Advances in the Diagnosis and Management of the Diabetic Triopathy

R A Malik
Professor of Medicine
Weill Cornell Medicine
Doha & New York
Speaker:

Rayaz A. Malik, MD

• Has disclosed that he serves on the Speaker’s Bureau for Pfizer and Lilly

• Will not be discussing the off-label or investigational use of products
Diabetic Triopathy: Unholy Trinity
The Cinderella Complication

Diabetic Retinopathy

Diabetic Nephropathy

Diabetic Neuropathy
Corneal Confocal Microscopy: Neuropathy
21st Century Diagnostics

- Rapid (2 min)
- Non-invasive
- Images Corneal nerves.
Neuropathy precedes Retinopathy & Microalbuminuria

53 T1DM

Risk Factors for Neuropathy

- Hypertension: 1.57
- Smoking: 1.38
- HbA1c: 1.48
- Change in HbA1c: 1.36
- Diabetes duration: 1.40
- BMI: 1.27
- Triglycerides: 1.21
- Total cholesterol: 1.15

Hyperglycaemia

“Men are nearly always willing to believe what they wish”

Gaius Julius Caesar 62 BC
Enhanced glucose control for preventing and treating diabetic neuropathy

<table>
<thead>
<tr>
<th>Type 1</th>
<th>N=1228</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or subgroup</td>
<td>Enhanced nN</td>
</tr>
<tr>
<td>DCCT 1993a</td>
<td>377</td>
</tr>
<tr>
<td>DCCT 1993b</td>
<td>30377</td>
</tr>
<tr>
<td>Linn 1996</td>
<td>103</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>602</td>
</tr>
</tbody>
</table>

P<0.00001

<table>
<thead>
<tr>
<th>Type 2</th>
<th>N=6669</th>
</tr>
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<tbody>
<tr>
<td>Study or subgroup</td>
<td>Enhanced nN</td>
</tr>
<tr>
<td>Accord 2010</td>
<td>12772815</td>
</tr>
<tr>
<td>Azad 1999</td>
<td>1195</td>
</tr>
<tr>
<td>Duckworth 2009</td>
<td>178464</td>
</tr>
<tr>
<td>Tonl 1998</td>
<td>016</td>
</tr>
</tbody>
</table>

NS

ACEi Neuropathy

FIELD study

<table>
<thead>
<tr>
<th></th>
<th>Fenofibrate (n=4895)</th>
<th>Placebo (n=4900)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First amputation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>28 (0.6%)</td>
<td>52 (1.1%)</td>
<td>0.54 (0.34–0.85)</td>
<td>0.007</td>
</tr>
<tr>
<td>Major</td>
<td>24 (0.5%)</td>
<td>26 (0.5%)</td>
<td>0.93 (0.53–1.62)</td>
<td>0.79</td>
</tr>
<tr>
<td>Minor, without large-vessel disease</td>
<td>18 (0.4%)</td>
<td>34 (0.7%)</td>
<td>0.53 (0.30–0.94)</td>
<td>0.027</td>
</tr>
<tr>
<td>Major or minor, with large-vessel disease</td>
<td>34 (0.7%)</td>
<td>42 (0.9%)</td>
<td>0.81 (0.52–1.28)</td>
<td>0.37</td>
</tr>
<tr>
<td>Any amputation</td>
<td>45 (0.9%)</td>
<td>70 (1.4%)</td>
<td>0.64 (0.44–0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Multiple events analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All amputations</td>
<td>73</td>
<td>117</td>
<td>0.63 (0.40–0.97)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Painful Neuropathy

Throbbing sensation

Stabbing sensation

Numb sensation

Burning sensation

Pins and needles sensation

Electric shock-like sensation

Shooting sensation


DM: 15692

21%
Is pain due to DSPN confirmed?

Yes

- Assess comorbidities, potential for AEs, drug interactions, costs to select initial therapy from the 3 choices below

- Voltage gated $\alpha_2$-$\delta$ ligand (Pregabalin, Gabapentin)
- Serotonin-norepinephrine reuptake inhibitor (Duloxetine, venlafaxine)
- Tricyclic Antidepressant (Nortriptiline/Desipramine)

No clinically meaningful effect

- a. Switch to another agent from above
- b. Combinations
- c. May add Tapentadol or Tramadol if a and b fail

No clinically meaningful effect/Not tolerated

Refer to Pain Clinic

2017 ADA DPN consensus

Pop Busui et al Diabetes Care 2017; 40: 136-154
“Sometimes obvious conditions and treatments are the most difficult to grasp”
OR for Painful Diabetic Neuropathy:
Vit D deficiency (<20 ng/ml): 9.8 (95% CI 2.2-76.4), P<0.003
Vitamin D insufficiency (<30 ng/ml): 4.4 (95% CI 1.1-19.8), P=0.03

25(OH)D

C  PN  PN+
P<0.01
IM Vitamin D

D3 600,000 IU IM: FU 20 weeks

143 T2DM:
25OHD 31.7 + 23.3 ng/ml
25OHD 46.2 + 10.2 ng/ml

Basit et al. 2016 BMJ Open DRC
**Vitamin D protocol**

- **25 OHD**
  - <20ng/ml: Severely Vit D deficient X9.8
  - < 30ng/ml: Moderately Vit D deficient X4.4

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**Loading dose**
Cholecalciferol (vitamin D₃): 40,000 IU daily for 21 days (840,000 IU).

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**Maintenance**
Cholecalciferol (vitamin D₃): 40,000 IU once weekly
Cholecalciferol (vitamin D₃): 80,000 IU once weekly

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**Repeat vitamin D & calcium after 3 months**

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If <50ng/ml
Target: 50-80 ng/ml

---

Note: Threshold for Vit D toxicity: 100,000U daily for ~8 weeks
Diabetic Autonomic Neuropathy

**Pupillary**
Decreased diameter of dark adapted pupil
Argyll-Robertson type pupil

**Neurovascular**
Areas of symmetrical anhidrosis
Gustatory sweating
Hyperhidrosis
Alterations in skin blood flow
Heat intolerance

**Gastrointestinal**
Constipation
Gastroparesis
Diarrhoea
Faecal incontinence
Oesophageal dysfunction

**Cardiovascular**
Tachycardia
Exercise intolerance
Cardiac denervation
Orthostatic hypotension

**Genitourinary**
Erectile dysfunction
Retrograde ejaculation
Cystopathy
Neurogenic bladder
Defective vaginal lubrication
The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension

Christopher H. Gibbons¹ · Peter Schmidt² · Italo Biaggioni³ · Camille Frazier-Mills⁴ · Roy Freeman¹ · Stuart Isaacson⁵ · Beverly Karabin⁶ · Louis Kuritzky⁷ · Mark Lew⁸ · Phillip Low⁹ · Ali Mehdirad¹⁰ · Satish R. Raj¹¹ · Steven Vernino¹² · Horacio Kaufmann¹³

Diagnosis

BP after 5 minute supine, 1 and 3 minutes after standing
Healthy: <-10 systolic and +2.5 Diastolic, +10–20 bpm HR

OH: >20/10 fall
If baseline BP >150/90: – 30/15 fall

nOH: HR <15 bpm
OH: >15 bpm

Is it OH or nOH?

Yes
Assess comorbidities, Drugs

No/Not sure
Refer to Specialist TILT testing

Midodrine (α1-adrenoreceptor agonist)
2.5–15 mg tds
Supine hypertension

Droxidopa (norepinephrine)
100–600 mg tds
Supine hypertension

Fluid, 3L
Rapid 500 ml +30 mmHg
Salt 2 teaspoons
Head up position (6–9 inches)
Compression stockings (abdominal, not knee)

No clinically meaningful effect

Switch to another agent from above
Try combining agents from above

Fludrocortisone 0.1–0.2 mg/day
Hypokalemia, oedema, SH

Pyridostigimine (Acholinesterase i)
30–60 mg tds

2017 OH/nOH consensus

Diabetic Retinopathy
Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials

1421 T1DM Candesartan 16mg v placebo over 5 years

<table>
<thead>
<tr>
<th></th>
<th>DIRECT-Prevent 1</th>
<th>DIRECT-Protect 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candesartan (N=711)</td>
<td>Placebo (N=710)</td>
</tr>
<tr>
<td>Men</td>
<td>413 (58%)</td>
<td>392 (55%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.6 (8.0)</td>
<td>29.9 (8.1)</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>6.6 (3.9)</td>
<td>6.8 (3.9)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>690 (57%)</td>
<td>685 (97%)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.0 (1.7)</td>
<td>8.2 (1.7)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>116 (9.5)</td>
<td>116 (9.6)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>72 (6.9)</td>
<td>72 (7.3)</td>
</tr>
</tbody>
</table>

Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

9795 T2DM Fenofibrate 200mg v placebo over 5 years

Fenofibrate licensed for retinopathy in Australia

Keech et al Lancet 2007; 370: 1687-97
### Intravitreal Injections

**Diabetic Macular Oedema/PDR**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target/Mechanism</th>
<th>Route of Administration</th>
<th>Clinical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-VEGF</td>
<td></td>
<td>IVT</td>
<td>Phase III</td>
</tr>
<tr>
<td>Pegaptanib</td>
<td>VEGF 165</td>
<td>IVT</td>
<td>Phase III</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF-A all isoforms</td>
<td>IVT</td>
<td>Phase III</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>VEGF-A all isoforms</td>
<td>IVT</td>
<td>Phase III; FDA approved</td>
</tr>
<tr>
<td>Afibriccept</td>
<td>VEGF-B, placental growth factor</td>
<td>IVT</td>
<td>Phase III; FDA approved</td>
</tr>
<tr>
<td>VEGF DARPin</td>
<td>mTOR (VEGF, HIF-1α)</td>
<td>SC, IVT</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>mTOR (VEGF, HIF-1α)</td>
<td>IVT</td>
<td>Phase II (DIEPAS and MATISSE)</td>
</tr>
<tr>
<td></td>
<td>mTOR (VEGF, HIF-1α)</td>
<td>IVT</td>
<td>Phase II (IDEAL)</td>
</tr>
<tr>
<td></td>
<td>cRaf kinase mRNA</td>
<td>IVT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blocks VEGF, IGF-1, HGF</td>
<td>Topical, IVT</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>VEGF, PDGF, HGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Inhibits cytokines, inhibits</td>
<td>IVT, Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>leukaemia, enhances TJ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(above as steroid)</td>
<td>IVT implant</td>
<td>Phase III; FDA approved</td>
</tr>
<tr>
<td></td>
<td>(above as steroid)</td>
<td>IVT implant</td>
<td>Phase III; FDA approved</td>
</tr>
<tr>
<td></td>
<td>(nano drug delivery)</td>
<td>IVT implant</td>
<td>Phase III; FDA approved</td>
</tr>
<tr>
<td></td>
<td>(above as steroid)</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>(above as steroid)</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>(above as steroid)</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Longedrol</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Danazol</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td>II. NSAIDs:</td>
<td>Aspirin</td>
<td>Oral</td>
<td>ETDS, DAMAD</td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Buprenorphine</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>III. Chemokine and cytokine inhibitors</td>
<td></td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflazumab</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ang-2 inhibitor (AKB978)</td>
<td>Oral</td>
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</tr>
<tr>
<td></td>
<td>LFA-1 (SAR 1118; SARcode BioScience, Brisbane, CA)</td>
<td>Oral, IVT</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Chemokine inhibitor</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>CCR2/CCR5 (receptors)</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Daragluc (GlaxoSmithKline, Middlesex, UK)</td>
<td>Oral, IVT</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Micropod, MMP</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>KK inhibitors</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>MMP inhibitors</td>
<td>Oral, IVT</td>
<td>Phase III; FDA approved</td>
</tr>
<tr>
<td></td>
<td>IL-6 inhibitors</td>
<td>Oral, IVT</td>
<td>Phase III; FDA approved</td>
</tr>
<tr>
<td></td>
<td>VAP-1 inhibitor</td>
<td>Oral</td>
<td>Predichel</td>
</tr>
<tr>
<td></td>
<td>uPA integrin inhibitor (ALG-101; Allegro Ophthalmics, LLC; San Juan Capistrano, CA)</td>
<td>Oral, IVT</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>Integrein</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td>Hormone modulators:</td>
<td>GLI receptor agonist</td>
<td>SC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GH, TSH, insulin, glucagon</td>
<td>SC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuropeptide / antipsychotic agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuropeptide / antipsychotic agent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Injections every 2 months**

BCVA (20/40) & CRT <300 um: 16-40%

**Traction Retinal Detachment**

Macular Hole

Uveitis (0.1-1.9%)

Endophthalmitis (0.05-1.2%)
Diabetic Nephropathy

- Proteinuria
- GFR
Non-proteinuric pathways in loss of renal function in patients with type 2 diabetes

Esteban Porrini, Piero Ruggenenti, Carl Erik Mogensen, Drazenka Pongrac Barlovic, Manuel Praga, Josep M Cruzado, Radovan Hojs, Manuela Abbate, Aiko P J de Vries, for the ERA-EDTA diabetes working group.

Panel: Key features of non-proteinuric renal disease in type 2 diabetes

- Decreased renal function without concomitant proteinuria is reported in about 50% of people with type 2 diabetes and renal disease
- Declining glomerular filtration rate (GFR) can be recorded before (or without) progression to macroalbuminuria
- High prevalence in women with metabolic syndrome
- Accelerated GFR decline and the sequential increment in albuminuria (normoalbuminuria, microalbuminuria, and macroalbuminuria) can be viewed as two different pathways that might or might not converge in the same patient
- Uncertain benefit from angiotensin-converting enzyme inhibitors or angiotensin-receptor blocker therapy
Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

VA NEPHRON-D

<table>
<thead>
<tr>
<th>End Point</th>
<th>Losartan plus Placebo (N=724)</th>
<th>Losartan plus Lisinopril (N=724)</th>
<th>Hazard Ratio with Losartan plus Lisinopril (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point†</td>
<td>152 (21.0)</td>
<td>132 (18.2)</td>
<td>0.88 (0.70–1.12)</td>
<td>0.30</td>
</tr>
<tr>
<td>Secondary end point‡</td>
<td>101 (14.0)</td>
<td>77 (10.6)</td>
<td>0.78 (0.58–1.05)</td>
<td>0.10</td>
</tr>
<tr>
<td>ESRD</td>
<td>43 (5.9)</td>
<td>27 (3.7)</td>
<td>0.66 (0.41–1.07)</td>
<td>0.07</td>
</tr>
<tr>
<td>Death</td>
<td>60 (8.3)</td>
<td>63 (8.7)</td>
<td>1.04 (0.73–1.49)</td>
<td>0.75</td>
</tr>
<tr>
<td>Myocardial infarction, heart failure, or stroke</td>
<td>136 (18.8)</td>
<td>134 (18.5)</td>
<td>0.97 (0.76–1.23)</td>
<td>0.79</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>40 (5.5)</td>
<td>52 (7.2)</td>
<td>1.30 (0.87–1.97)</td>
<td>0.20</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>106 (14.6)</td>
<td>89 (12.3)</td>
<td>0.82 (0.62–1.09)</td>
<td>0.17</td>
</tr>
<tr>
<td>Stroke</td>
<td>18 (2.5)</td>
<td>18 (2.5)</td>
<td>0.98 (0.52–1.85)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

A. Acute Kidney Injury

B. Hyperkalemia

Fried et al. NEJM 2013, 369: 1892-903
What Next

• Despite ACEi or ARB & adequate BP control.

• Proteinuria continues
Spironolactone

Overall further reduction UAER 30%.

Type 2-Rossing et al. Diabetes Care. 2005;28:2106-12
Type 1 + Type 2 Schjoedt et al. Kidney Int June 2006; 1-7
What Next

• Despite ACEi or ARB & adequate BP control.

• Proteinuria continues
VITAL study

Change in UACR* from baseline to the last measurement during treatment

Change in systolic blood pressure during treatment and withdrawal

Change in UACR* from baseline to the last measurement during treatment
- Placebo
- Combined paricalcitol
- 1 µg paricalcitol
- 2 µg paricalcitol

Change in systolic blood pressure during treatment and withdrawal
- Placebo
- 1 µg paricalcitol
- 2 µg paricalcitol

Zeeuw, D et al., *Lancet* 2010;376:543–51
What Next

• Despite ACEi or ARB & adequate BP control.

• Proteinuria continues
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Nephropathy: New onset macroalbuminuria or a doubling of the serum creatinine, eGFR of ≤45, renal-replacement therapy, or death from renal disease.
Retinopathy: Retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, blindness.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Liraglutide (N=4668) Incidence Rate</th>
<th>Placebo (N=4672) Incidence Rate</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>no. of events/100 patient-yr</td>
<td>no. of patients (%)</td>
<td>no. of events/100 patient-yr</td>
</tr>
<tr>
<td>Microvascular event</td>
<td>355 (7.6)</td>
<td>2.0</td>
<td>416 (8.9)</td>
<td>2.3</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>106 (2.3)</td>
<td>0.6</td>
<td>92 (2.0)</td>
<td>0.5</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>268 (5.7)</td>
<td>1.5</td>
<td>337 (7.2)</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Marso et al. NEJM 2016; 375: 311-22
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Nephropathy: New onset macroalbuminuria or a doubling of the serum creatinine, eGFR of ≤45, renal-replacement therapy, or death from renal disease.
Retinopathy: Retinal photocoagulation or treatment with intravitreal agents, vitreous hemorrhage, blindness.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Semaglutide (N=1648)</th>
<th>Placebo (N=1649)</th>
<th>Hazard Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td>no./100 person-yr</td>
<td>no. (%)</td>
<td>no./100 person-yr</td>
</tr>
<tr>
<td>Retinopathy complications¶</td>
<td>50 (3.0)</td>
<td>1.49</td>
<td>29 (1.8)</td>
<td>0.86</td>
</tr>
<tr>
<td>New or worsening nephropathy¶¶</td>
<td>62 (3.8)</td>
<td>1.86</td>
<td>100 (6.1)</td>
<td>3.06</td>
</tr>
</tbody>
</table>

Marso et al. NEJM 2016; 375: 1835-44
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

A Incident or Worsening Nephropathy

Hazard ratio, 0.61 (95% CI, 0.53–0.70)
P<0.001

B Post Hoc Renal Composite Outcome

Hazard ratio, 0.54 (95% CI, 0.40–0.75)
P<0.001

Wanner et al. NEJM 2016; 375: 323-34
Thank you

http://qatar-weill.cornell.edu
http://www.medicine.manchester.ac.uk/ena/