Review of the Clinical Trials on Vascular Complications of Diabetes

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Disclosures

• No conflicts of interest
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• Introduction

• Atherosclerosis

• Diabetic Nephropathy

• Diabetic Retinopathy

• Summary
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

New-onset DR

Progression of pre-existing DR

\[ \text{RR} = 0.57 \]  
\[ (95\% \text{ CI } 0.37 - 0.88) \]  
\[ P = 0.01 \]


Nat Rev Endocrinol, 2010
Steno-2: Risk of Diabetic Retinopathy

New-onset DR

Progression of pre-existing DR

Nat Rev Endocrinol, 2010
Steno-2: Risk of Diabetic Retinopathy

New-onset DR

Progression of pre-existing DR

Nat Rev Endocrinol, 2010
Steno-2: Risk of Diabetic Nephropathy

Risk of new-onset diabetic nephropathy

- **Conventional treatment**
- **Intensive treatment**

<table>
<thead>
<tr>
<th>Duration of follow-up (years)</th>
<th>Percentage of patients</th>
<th>Residual risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.8</td>
<td>24 (P=0.01)</td>
<td></td>
</tr>
<tr>
<td>7.8</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>13.3</td>
<td>20 (P=0.004)</td>
<td>RR=0.44 (95% CI 0.25–0.77)</td>
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<tr>
<td></td>
<td>25</td>
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</tr>
</tbody>
</table>

Nat Rev Endocrinol, 2010*
Steno-2: Risk of Diabetic Nephropathy

Risk of new-onset diabetic nephropathy

- Duration of follow-up (years)
  - 3.8: 24% (P=0.01), 10% (Intensive treatment)
  - 7.8: 39%, 20% (Intensive treatment)
  - 13.3: 46%, 25% (Intensive treatment)

- RR=0.44 (95% CI 0.25–0.77), P=0.004

Nat Rev Endocrinol, 2010
Steno-2: Risk of Diabetic Nephropathy

Risk of new-onset diabetic nephropathy

- Duration of follow-up (years)
  - 3.8
  - 7.8
  - 13.3

- Percentage of patients
  - Conventional treatment
  - Intensive treatment

- Residual risk

- RR = 0.44
  - (95% CI: 0.25–0.77)
  - P = 0.004

Nat Rev Endocrinol, 2010
<table>
<thead>
<tr>
<th>Atherosclerosis</th>
<th>Diabetic Nephropathy</th>
<th>Diabetic Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aleglitazar</td>
<td>Dual blocker – Fail</td>
<td>Plasma Kallikrein Inhibitor</td>
</tr>
<tr>
<td>Protein kinase C-δ inhibitors</td>
<td>Protein kinase C-β inhibitors</td>
<td>Angiopoietin-2</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>Bardoxolone methyl</td>
<td>Intravenous infliximab</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>Inhibitors of AGE formation</td>
<td>CCR2/CCR5 receptor antagonist</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Endothelin-receptor antagonists</td>
<td></td>
</tr>
<tr>
<td>Darapladib</td>
<td>Mineralocorticoid receptor antagonists</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CCR2/CCR5 receptor antagonist</td>
<td></td>
</tr>
</tbody>
</table>
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

PPARγ
Improve insulin sensitivity

↑ Insulin sensitivity
↑ Beta cell function
↑ Fatty acid uptake
↑ Adiponectin secretion
Anti inflammatory
<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Drug</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01715818</td>
<td>III</td>
<td>Aleglitazar</td>
<td>T2DM, with evidence of prior MI or ischemic stroke ≥ 3 months</td>
</tr>
<tr>
<td>NCT01042769</td>
<td>III</td>
<td>Aleglitazar</td>
<td>T2DM, hospitalization for ACS event within 12 wks</td>
</tr>
</tbody>
</table>
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

Canakinumab
Anakinra
Colchicine

Low dose MTX
<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Drug</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00605475</td>
<td>II</td>
<td>Canakinumab</td>
<td>T2DM</td>
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<tr>
<td>NCT01068860</td>
<td>II</td>
<td>Canakinumab</td>
<td>T2DM or IGT</td>
</tr>
<tr>
<td>NCT00947427</td>
<td>II</td>
<td>Canakinumab</td>
<td>T1DM</td>
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<tr>
<td>NCT00995930</td>
<td>II</td>
<td>Canakinumab</td>
<td>T2DM for ≤ 14 years or IGT, known atherosclerotic disease</td>
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<tr>
<td>NCT01327846</td>
<td>III</td>
<td>Canakinumab</td>
<td>T2DM, spontaneous MI at least 30 days before randomization. hsCRP≥2 mg/L</td>
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<tr>
<td>NCT01594333</td>
<td>III</td>
<td>Methotrexate</td>
<td>T2DM or MS, MI or multi-vessel CAD in the past 5 yrs</td>
</tr>
</tbody>
</table>
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI)
On Statin, ACEi/ARB, BB, ASA
hsCRP ≥ 2 mg/L

Canakinumab 150mg SC q3months
Canakinumab 300mg SC q3months
Placebo

Primary endpoints: Nonfatal MI, Nonfatal stroke, CV Death

Secondary endpoints: Total mortality, new onset diabetes, other vascular events

Estimated Enrollment: 10,000
Study: April 2011 ~ April 2017
Cardiovascular Inflammation Reduction Trial (CIRT)

- Stable CAD (post MI)
  - On Statin, ACEi/ARB, BB, ASA
  - T2DM or Metabolic syndrome

- Low dose MTX 10mg/kg + folate
- Placebo + folate

Primary endpoints: Nonfatal MI, Nonfatal stroke, CV Death

Secondary endpoints: Total mortality, new onset diabetes (in MS), other vascular events

Estimated Enrollment: 7,000
April 2013 ~ December 2018
## Studies Assessing CV Outcomes in T2DM Drugs (Recently Completed or Ongoing)

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

**Metabolic**
- Glucose lowering
- Statins
- AGE or RAGE inhibition
- PKC inhibitors

**Hemodynamic**
- RAS inhibition
- Aldosterone blocker
- ET-1R antagonists
- Antioxidant

**Glucose**
- Glucose lowering

**Lipids**
- Statins

**AGEs**
- AGE or RAGE inhibition
- PKC inhibitors

**Kinase cascades, transcription factors**
- Chemokines/Cytokines
- Adhesion molecules
- Growth factors

**Fibrosis**
- TGFβ/CDGF inhibition

**Inflammation**
- CCR2/5 antagonists
- ICAM-1 neutralization

**Albuminuria**
- TNFα neutralization
- VEGF antibody

**Diabetic Nephropathy**
Diabetic Nephropathy

**Metabolic**
- Glucose lowering
- Statins
- AGE or RAGE inhibition
- PKC inhibitors

**Hemodynamic**
- RAS inhibition
- Aldosterone blocker
- ET-1R antagonists
- Antioxidant

Glucose Lipids → AGEs → Kinase cascades, transcription factors → Chemokines/Cytokines
- Adhesion molecules
- Growth factors
  - Fibrosis
  - Inflammation
  - Albuminuria
## 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

<table>
<thead>
<tr>
<th>ETA receptor</th>
<th>ETB receptor</th>
</tr>
</thead>
</table>
| 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 |
<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Drug</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01424319</td>
<td>II</td>
<td>Atrasentan</td>
<td>T2DM, GFR &gt;30 ml/min/1.73 m2, UACR ≥200 mg/g, on RAS blockade</td>
</tr>
<tr>
<td>NCT 1356849</td>
<td>II</td>
<td>Atrasentan</td>
<td>T2DM, eGFR 30–75 ml/min/1.73 m2, UACR 300–3,500 mg/g, on RAS blockade</td>
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<tr>
<td>NCT00920764</td>
<td>II</td>
<td>Atrasentan</td>
<td>T2DM, eGFR &gt;20 ml/min/1.73 m2, UACR 100–3,000 mg/g, on RAS blockade</td>
</tr>
<tr>
<td>NCT00160225</td>
<td>II</td>
<td>Daglutril (ECE inhibitor)</td>
<td>T2DM, eGFR 70-90 ml/min/1.73m2 UACR 20-999 µg/min, on RAS blockade</td>
</tr>
<tr>
<td>Trial</td>
<td>Phase</td>
<td>Drug</td>
<td>Study population</td>
</tr>
<tr>
<td>---------------</td>
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<td>-------------------------------------------------------</td>
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<tr>
<td>NCT01399580</td>
<td>II</td>
<td>Atrasentan</td>
<td>T2DM, eGFR 30–75 ml/min/1.73 m2, UACR 300–3,500 mg/g, on RAS blockade</td>
</tr>
<tr>
<td>NCT00120328</td>
<td>III</td>
<td>Avosentan</td>
<td>T2DM, sCr 114.92–265.2 µmol/l (M) or 106.08–265.2 µmol/l (F), UACR ≥300 mg/g, on RAS blockade</td>
</tr>
<tr>
<td>NCT01858532</td>
<td>III</td>
<td>Atrasentan</td>
<td>T2DM, eGFR 25-75 ml/min/1.73 m2, UACR 300–5,000 mg/g, on RAS blockade</td>
</tr>
</tbody>
</table>
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

Premature termination
✓ After a median follow up of 4 months because of an excess of CV events with avosentan (19.6% vs. 11.5% for placebo) dominated by fluid overload and congestive heart failure
✓ Avosentan significantly reduced ACR

Avosentan reduced albuminuria, but induced fluid overload and congestive heart failure
Study of diabetic Nephropathy with atrasentan (SONAR)

T2DM, eGFR 25-75 ml/min/1.73 m², UACR 300–5,000 mg/g, On ACEi/ARB

Atrasentan low dose  
Placebo

Primary endpoints: Composite renal endpoint (doubling of serum Cr, onset of ESRD (dialysis or renal transplantation or renal death))

Secondary endpoints: Change of UACR, 30% eGFR reduction, composite CV endpoint

Estimated Enrollment: 4,148  
March 2013 ~ March 2017
Diabetic Nephropathy

**Metabolic**
- Glucose lowering
- Statins
- AGE or RAGE inhibition
- PKC inhibitors

**Hemodynamic**
- RAS inhibition
- Aldosterone blocker
- ET-1R antagonists
- Antioxidant

**Kinase cascades, transcription factors**
- Chemokines/Cytokines
- Adhesion molecules
- Growth factors

**Inflammation**
- Fibrosis
- Albuminuria

**Glucose Lipids**
- Glucose
- Lipids

**AGEs**
- AGEs

**ROS**
- ROS

**ET21R antagonists**
- RASA inhibition

**Glucose Alowering**
- AGE or ARAGE inhibition

**PKCα inhibitors**
- Statins

**VEGFA antibody**
- TGFβ/CDGF inhibition

**CCR2/5 antagonists**
- ICAM-1 neutralization

**TGFβ/CDGF inhibition**
- VEGF antibody

**Antioxidant**
- TNFα neutralization
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
<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Drug</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01712061</td>
<td>II</td>
<td>PF-04634817 (dual CCR2/5 antagonist)</td>
<td>T2DM, eGFR 20–75 ml/min/1.73 m², UACR ≥300 mg/g, on RAS blockade</td>
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<tr>
<td>NCT01752985</td>
<td>II</td>
<td>BMS-813160 (dual CCR2/5 antagonist)</td>
<td>T2DM, UACR 200–3,500 mg/g, on RAS blockade</td>
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<tr>
<td>NCT01440257</td>
<td>II</td>
<td>CCX140-B (CCR2 antagonist)</td>
<td>T2DM, eGFR ≥25 ml/min/1.73 m², UACR 100–3,000 mg/g, on RAS blockade</td>
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<tr>
<td>NCT01447147</td>
<td>II</td>
<td>CCX140-B (CCR2 antagonist)</td>
<td>T2DM, eGFR ≥25 ml/min/1.73 m², UACR 100–3,000 mg/g, on RAS blockade</td>
</tr>
</tbody>
</table>
• 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

![Diabetic Retinopathy Image]

- Large cysts
- Retinal thickness increase

macular edema

normal macula
Hyperglycemia

Biochemical changes

Sorbitol and AKP

AGE

Inflammation

RAS

Diabetic Retinopathy

Oxidative Stress

Growth Hormone e.g. VEGF

Diabetes, 2013

Angiogenesis and vascular permeability

Inflammation

Ang2

VEGF

TNF

PDGFβ

endothelial cell

pericyte

pericyte glial cell

glia cell

erthrocyte

Vascular permeability

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

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

Ophthalmology, 2014
<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Drug</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00789477 (DA VINCI)</td>
<td>II</td>
<td>Aflibercept</td>
<td>T1/T2 DM, clinically significant DME with central involvement</td>
</tr>
<tr>
<td>NCT01512966 (VIVID-Japan)</td>
<td>III</td>
<td>Aflibercept</td>
<td>T1/T2 DM, clinically significant DME with central involvement, Japanese</td>
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<tr>
<td>NCT01909791</td>
<td>III</td>
<td>Aflibercept</td>
<td>T1/T2 DM, confirmed DME on OCT</td>
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<tr>
<td>NCT01363440 (VISTA-DME)</td>
<td>III</td>
<td>Aflibercept</td>
<td>T1/T2 DM, decrease in vision due to DME</td>
</tr>
<tr>
<td>NCT01331681 (VIVID-DME)</td>
<td>III</td>
<td>Aflibercept</td>
<td>T1/T2 DM, decrease in vision due to DME</td>
</tr>
</tbody>
</table>
Intravitreal Afibercept 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

- **Afibercept showed superiority in all visual and anatomic endpoints with similar efficacy in the 2q4 and 2q8 treatment groups**

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

ARVO 2014 Annual Meeting
Hyperglycemia leads to biochemical changes such as sorbitol and PKC activation, AGE formation, and inflammation. This can contribute to diabetic retinopathy and oxidative stress. Growth hormone, e.g., VEGF, plays a role in angiogenesis and vascular permeability. Inflammation-induced factors like TNF, Ang2, VEGF, and PDGFβ contribute to pericyte cell survival and endothelial cell dysfunction, leading to inflammation and vascular permeability. The diagram illustrates the interaction between pericyte, glial cell, and erythrocyte, with key molecules and pathways such as PDGFR, PDGFβ, and carbonic anhydrase involved in lysis and differentiation. The image is from 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
<table>
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<th>Trial</th>
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<th>Drug</th>
<th>Study population</th>
</tr>
</thead>
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<td>NCT01702441</td>
<td>I/II</td>
<td>AKB-9778 (Tie-2 activator)</td>
<td>T1/T2 DM, decrease in vision due to DME</td>
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<tr>
<td>NCT02050828</td>
<td>II</td>
<td>AKB-9778 (Tie-2 activator)</td>
<td>T1/T2 DM, decrease in vision due to DME</td>
</tr>
</tbody>
</table>

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)

T1/T2DM,
Decrease in d/t primarily the result of DME
Definite retinal thickening d/t diffuse DME

AKB-9778 15 mg BID monotherapy

Primary endpoints: Mean decrease in macular domain OCT

Secondary endpoints: Mean change in ETDRS BCVA letter score

AKB-9778 15 mg BID + ranibizumab 0.3 mg

Currently recruiting participants
Estimated Enrollment: 144
January 2014 - March 2015
Hyperglycemia
Biochemical changes
Sorbitol and PKC
AGE
Inflammation
RAS
Diabetic Retinopathy
Oxidative Stress
Growth Hormone e.g. VEGF
Ang2
VEGF
TNF
Inflammation
TNF
PDGFβ
endothelial cell
glial cell
pericyte
Tie2
 Angiogenesis and vascular permeability
Angiogenesis
Inflammation
endothelial cell
Vascular permeability
pericyte
PDGFR
PDGFβ
vascular permeability
Kallikrein
glial cell
erythrocyte
brahdykinin
lysis
Carbonic Anhydrase
Kallikrein
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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Drug</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02193113</td>
<td>I</td>
<td>KVD001 (plasma kallikrein inhibitor)</td>
<td>T1/T2 DM, decrease in vision due to DME</td>
</tr>
</tbody>
</table>

*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!!!