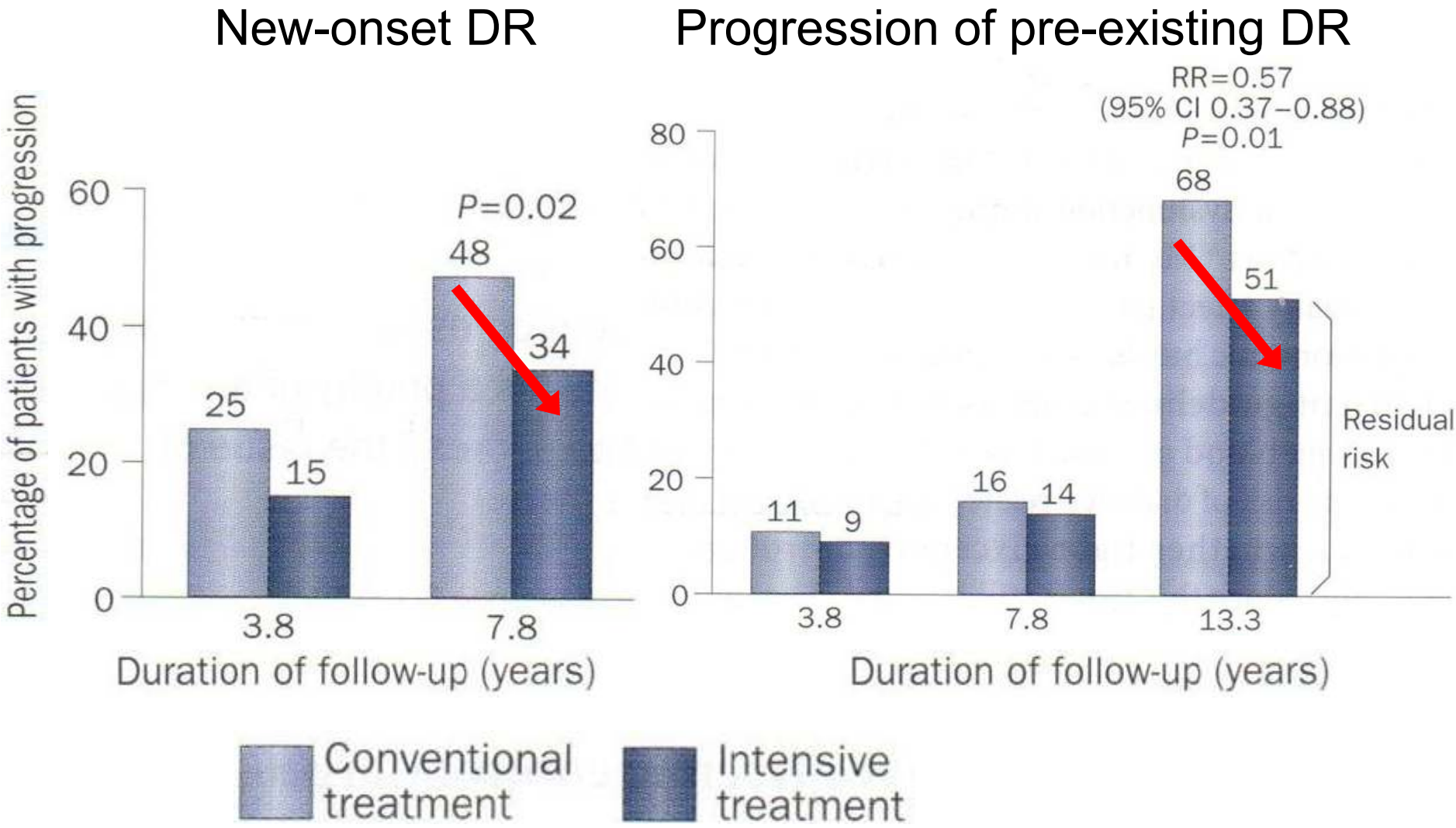

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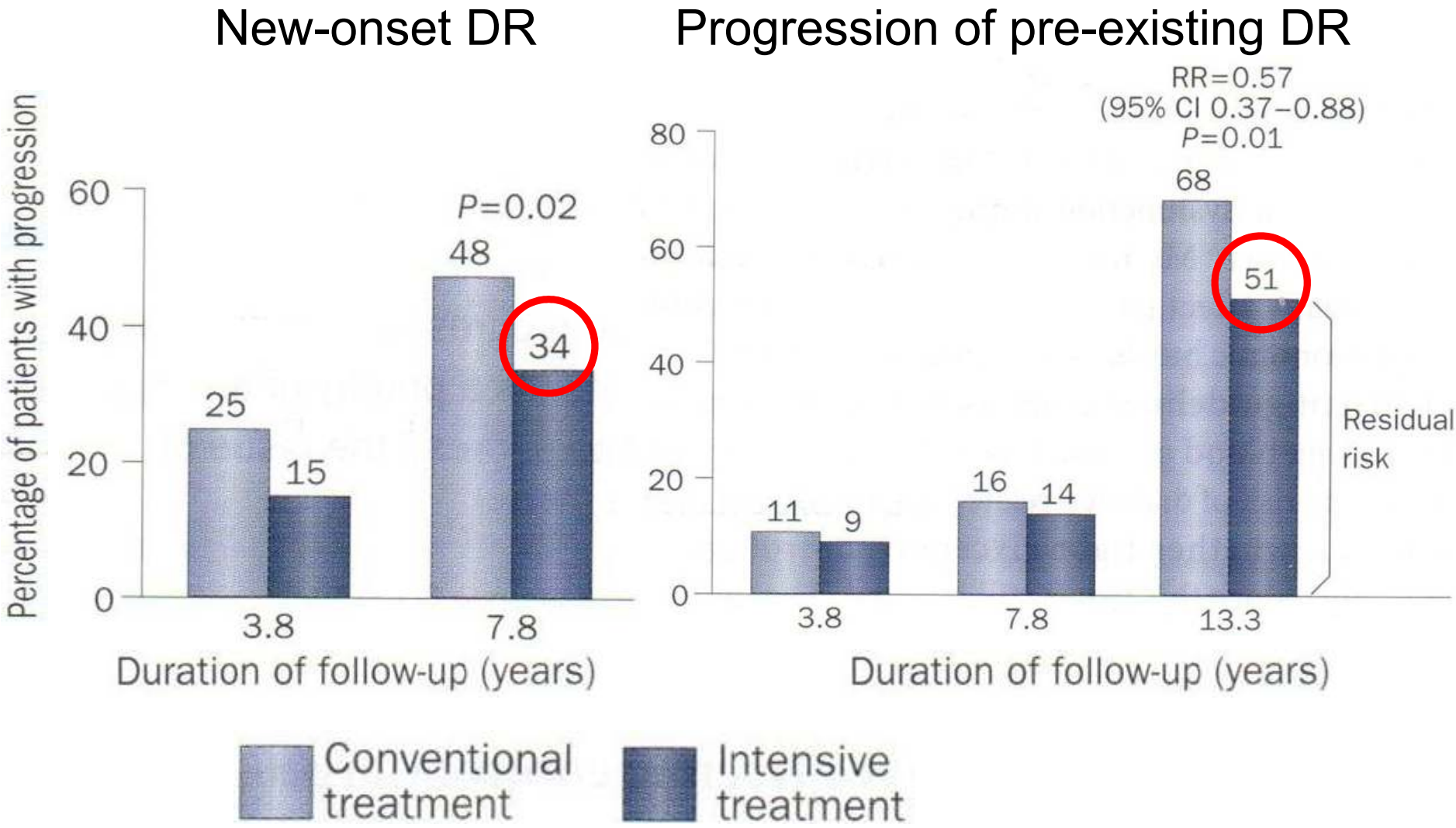

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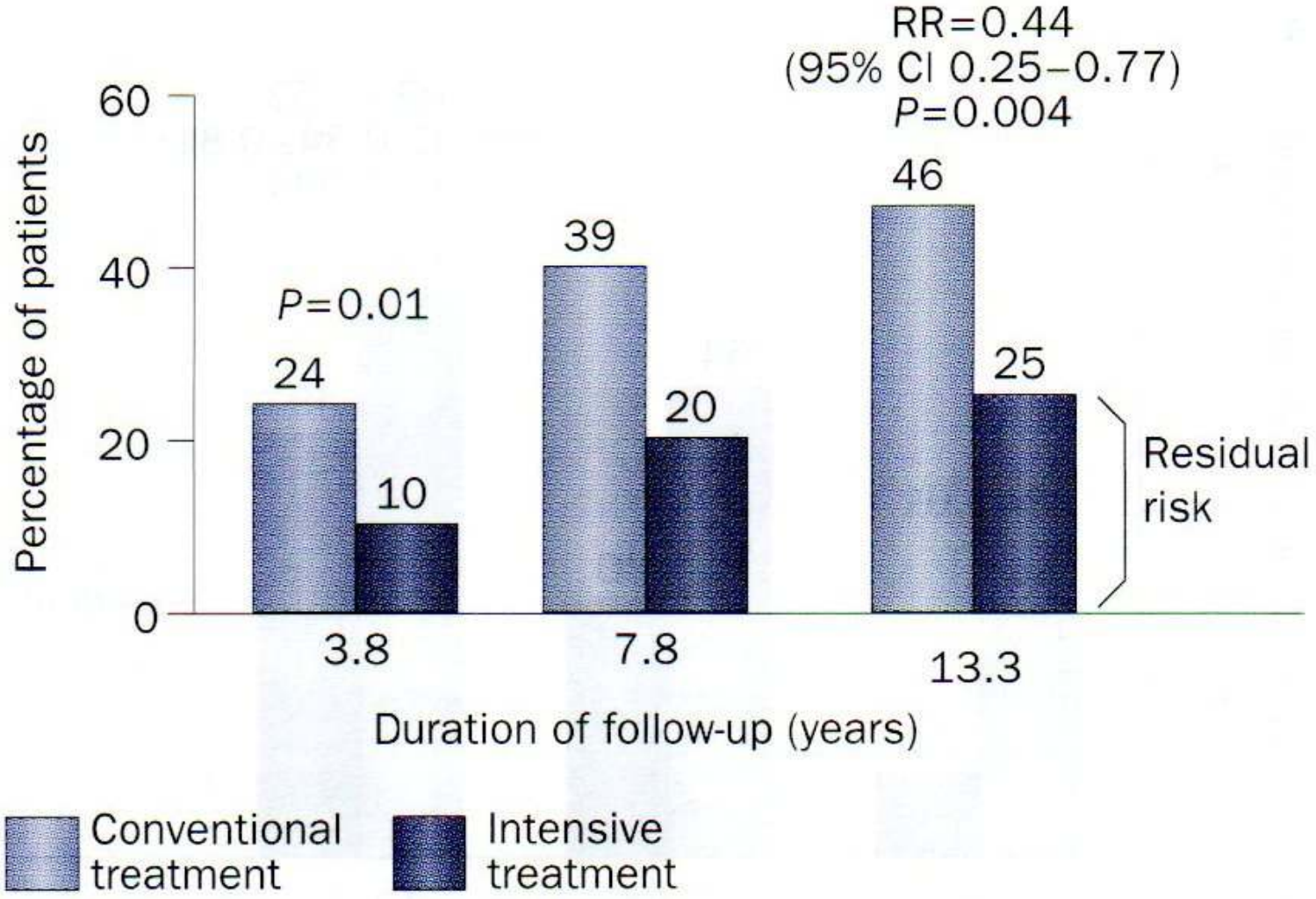
Steno-2 : Risk of Diabetic Nephropathy

Risk of new-onset diabetic nephropathy



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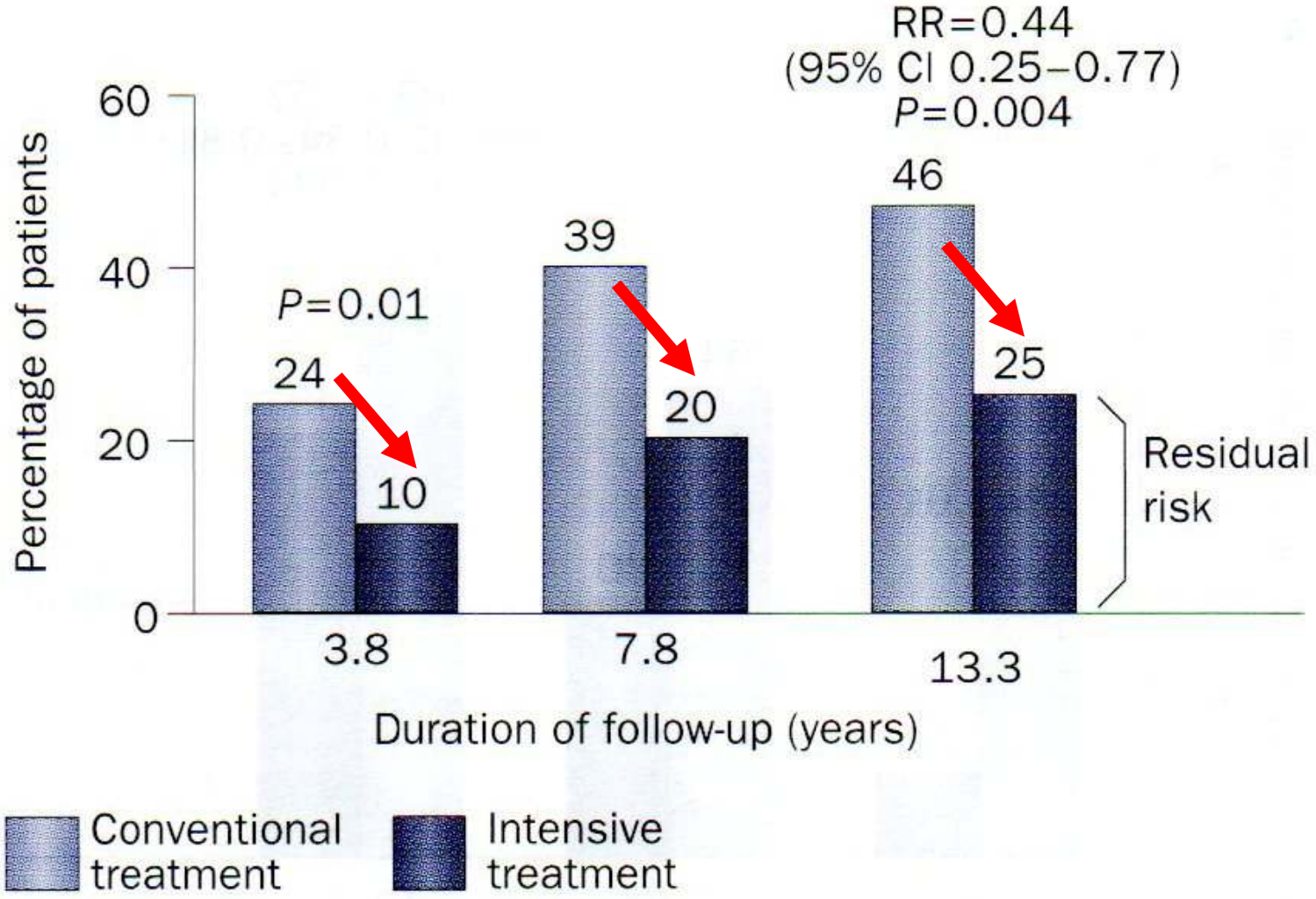

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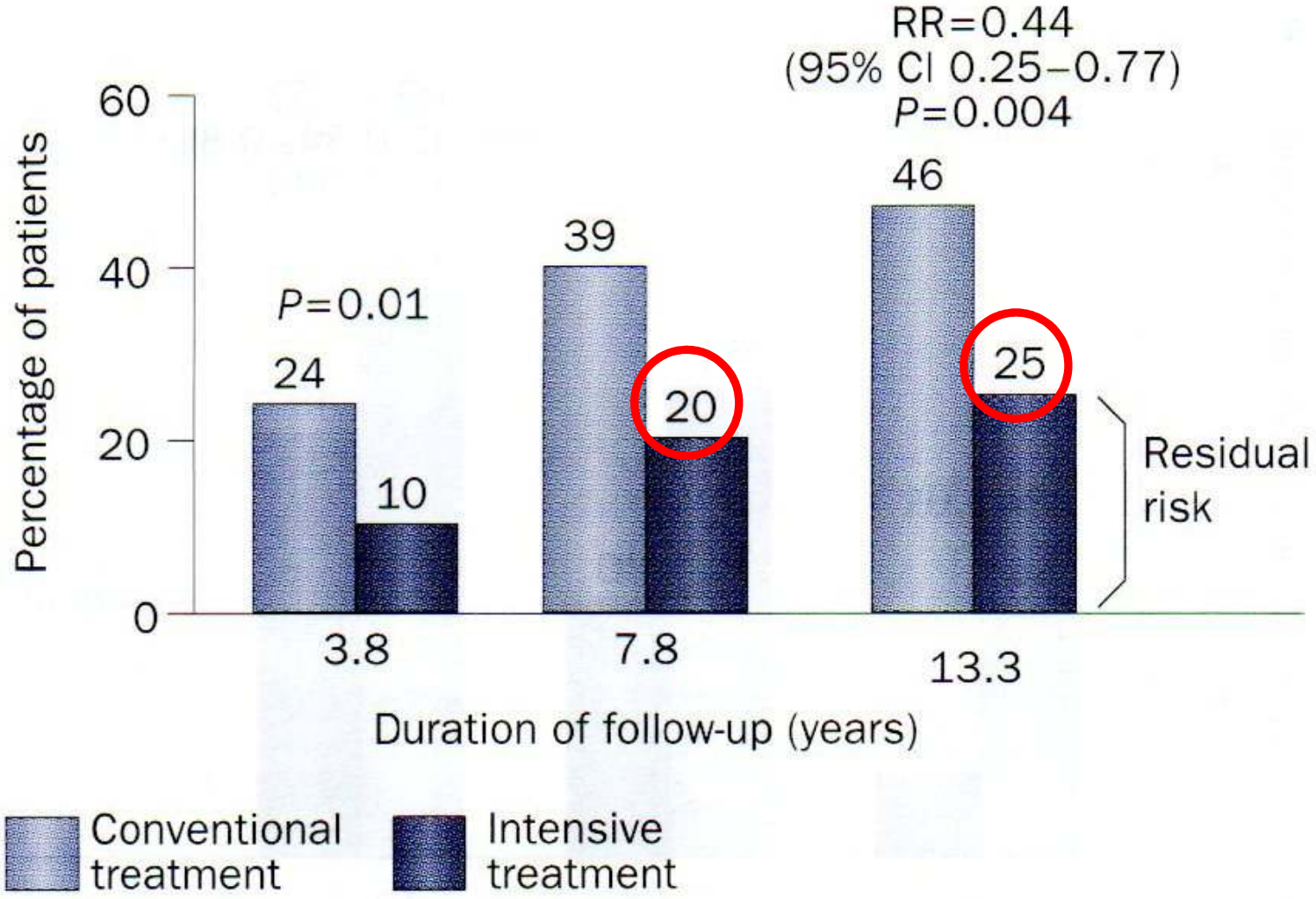
Steno-2 : Risk of Diabetic Nephropathy

Risk of new-onset diabetic nephropathy



N Engl J Med, 2008
Nat Rev Endocrinol, 2010

Atherosclerosis	Diabetic Nephropathy	Diabetic Retinopathy
	Dual blocker – Fail	
Aleglitazar	Protein kinase C-β inhibitors	Plasma Kallikrein Inhibitor
Protein kinase C-δ inhibitors	Bardoxolone methyl	
	Inhibitors of AGE formation	Angiopoietin-2
Canakinumab	Endothelin-receptor antagonists	Intravenous infliximab
Aliskiren Eplerenone	Mineralocorticoid receptor antagonists	CCR2/CCR5 receptor antagonist
Darapladib	CCR2/CCR5 receptor antagonist	

Atherosclerosis

- Atherosclerosis is the primary cause of cardiovascular diseases, and these conditions that affect the cerebral, coronary and peripheral vasculature represent the most common cause of morbidity and mortality in diabetic patients
  - Traditionally, viewed as a passive process of lipid accumulation trapped in the vessel wall resulting formation of an atherosclerotic plaque
  - In the past two to three decades, identified the importance of inflammation as a critical pathway responsible for the initiation and perpetuation of atherosclerosis

WHO, 2012
J Am Coll Cardiol, 2009
Expert Opin. Emerging Drugs, 2013

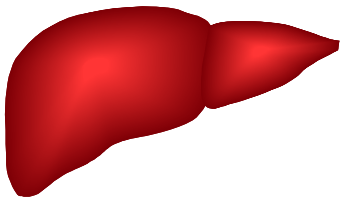
Current Therapy

- Smoking cessation
- Blood glucose control
- Blood pressure control
- Cholesterol management with statin therapy
- Antiplatelet agents
- Renin-angiotensin-aldosterone blockers
- β-adrenergic blockers
- Increased physical activity
- Weight reduction
- Influenza vaccination, depression screening and cardiac rehabilitation

Circulation, 2011

Aleglitazar

- Potent dual PPARα/γ agonist with balanced affinity



↑ Fatty acid uptake

↑ Fatty acid oxidation

↑ ApoA1, HDL

↓ VLDL-TG

↓ Apo-CIII

Anti inflammatory

PPARα

Improve plasma lipid profile

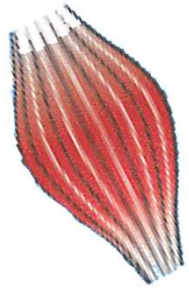
↑ Insulin sensitivity

↑ Beta cell function

↑ Fatty acid uptake

↑ Adiponectin secretion

Anti inflammatory



PPARγ

Improve insulin sensitivity

Trial	Phase	Drug	Study population
NCT01715818	III	Aleglitazar	T2DM, with evidence of prior MI or ischemic stroke ≥ 3 months
NCT01042769	III	Aleglitazar	T2DM, hospitalization for ACS event within 12 wks

AleCardio

- Phase III, double blinded, randomized controlled, multicenter study
- 7226 patients hospitalized for ACS (MI or UA) with T2DM
- Aleglitazar 150µg *vs.* placebo
- Followed-up for at least 2.5 years

Conclusions

✓ improved A1C, TG, and HDL-cholesterol levels

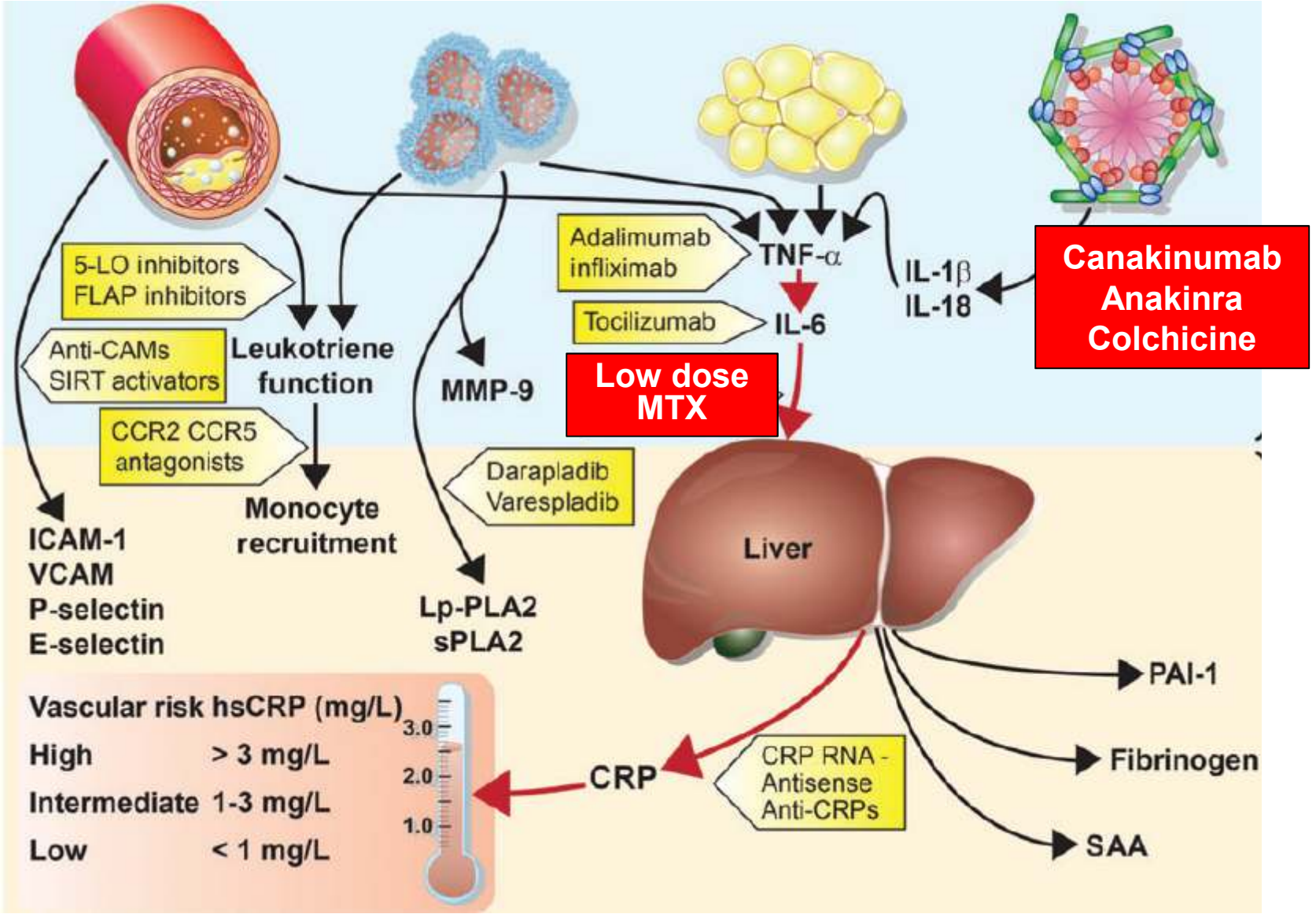
✓ did not reduce the risk of cardiac mortality, MI, or stroke

✓ increased risk of heart failure, renal dysfunction (reversible), bone fractures, and GI hemorrhage

These findings do not support the use of aleglitazar to reduce CV risk

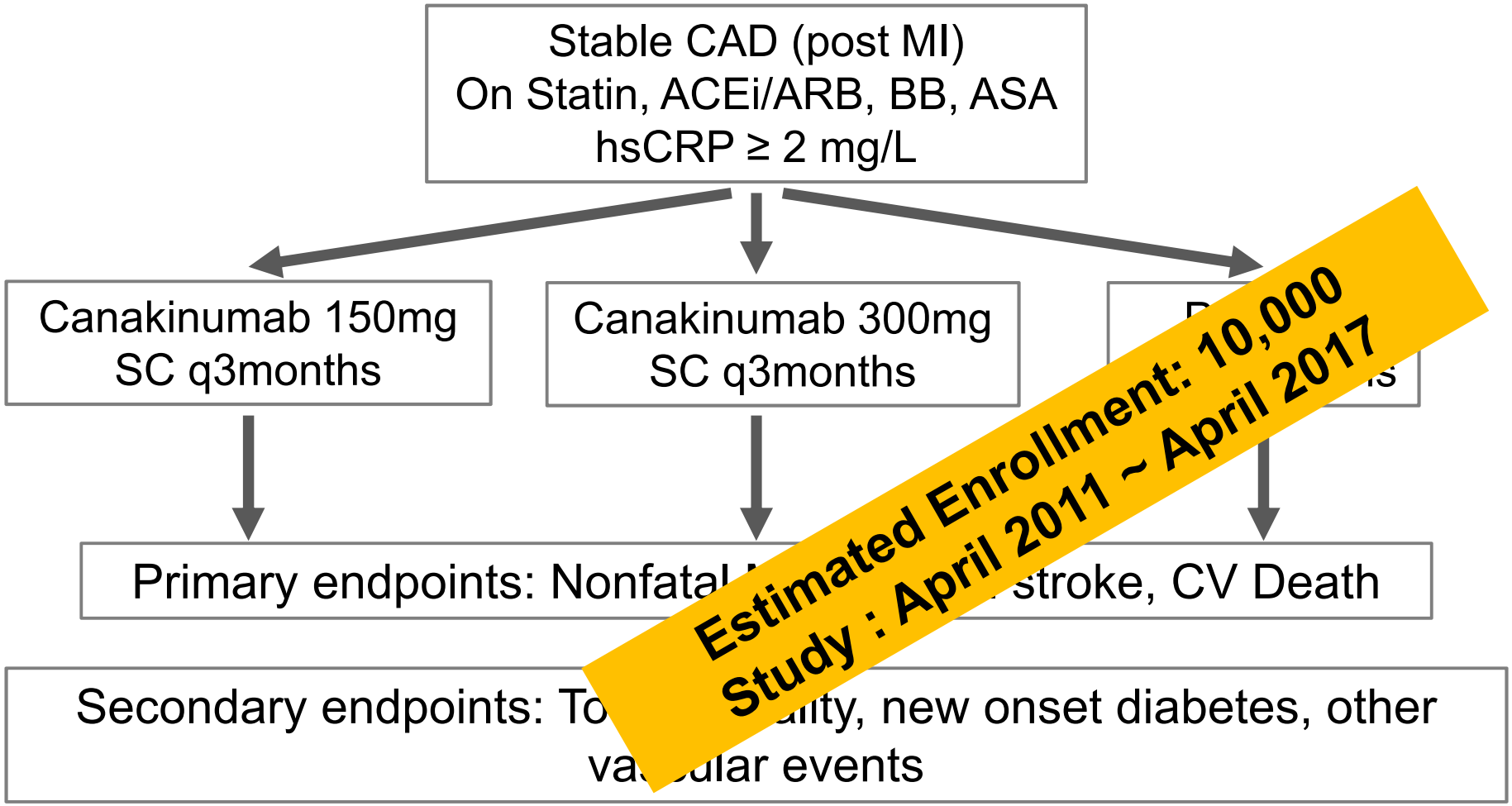
JAMA, 2014

Anti-inflammatory therapy

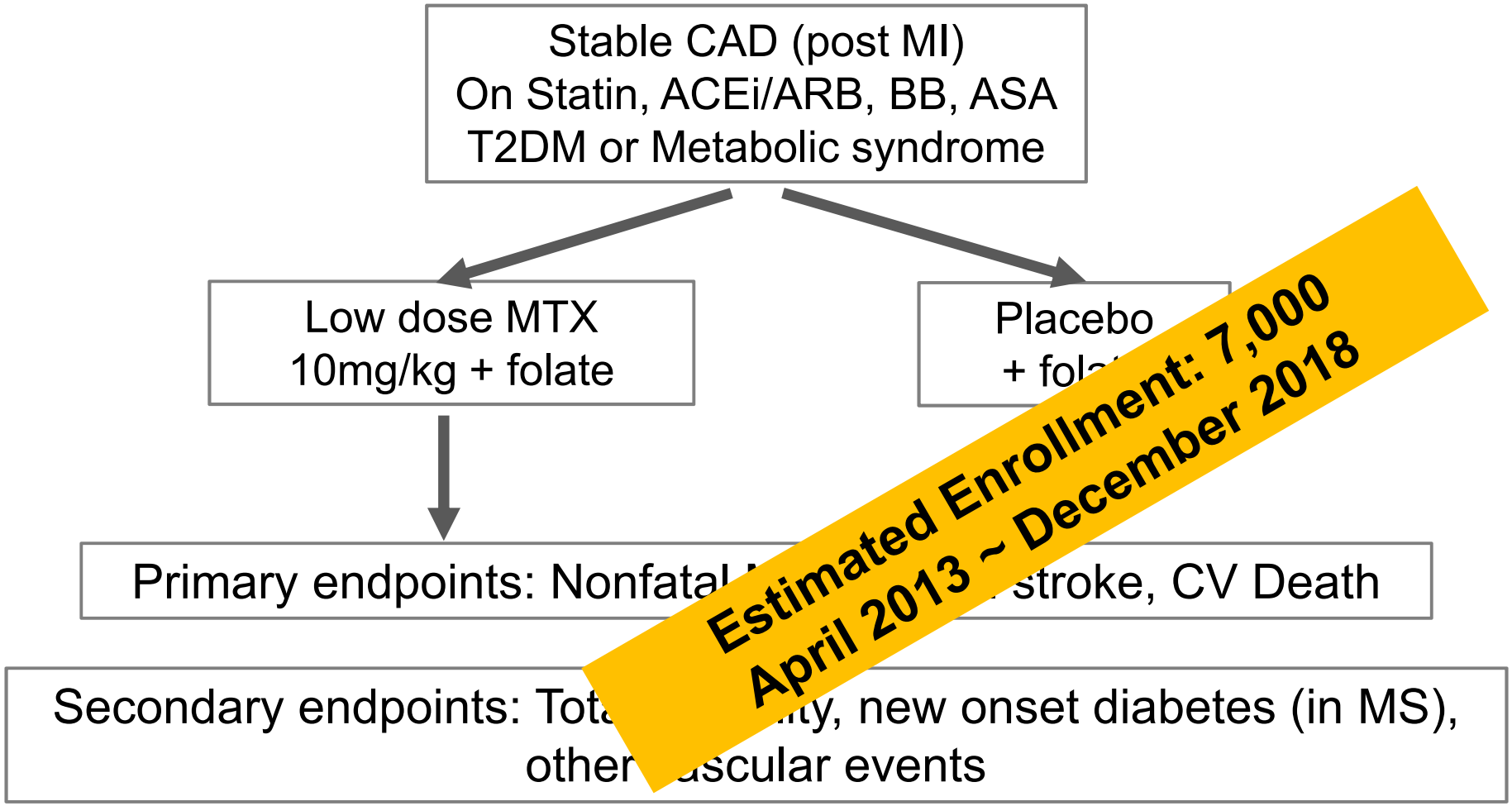


Trial	Phase	Drug	Study population
NCT00605475	II	Canakinumab	T2DM
NCT01068860	II	Canakinumab	T2DM or IGT
NCT00947427	II	Canakinumab	T1DM
NCT00995930	II	Canakinumab	T2DM for ≤ 14 years or IGT, known atherosclerotic disease
NCT01327846	III	Canakinumab	T2DM, spontaneous MI at least 30 days before randomization. hsCRP≥2 mg/L
NCT01594333	III	Methotrexate	T2DM or MS, MI or multi-vessel CAD in the past 5 yrs

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)



Cardiovascular Inflammation Reduction Trial (CIRT)



Studies Assessing CV Outcomes in T2DM Drugs (Recently Completed or Ongoing)

Trial Name	Drug	No.	Timing
DPP-4 Inhibitors			
SAVOR	Saxagliptin	16,492	Began 2010; Complete
EXAMINE	Alogliptin	5384	Began 2009; Complete
TECOS	Sitagliptin	14,000	Began 2008; Ending 2014
CAROLINA	Linagliptin	6000	Began 2010; Ending 2018
CARMELINA	Linagliptin	8300	Began 2013; Ending 2018
GLP-1 Agonists			
ELIXA	Lixisenatide	6000	Began 2010; Ending 2014
EXSCEL	Exenatide	9500	Began 2010; Ending 2017
LEADER	Liraglutide	9340	Began 2010; Ending 2016
REWIND	Dulaglutide	9622	Began 2011; Ending 2019
SGLT-2 Inhibitors			
CANVAS	Canagliflozin	4410	Began 2009; Ending 2018
C-SCADE 8	Empagliflozin	7000	Began 2010; Ending 2018
DECLARE	Dapagliflozin	17,150	Began 2013; Ending 2019

Diabetic Nephropathy

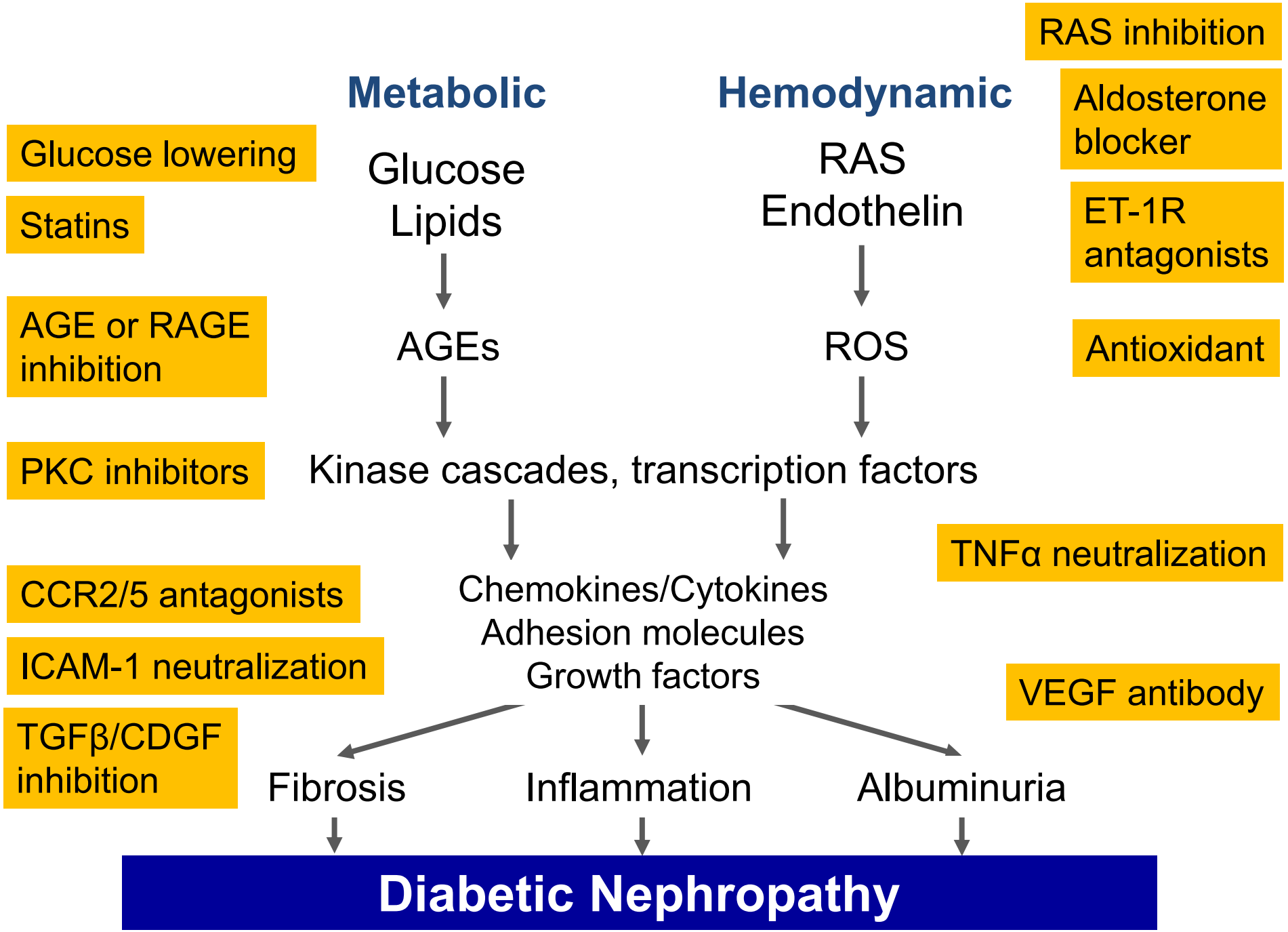
- Diabetic kidney disease remains the most common cause of ESRD in developed countries, accounting for 25–40% of incident patients, indicating the need for additional therapeutic approaches beyond the RAS

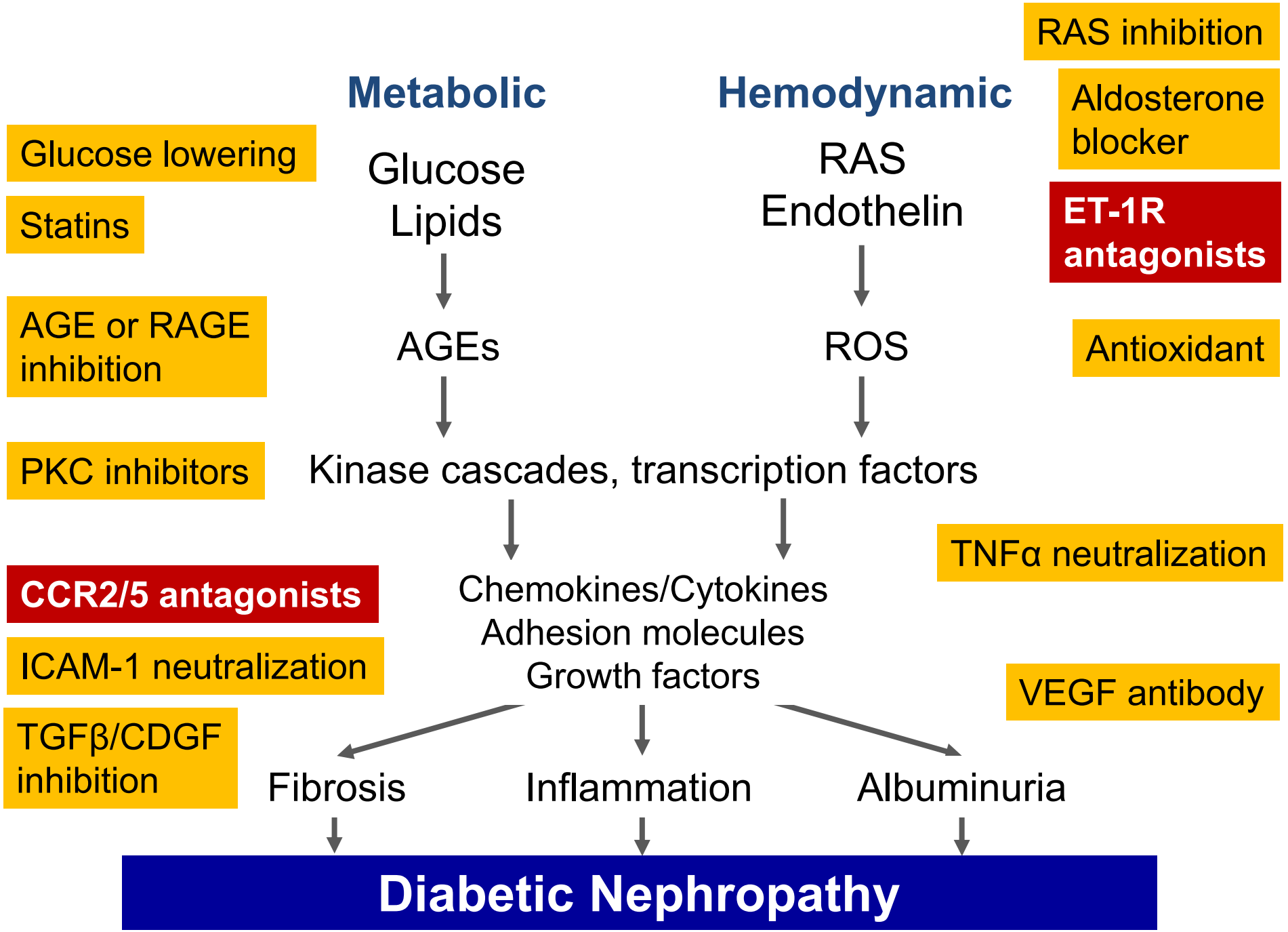
- In the past few years, several major trials have failed to show a favorable risk to benefit ratio for diabetic kidney disease
  - Dual blockade of RAS, PKC-β inhibitor (ruboxistaurin), sulodexide, AGE formation inhibitors (pimagedine, pyridoxamine)

Nat Rev Nephrol, 2014

Current Therapy

- Blood pressure control
- Blood glucose control
- Renin–angiotensin system (RAS) blockers
  - antialbuminuric and antihypertensive effects


RAS inhibition
Metabolic
Hemodynamic
Aldosterone blocker
Glucose lowering
Glucose
Lipids
RAS
Endothelin
ET-1R antagonists
Statins
AGE or RAGE inhibition
AGEs
ROS
Antioxidant
PKC inhibitors
Kinase cascades, transcription factors
TNFα neutralization
CCR2/5 antagonists
Chemokines/Cytokines
Adhesion molecules
Growth factors
ICAM-1 neutralization
VEGF antibody
TGFβ/CDGF inhibition
Fibrosis
Inflammation
Albuminuria
Diabetic Nephropathy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Adhesion molecules
Growth factors
Fibrosis
Inflammation
Albuminuria
Diabetic Nephropathy

Endothelin-receptor antagonists

Endothelin

Most potent and long lasting vasoconstrictor

Autocrine & Paracrine

Affects multiple system

Three isoforms - ET1, ET2, and ET3

Two receptor isoforms - ETA and ETB

ETA receptor	ETB receptor
Affinity : ET1 , ET2 > ET3 Primary vasoconstrictor, growth promoting Vascular smooth muscle cells	Affinity : ET1 = ET2 = ET3 Vasodilator, vasoconstrictor, inhibit cell growth Vascular smooth muscle cells, endothelial cells

Trial	Phase	Drug	Study population
NCT01424319	II	Atrasentan	T2DM, GFR >30 ml/min/1.73 m2, UACR ≥200 mg/g, on RAS blockade
NCT 1356849	II	Atrasentan	T2DM, eGFR 30–75 ml/min/1.73 m2, UACR 300–3,500 mg/g, on RAS blockade
NCT00920764	II	Atrasentan	T2DM, eGFR >20 ml/min/1.73 m2, UACR 100–3,000 mg/g, on RAS blockade
NCT00160225	II	Daglutril (ECE inhibitor)	T2DM, eGFR 70-90 ml/min/1.73m2 UACR 20-999 µg/min, on RAS blockade

Trial	Phase	Drug	Study population
NCT01399580	II	Atrasentan	T2DM, eGFR 30–75 ml/min/1.73 m2, UACR 300–3,500 mg/g, on RAS blockade
NCT00120328	III	Avosentan	T2DM, sCr 114.92–265.2 µmol/l (M) or 106.08–265.2 µmol/l (F), UACR ≥300 mg/g, on RAS blockade
NCT01858532	III	Atrasentan	T2DM, eGFR 25-75 ml/min/1.73 m2, UACR 300–5,000 mg/g, on RAS blockade

Avosentan for Overt Diabetic Nephropathy (ASCEND)

- 1,392 patients with T2DM, UACR ≥300 mg/g, on RAS blockade
- 25mg/d avosentan vs. 50mg/d avosentan vs. placebo

Prem

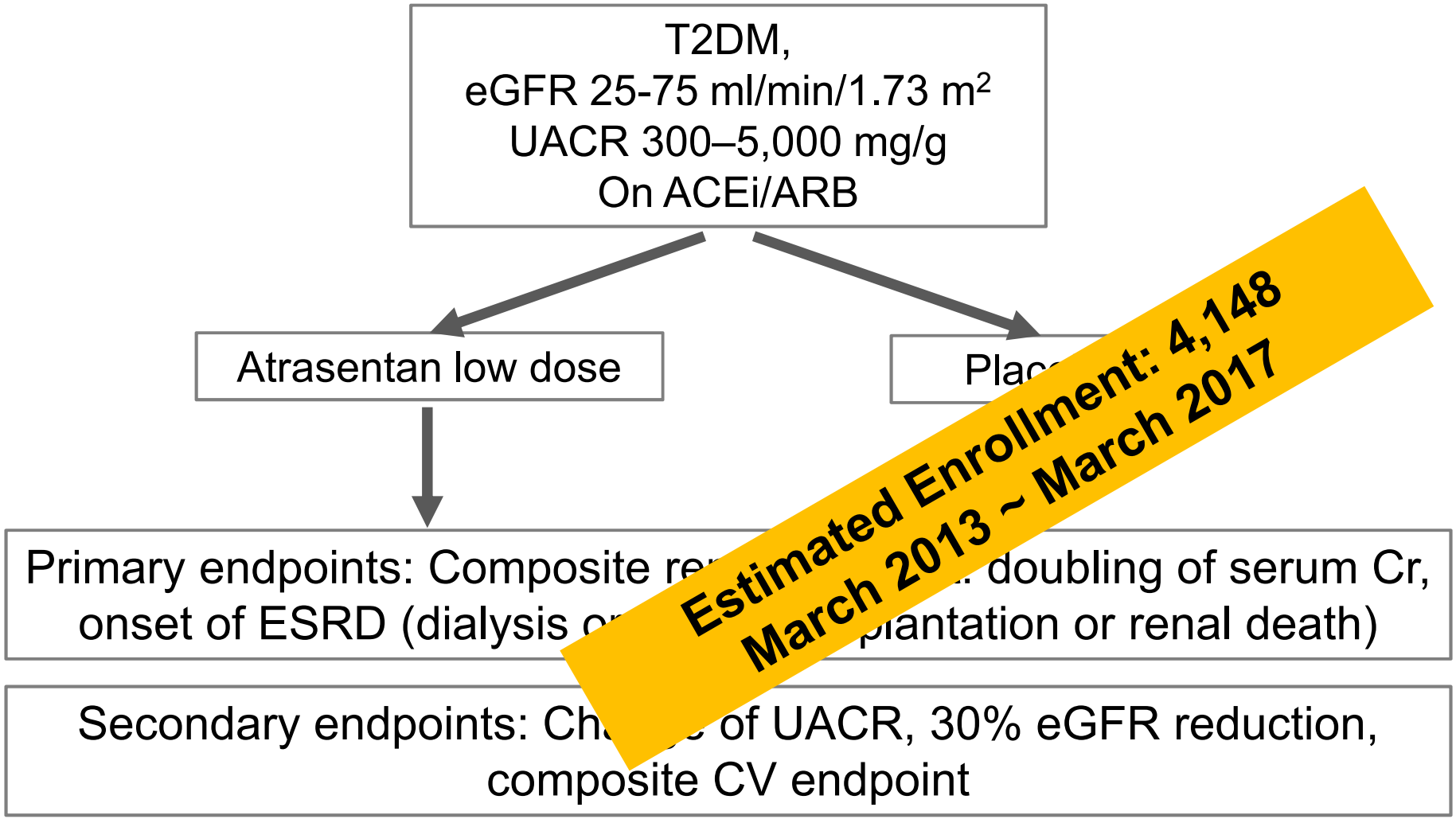
Avosentan reduced albuminuria, but induced fluid overload and congestive heart failure

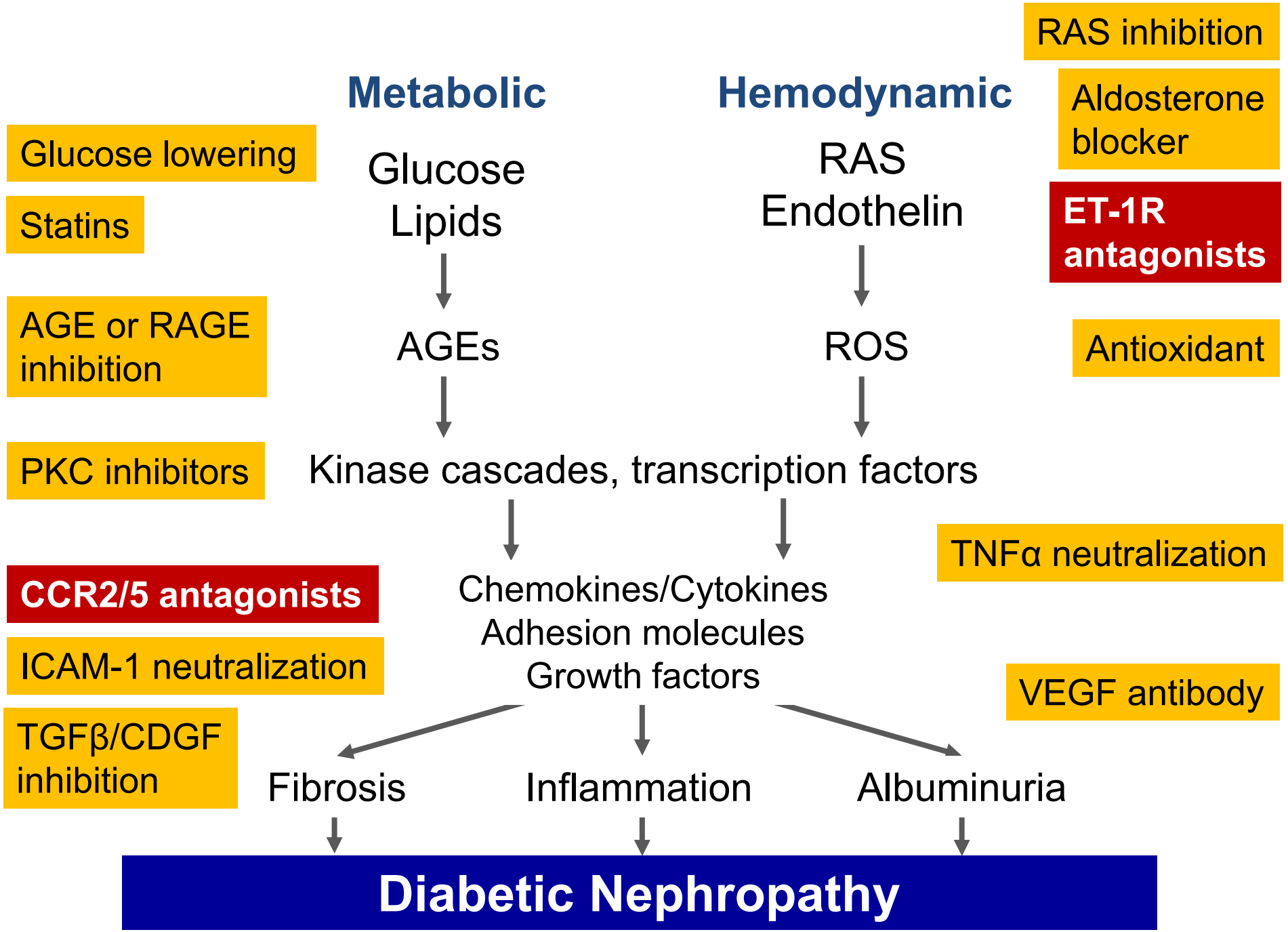
✓ Afte… …n exc… …2 *vs.* 11.5% for placebo) dominated by fluid overload and congestive heart failure

✓ Avosentan significantly reduced ACR

J Am Soc Nephrol, 2010

Study of diabetic Nephropathy with atrasentan (SONAR)

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Growth factors
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Inflammation
Albuminuria
Diabetic Nephropathy

CCR2/CCR5 antagonists

CCR2

- Expressed abundantly inflammatory subset of blood monocytes, dendritic cells, and memory Th1 cells
- CCR2/MCP-1 axis has an essential role in the tissue recruitment of inflammatory cells

CCR5

- Expressed on macrophages, osteoclasts, and VSMCs
- In vivo function of CCR5 is less well defined
- Possible role atherosclerosis and accelerated intimal hyperplasia

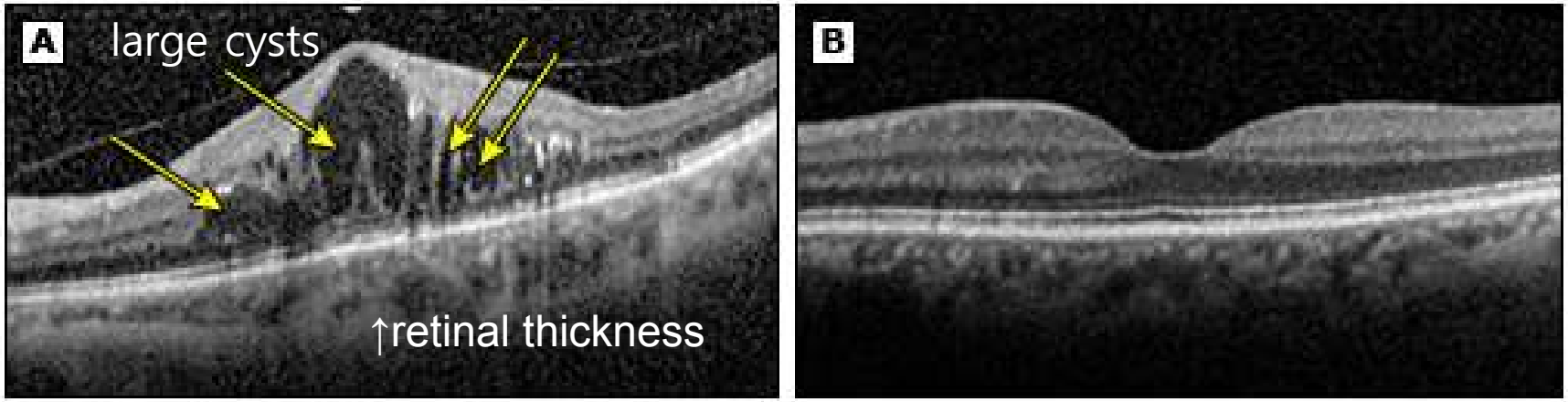
Journal of Leukocyte Biology, 2010

Trial	Phase	Drug	Study population
NCT01712061	II	PF-04634817 (dual CCR2/5 antagonist)	T2DM, eGFR 20–75 ml/min/1.73 m^2, UACR ≥300 mg/g, on RAS blockade
NCT01752985	II	BMS-813160 (dual CCR2/5 antagonist)	T2DM, UACR 200–3,500 mg/g, on RAS blockade
NCT01440257	II	CCX140-B (CCR2 antagnoist)	T2DM, eGFR ≥25 ml/min/1.73 m^2, UACR 100–3,000 mg/g, on RAS blockade
NCT01447147	II	CCX140-B (CCR2 antagnoist)	T2DM, eGFR ≥25 ml/min/1.73 m^2, UACR 100–3,000 mg/g, on RAS blockade

Diabetic Retinopathy

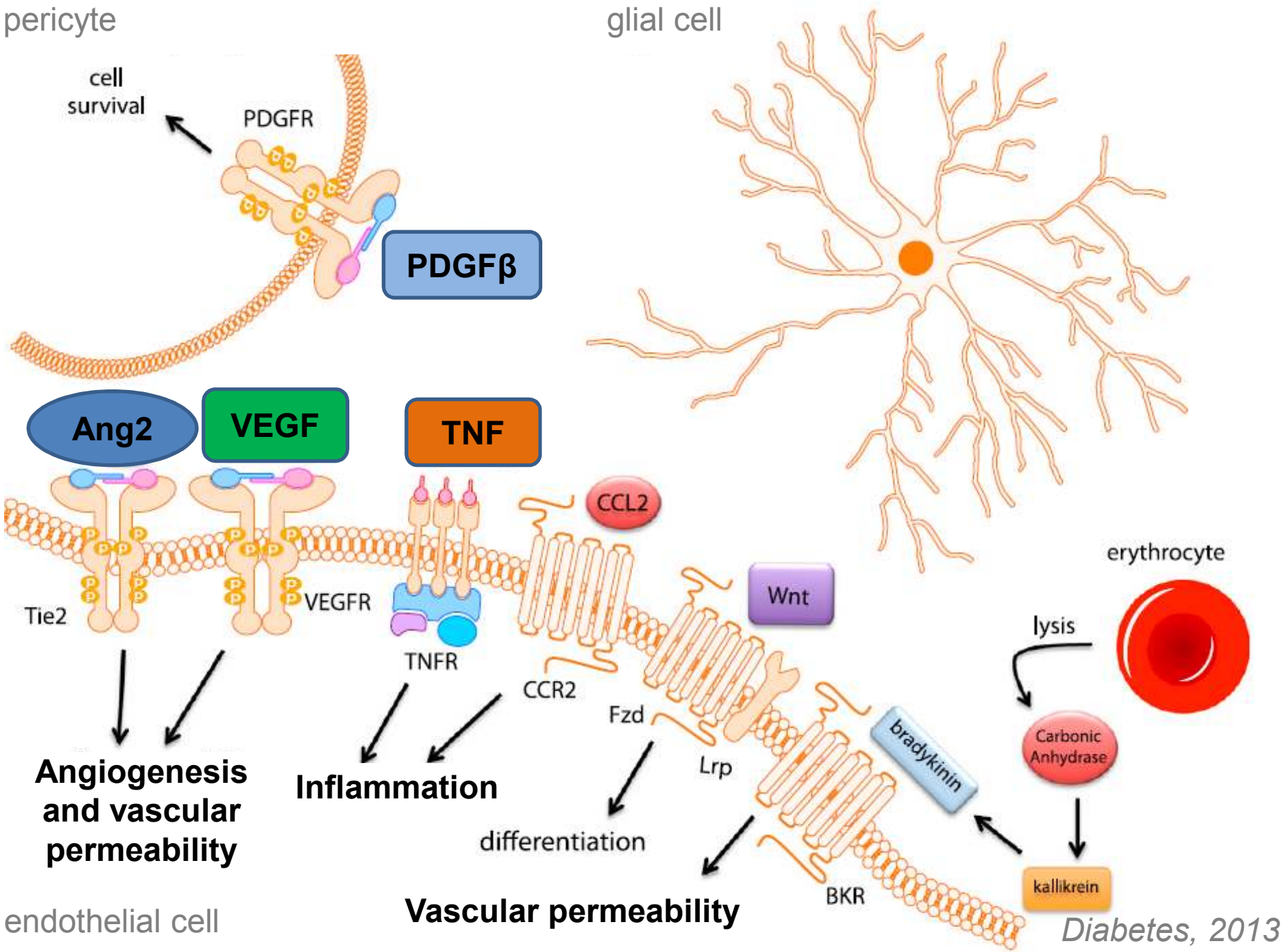
- Diabetic eye disease is a leading cause of vision loss in adults

- **Diabetic macular edema (DME)**
  - It affects central vision and can lead to decline in vision ranging from slight visual blurring to blindness



macular edema

normal macula


pericyte
glial cell
cell survival
PDGFR
PDGFβ
Ang2
VEGF
TNF
CCL2
Wnt
erythrocyte
lysis
Tie2
VEGFR
TNFR
CCR2
Fzd
Lrp
bradykinin
Carbonic Anhydrase
kallikrein
BKR
differentiation
Angiogenesis and vascular permeability
Inflammation
Vascular permeability
endothelial cell
Diabetes, 2013

Current Therapy

- Laser photocoagulation
- Vitrectomy
- Intravitreal steroids

- Intraocular anti-VEGF therapy

VEGF inhibitors

- Ranibizumab: approved by FDA for DME (August 2012)
- Aflibercept
- Bevacizumab
- Pegaptanib sodium

Trial	Phase	Drug	Study population
NCT00284050 (RESOLVE)	II	Ranibizumab	T1/T2 DM, clinically significant DME with central involvement
NCT00989989 (REVEAL)	II	Ranibizumab	T1/T2 DM, visual acuity impairment d/t DME
NCT00687804 (RESTORE)	III	Ranibizumab	T1/T2 DM, visual acuity impairment d/t DME
NCT01982435 (REACT)	I/II	Ranibizumab	T1/T2 DM, clinically significant DME, previous bevacizumab injections

3-Year Outcomes of Individualized Ranibizumab Treatment in Patients with DME: The RESTORE Extension Study

- Phase IIIb, multicenter, 12-month, randomized core study and 24-month open-label extension study
- 240 patients with T1DM or T2DM, visual acuity impairment d/t DME
-
- Ranibizumab was effective in visual and anatomic endpoints with a progressively declining number of injections over 3 years of individualized dosing.
- Ranibizumab was generally well tolerated over 3 years

These results confirmed the favorable efficacy and safety profiles of ranibizumab in the long-term treatment of DME

Ophthalmology, 2014

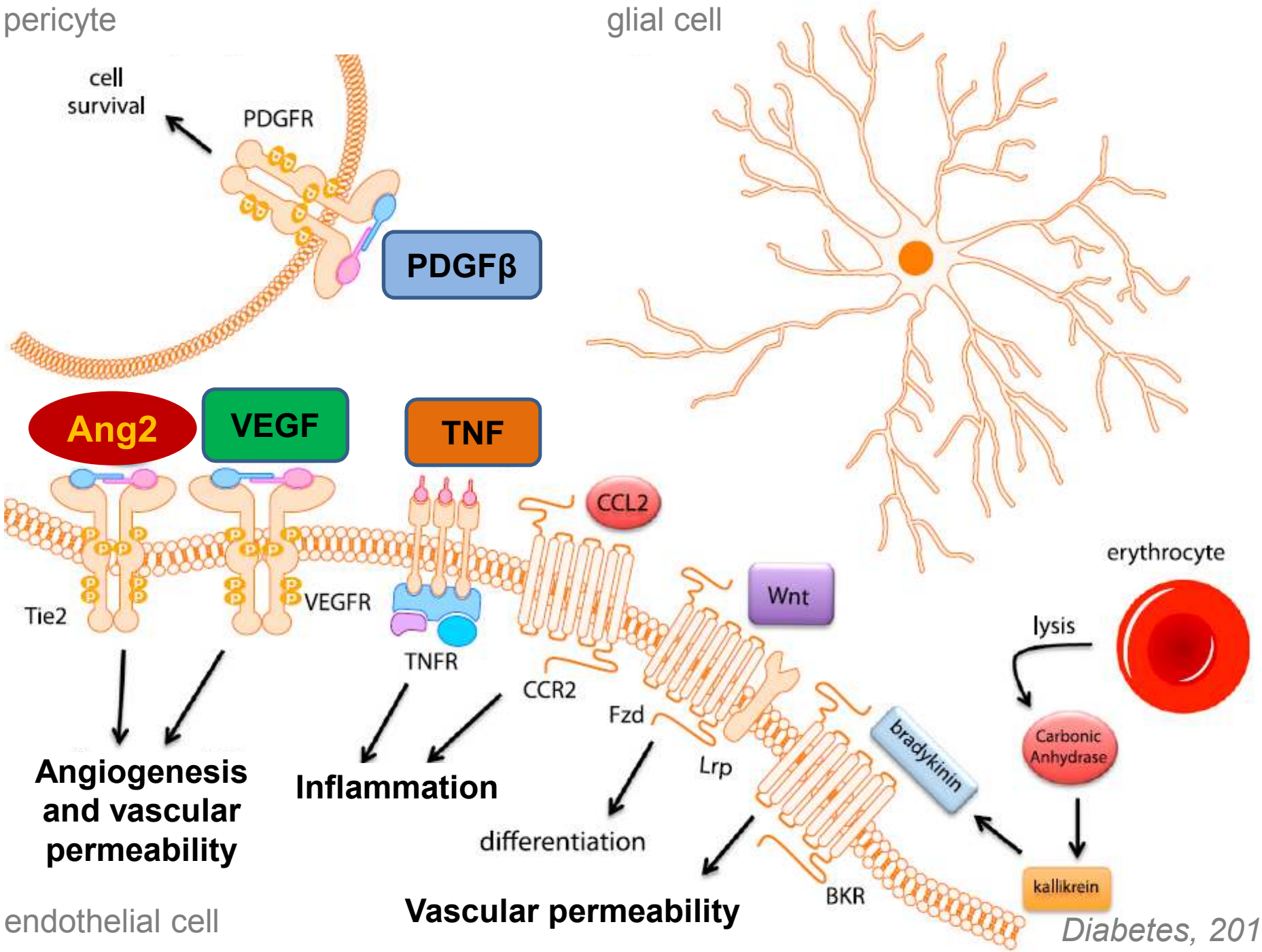
Trial	Phase	Drug	Study population
NCT00789477 (DA VINCI)	II	Aflibercept	T1/T2 DM, clinically significant DME with central involvement
NCT01512966 (VIVID-Japan)	III	Aflibercept	T1/T2 DM, clinically significant DME with central involvement, Japanese
NCT01909791	III	Aflibercept	T1/T2 DM, confirmed DME on OCT
NCT01363440 (VISTA-DME)	III	Aflibercept	T1/T2 DM, decrease in vision due to DME
NCT01331681 (VIVID-DME)	III	Aflibercept	T1/T2 DM, decrease in vision due to DME

Intravitreal Aflibercept Injection for DME: Primary and Additional Endpoint Results from Phase 3 VISTA-DME & VIVID-DME Studies

- T1/T2 DM, clinically significant DME
- IVT-AFL 2 mg every 4 weeks (2q4) plus sham laser *vs.* IVT-AFL 2 mg every 8 weeks (2q8) plus sham laser *vs.* Macular laser treatment plus IVT-sham treatment
- **Aflibercept showed superiority in all visual and anatomic endpoints with similar efficacy in the 2q4 and 2q8 treatment groups**

Conclusion

- Aflibercept groups demonstrated significant and robust superiority of VA endpoints over laser photocoagulation with similar efficacy in the 2q4 and 2q8 treatment groups


pericyte
glial cell
cell survival
PDGFR
PDGFβ
Ang2
VEGF
TNF
CCL2
Wnt
erythrocyte
lysis
Tie2
VEGFR
TNFR
CCR2
Fzd
Lrp
bradykinin
Carbonic Anhydrase
kallikrein
BKR
differentiation
Angiogenesis and vascular permeability
Inflammation
Vascular permeability
endothelial cell
Diabetes, 2013

Angiopoietin -TIE Receptor Pathway

- **Angiopoietin**
  - Ang1 (agonist for Tie2 receptor), essential for angiogenesis and stabilizes vessels
  - Ang2 (competitive antagonist of Tie2 receptor), promotes vessel destabilization

✓ **AKB-9778**

  - First-in-class small molecule that works by inhibiting the human protein tyrosine phosphatase β (HPTPβ) enzyme, which acts as a negative regulator of the Tie2 receptor

Journal of Leukocyte Biology, 2010
Diabetes, 2013

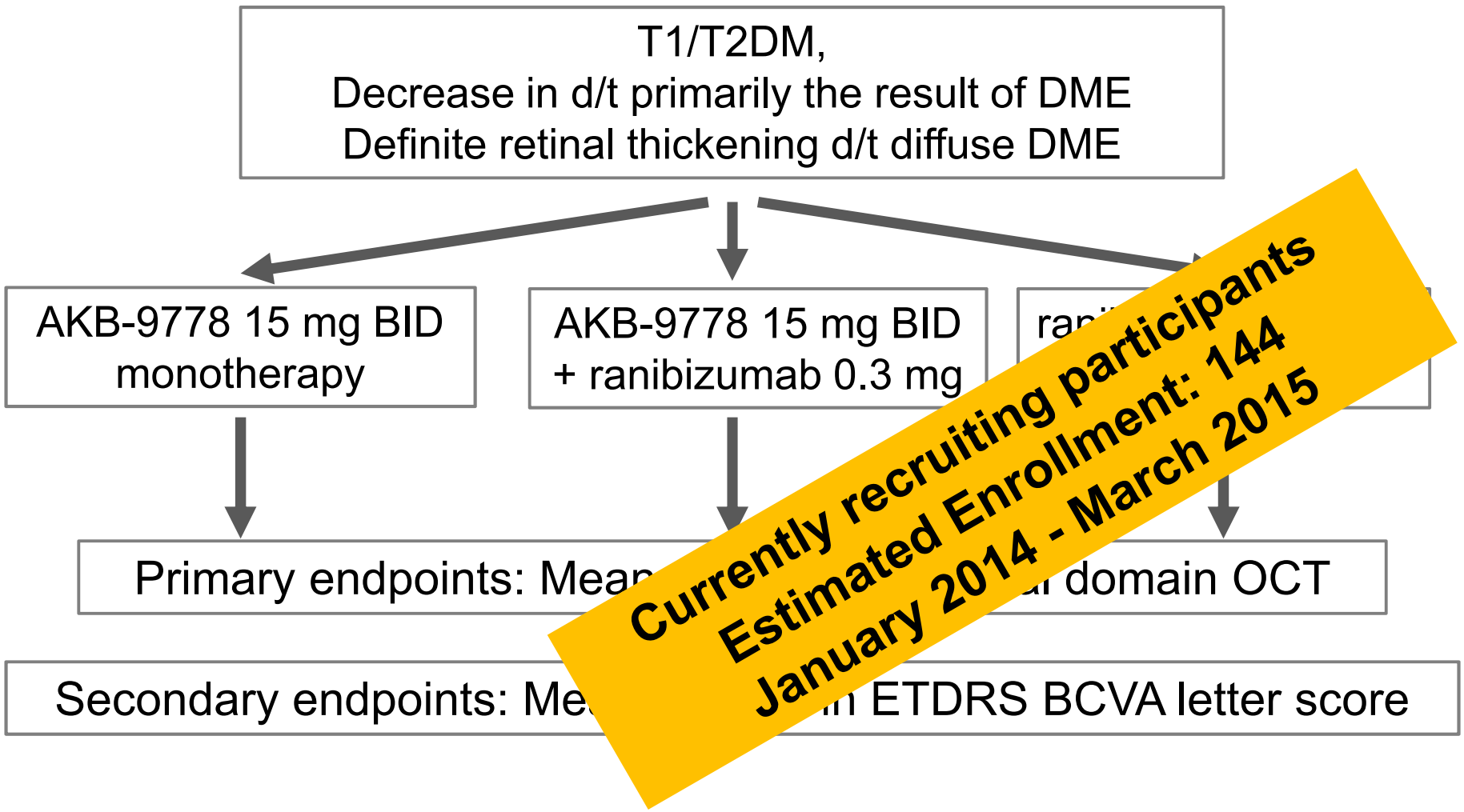
Trial	Phase	Drug	Study population
NCT01702441	I/II	AKB-9778 (Tie-2 activator)	T1/T2 DM, decrease in vision due to DME
NCT02050828	II	AKB-9778 (Tie-2 activator)	T1/T2 DM, decrease in vision due to DME

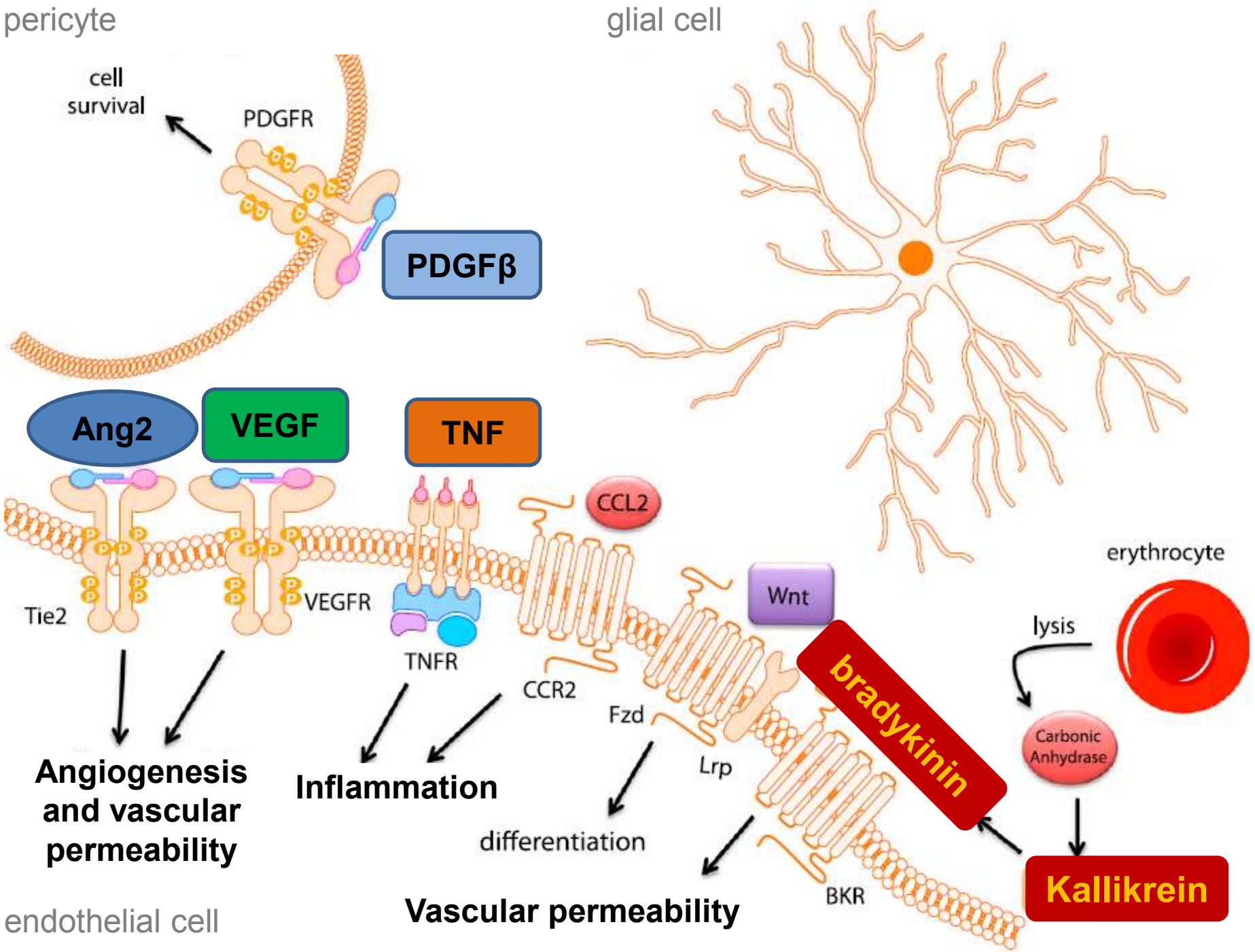
PF-04856884 (Metastatic RCC, Phase 2, NCT01441414)

CEP-11981 (Advanced cancer, Phase 1, NCT00875264)

AMG-386 (Ovarian cancer, Phase 3, NCT01204749)

Novel Tie-2 Activator, in Patients With Diabetic Macular Edema (TIME-2 Study)




pericyte
glial cell
cell survival
PDGFR
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Ang2
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TNF
CCL2
Wnt
erythrocyte
lysis
Tie2
VEGFR
TNFR
CCR2
Fzd
Lrp
bradykinin
Carbonic Anhydrase
Angiogenesis and vascular permeability
Inflammation
differentiation
Vascular permeability
BKR
Kallikrein
endothelial cell

Plasma kallikrein inhibitor

Plasma kallikrein-kinin system (KKS)

- Activated during vascular injury
- Intraocular KKS induces retinal vascular permeability, vasodilation, and retinal thickening, and exacerbated response → potential therapeutic targets for DME

Trial	Phase	Drug	Study population
NCT02193113	I	KVD001 (plasma kallikrein inhibitor)	T1/T2 DM, decrease in vision due to DME

Biol. Chem. 2013

Summary

- Despite major advances in our understanding of the mechanisms, few new drugs are coming to market
- Ongoing clinical trials are testing novel approaches that target signaling pathways, inflammation, or angiogenesis
  - **Atherosclerosis:** canakinumab, low dose MTX
  - **Nephropathy:** atrasentan, CCR2/5 antagonists
  - **Diabetic macular edema:** aflibercept, Tie-2 activator, plasma kallikrein inhibitor
- The safety profile of novel agents is critical since drugs for diabetic vascular complication must be designed for long-term administration

Thank you for your attention!!!