Real World Evidence for Insulin Treatment: focus on clinical inertia

Melanie Davies CBE
Learning objectives

After this presentation, you should be able to:

• Have an understanding of real world data with insulin therapy

• Explain the role of clinical inertia in insulin management
Outline

• Guidelines for use of insulin
• Clinical inertia of initiation and intensification of insulin
• When is insulin started in the RW
• What regimens are chosen in the RW
• Impact and efficacy in the RW
• Rates of hypoglycaemia in the RW
• Summary
ADA/EASD 2015: position statement for managing hyperglycaemia

Healthy eating, weight control, increased physical activity

Initial monotherapy

Two-drug combinations

Three-drug combinations

More complex strategies

Insulin (MDI)

Escalate therapy at 3 months if target not achieved.

Individualization of targets


Patient attitude and expected treatment efforts

- More intensive: Highly motivated, adherent, excellent self-care
- Less intensive: Less motivated, non-adherent, poor self-care

Risks potentially associated with hypoglycaemia, other adverse events

- More intensive: Low
- Less intensive: High

Disease duration

- More intensive: Newly diagnosed
- Less intensive: Long standing

Life expectancy

- More intensive: Long
- Less intensive: Short

Important comorbidities

- More intensive: Absent
- Less intensive: Few/mild

Established vascular complications

- More intensive: Absent
- Less intensive: Few/mild

Resources, support system

- More intensive: Readily available
- Less intensive: Limited
Clinical Assessment of Individualized Glycemic Goals in Patients with T2DM: Survey Among Leading Worldwide Diabetologists

A

Ranking of the parameters by the experts

- Risk of hypoglycemia from treatment: 51%
- Life expectancy: 48%
- Risk associated with hypoglycemia: 45%
- Important comorbidities: 29%
- Macrovascular complications: 30%
- Cognitive function: 21%
- Microvascular complications: 19%
- Adherence: 13%
- Functional attitude: 14%
- Disease duration: 22%
- Resources and support system: 8%

MEAN
The challenge when improving HbA$_{1c}$
Outline

• Guidelines for use of insulin
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• Summary
Clinical inertia in stepwise management of type 2 diabetes

Biggest clinical hurdle?
Intensification inertia

- Diet and exercise
- Oral monotherapy
- Oral combination
- Oral plus insulin/GLP-1
- Insulin intensification

[Diagram showing progression from diet and exercise to insulin intensification]
Clinical inertia contributes to poor glycaemic control

Median time (years) to intensification with an additional OAD in T2D

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Two OADs</th>
<th>One OAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;7.2</td>
<td>&gt;7.2</td>
<td>&gt;7.2</td>
</tr>
<tr>
<td>7.0</td>
<td>6.9</td>
<td>1.6</td>
</tr>
<tr>
<td>9.1</td>
<td>9.1</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Mean HbA1c (%) at intensification with an OAD in T2D

<table>
<thead>
<tr>
<th>ADA/EASD target</th>
<th>Three OADs</th>
<th>Two OADs</th>
<th>One OAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.0</td>
<td>9.7</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Khunti K, Davies MJ et al. Diabetes Care 2013; [Epub]
Clinical inertia: patient and physician barriers

- Lack of appropriate education
- Hypoglycaemia
- Impaired quality of life
- Lack of patient adherence to treatment
- Financial restrictions
- Beliefs about patient competence
- Resource issue
- Excess weight gain
- Complex regimens
- Risks in patients with comorbidities
- Resource issue

References:
Consequences of clinical inertia

- 105,477 newly diagnosed type 2 diabetes cases
- One-year delay in intensification in patients with HbA1c ≥ 7.0% (≥ 53 mmol/mol) associated with:
  - myocardial infarction: 67% (CI 1.39 to 2.01)
  - stroke: 51% (1.25 to 1.83)
  - heart failure: 64% (1.40 to 1.91)
  - composite cardiovascular events: 62% (1.46 to 1.80)


Abstract
Background: The aim of the study was to evaluate the effect of delay in treatment intensification (i.e., clinical inertia) in conjunction with glycemic burden on the risk of macrovascular events (CVE) in type 2 diabetes (T2DM) patients.

Methods: A retrospective cohort study was carried out using United Kingdom Clinical Practice Research Datalink, including T2DM patients diagnosed from 1990 with follow-up data available until 2012.

Results: In the cohort of 105,477 patients, mean HbA1c was 8.1% (65 mmol/mol) at diagnosis. 11% had a history of cardiovascular disease, and 7.1% experienced at least one CVE during 5.3 years of median follow-up. In patients with HbA1c consistently above 7.7-7.9% (58-59 mmol/mol); n = 23,101/11,281) during 2 years post diagnosis, 56.2% never received any IT compared with patients with HbA1c ≤7% (<53 mmol/mol), in patients with HbA1c ≥7%, 64% (5.5-58 mmol/mol), a 1 year delay in receiving IT was associated with significantly increased risk of MI, stroke, HF, and composite CVE by 64% (95% CI: 1.39, 2.01), 51% (1.25, 1.83), 64% (95% CI: 1.40, 1.91), and 62% (95% CI: 1.46, 1.80) respectively. One-year delay in IT in interaction with HbA1c above 7.5% (58 mmol/mol) was also associated with similar increased risk of CVE.

Conclusions: Among patients with newly diagnosed T2DM, 21% remained under poor glycemic control over 2 years, and 26% never received IT. Delay in IT by 1 year in conjunction with poor glycemic control significantly increased the risk of MI, HF, stroke, and composite CVE.

Keywords: Type 2 diabetes, Delay in treatment intensification, Cardiovascular risk, Longitudinal analysis, Clinical inertia

Background
Currently 8.3% of adults worldwide are estimated to have diabetes [1]. The risk of cardiovascular complications has been related to glycaemia in patients with type 2 diabetes mellitus (T2DM). Randomised controlled trials have conclusively demonstrated that the risk of microvascular complications can be reduced by intensive glycaemic control in patients with T2DM [2-4]. However, there are controversies regarding the benefits of intensive glucose control [HbA1C <7% (53 mmol/mol)] on macrovascular events (CVE), as some of the large trials have failed to show any significant reduction in CVE [1, 5]. The ACCORD trial failed to show any benefit of intensive glucose lowering on CVE, although the haemoglobin A1c (HbA1c) level was reduced to 6.4% (46.6 mmol/mol) in the intensive treatment arm compared to HbA1c level of 7.5% (58.5 mmol/mol) in the standard treatment arm [6]. The primary care based randomised trial ADDITION reported only a small, non-significant reduction in the incidence of CVE and death associated with early intensive management of the disease [7]. However, the UKPDS Post Trial Monitoring Study demonstrated that intensive glucose control starting at the time of diagnosis of diabetes could be associated with a significantly decreased risk of myocardial infarction (MI) and death from any
Barriers to insulin initiation

Patients not treated with insulin

- "Insulin makes you fat"
- Fear of hypoglycemia
- Pain from injection
- Pain from blood tests

Percentage, %

0 10 20 30 40 50 60 70 80 90

Barriers to insulin initiation

- Fear of hypoglycemia
- “Insulin makes you fat”
- Pain from injection
- Pain from blood tests

- Patients not treated with insulin
- Physicians

Patient-reported key barriers to initiating insulin

**Insulin as a last treatment resort**
- When I think about using insulin, I think about succumbing to the disease.
- If I have to take insulin, I probably haven’t looked after myself. It’s the last option.

**Insulin as evidence of personal failure to self-manage diabetes**

**Negative perceptions around insulin**
- After my grandmother went on insulin, she suffered from all sorts of complications and health problems like amputations. I am afraid of the same thing happening to me.
- I’ve heard that it’s insulin that causes weight gain, rather than the tablets.

**Treatment convenience**
- Injecting yourself is a bit of an awkward thing to do. It’s a hassle, too, bringing it along, always.

**Weight gain from insulin**
- If I see a needle, it doesn’t matter where, even at the dentist, it is hell for me. If possible, I would try to avoid it forever.

**Concerns of hypoglycemia**
- If it gets too low, so that you faint. That’s why I don’t want it. Because I don’t have anyone to look out for me, since I live on my own.

**Needles and injections**
- If I see a needle, it doesn’t matter where, even at the dentist, it is hell for me. If possible, I would try to avoid it forever.
Non-Adherence a Problem of Epidemic Proportions

- Non-adherence in chronic diseases averages 50% by 1 year disease duration\(^1\)
- In Europe, it costs €125 billion and contributes to 200,000 deaths/year\(^2\)
- 3/10 stop taking their medicines before their first supply runs out\(^3\)
- 25% take less than the recommended dose\(^3\)
- 33% do not fill the prescriptions they are given\(^3\)

Non-adherence to insulin treatment

Cross-sectional multi-country survey (N=1530)\(^1\)

An average of 33% of patients\(^a\) reported insulin non-adherence;\(^1\) insulin non-adherence rates in diabetes

\(^a\)T1DM or T2DM

Discontinuation with insulin therapy in T2DM

% of patients initiating insulin discontinue in the first 3 months and 82% in the first year post-initiation

Index date is date of first prescription

Positive Predictors of Adherence to Insulin

ADHERENCE RATES 46 – 86%

- Older age
- Support from diabetic nurse specialist
- Physical disability
- Higher household income
- Following a healthy diet
- Perceived self-efficacy
- Hypoglycemia awareness
- Previous experience of liaison psychiatry
- Previous experience of cognitive behavioral therapy
Risks of Over Medicalization

Protecting the person with diabetes from over medicalization is an important aspect of diabetes care

Protect from medical invasion

• Person with diabetes is already living a medically invaded life
• Important not to unnecessarily intrude into a patient's life
• Can be helped by increasing self-management skills at every medical contact
Emergency Hospitalisations for adverse Drug events in Older Americans

<table>
<thead>
<tr>
<th>Medication</th>
<th>Annual National Estimate of Hospitalizations (N=99,628)</th>
<th>Proportion of ER Visits Resulting in Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Commonly Implicated medications†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>33,171</td>
<td>33.3 (28.0-38.5)</td>
</tr>
<tr>
<td>Insulins</td>
<td>13,854</td>
<td>13.9 (9.8-18.0)</td>
</tr>
<tr>
<td>Oral antiplatelet agents</td>
<td>13,263†</td>
<td>13.3 (7.5-19.1)</td>
</tr>
<tr>
<td>Oral hypoglycemic agents</td>
<td>10,656</td>
<td>10.7 (8.1-13.3)</td>
</tr>
</tbody>
</table>

Glycaemic control and use of hypoglycaemic medications in older people with T2 DM and comorbid dementia

Thorpe CT et al Diabetes Care 2015 Jan 15 doi 10.2337/dc14-0599

| Characteristics of community-dwelling older veterans with diabetes and comorbid dementia by level of glycemic control |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Patient characteristics | All patients (n = 15,880) | Tightly controlled (n = 8,276) | Moderately controlled (n = 5,669) | Poorly controlled (n = 1,131) | Not monitored (n = 804) |
| Last HbA$_1c$ value in baseline year (FY2008)$\S$ | 6.8 (6.3-7.6) 51 (45-60) | 6.3 (6.0-6.6) 45 (42-49) | 7.5 (7.2-8.0) 58 (55-64) | 9.8 (9.3-10.7) 84 (78-93) | N/A |
| Medication use in follow-up period (first 120 days of FY2009) | | | | | |
| Medication regimen | Noninsulin monotherapy | 7,298 (46) | 4,942 (60) | 1,756 (31) | 156 (14) | 444 (55) |
| | Noninsulin multitherapy | 3,081 (19) | 1,438 (17) | 1,337 (24) | 180 (16) | 126 (16) |
| | Insulin alone | 3,308 (21) | 1,237 (15) | 1,502 (27) | 421 (37) | 148 (18) |
| | Insulin plus other agent | 2,193 (14) | 659 (8) | 1,074 (19) | 374 (33) | 86 (11) |
| Medication class$\#$ | Insulin | 5,501 (35) | 1,896 (23) | 2,576 (45) | 795 (70) | 234 (29) |
| | Sulfonylurea | 8,927 (56) | 4,690 (57) | 3,204 (57) | 548 (49) | 485 (60) |
| | Metformin | 6,487 (41) | 3,593 (43) | 2,238 (39) | 362 (34) | 274 (34) |
| | TZDs | 826 (5.2) | 339 (4) | 375 (7) | 74 (7) | 38 (5) |
| | a-Glucosidase inhibitors | 233 (1) | 81 (1) | 116 (2) | 28 (3) | 8 (1) |
| Use of medications with high hypoglycemic risk | No insulin/no sulfonylurea | 2,842 (18) | 2,063 (25) | 598 (11) | 42 (4) | 139 (17) |
| | No insulin/yes sulfonylurea | 7,537 (47) | 4,317 (52) | 2,495 (44) | 294 (26) | 431 (54) |
| | Yes insulin/no sulfonylurea | 4,111 (26) | 1,523 (18) | 1,867 (33) | 541 (48) | 180 (22) |
| | Yes insulin/yes sulfonylurea | 1,380 (9) | 373 (5) | 709 (13) | 254 (22) | 54 (7) |
Glycaemic control and use of hypoglycaemic medications in older people with T2 DM and comorbid dementia

• 52 % of patients had tight glycaemic control (< 7%)

• Among tightly controlled patients 75% used SUs and/or insulin

• Many older patients with T2DM and dementia are at high risk of hypoglycaemia associated with intense diabetes therapy

• De-intensification of therapy may be appropriate

Thorpe CT et al Diabetes Care 2015 Jan 15 doi 10.2337/dc14-0599
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• Summary
There is a need for earlier insulin initiation: baseline HbA1c

Clinical inertia exists despite:
- The benefits of timely glycaemic control
- Guidelines encouraging earlier use of insulin

At insulin initiation in SOLVE™:
- The average HbA1c was 8.9%

There is a need for earlier insulin initiation: baseline HbA1c (countries)

- Patients remain poorly controlled on OAD treatment for prolonged periods of time
- At insulin initiation in SOLVE™, mean pre-insulin HbA1c range was:

<table>
<thead>
<tr>
<th>Country</th>
<th>Mean HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>8.9</td>
</tr>
<tr>
<td>China</td>
<td>8.3</td>
</tr>
<tr>
<td>Germany</td>
<td>8.5</td>
</tr>
<tr>
<td>Israel</td>
<td>9.4</td>
</tr>
<tr>
<td>Italy</td>
<td>9.2</td>
</tr>
<tr>
<td>Poland</td>
<td>8.4</td>
</tr>
<tr>
<td>Portugal</td>
<td>9.1</td>
</tr>
<tr>
<td>Spain</td>
<td>8.9</td>
</tr>
<tr>
<td>Turkey</td>
<td>9.8</td>
</tr>
<tr>
<td>UK</td>
<td>9.8</td>
</tr>
</tbody>
</table>

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Factors influencing initial choice of insulin therapy in a large international non-interventional study of people with type 2 diabetes

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⁴ Global Medical Affairs, Sanofi, Bridgewater, NJ, USA
⁵ Groupe Hospitalier Bichat-Claude Bernard, Assistance Publique des Hôpitaux de Paris, INSERM U 695, Université Paris 7, Paris, France
⁶ Diabetology and Metabolic Disorders Centre, Madonna del Soccorso Hospital, San Benedetto del Tronto, Italy
⁷ Department of Medicine, Juntendo University, Tokyo, Japan
⁸ Institute of Cellular Medicine—Diabetes, Newcastle University, Newcastle upon Tyne, UK
What regimen is used in the RW

<table>
<thead>
<tr>
<th></th>
<th>Basal insulin alone</th>
<th>Basal + mealtime insulin</th>
<th>Mealtime insulin alone</th>
<th>Premix insulin</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number (non-Japan/Japan)</strong></td>
<td>1531/32</td>
<td>310/134</td>
<td>91/130</td>
<td>512/188</td>
<td>76/27</td>
</tr>
<tr>
<td><strong>Baseline HbA1c (% units, mean (s.d.) [95% CI])</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excluding Japan</td>
<td>9.2 (1.8) [9.1, 9.3]</td>
<td>9.8 (2.1) [9.5, 10.0]</td>
<td>8.2 (1.6) [7.9, 8.6]</td>
<td>9.8 (2.0) [9.6, 9.9]</td>
<td>8.8 (1.7) [8.3, 9.7]</td>
</tr>
<tr>
<td>Japan</td>
<td>9.8 (1.5) [9.2, 10.3]</td>
<td>10.8 (2.4) [10.4, 11.2]</td>
<td>10.1 (1.9) [9.8, 10.5]</td>
<td>10.1 (1.8) [9.8, 10.4]</td>
<td>10.0 (2.4) [9.1, 11.0]</td>
</tr>
<tr>
<td><strong>Number of treatments (% , 95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excluding Japan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>11.2 [9.6, 12.9]</td>
<td>60.0 [54.3, 65.5]</td>
<td>44.0 [33.6, 54.8]</td>
<td>38.9 [34.6, 43.2]</td>
<td>68.4 [56.7, 78.6]</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>37.6 [35.1, 40.0]</td>
<td>27.1 [22.2, 32.4]</td>
<td>24.2 [15.8, 34.3]</td>
<td>38.1 [33.9, 42.4]</td>
<td>17.1 [9.4, 27.5]</td>
</tr>
<tr>
<td>Dual therapy</td>
<td>43.0 [40.5, 45.6]</td>
<td>12.3 [8.8, 16.4]</td>
<td>29.7 [20.5, 40.2]</td>
<td>18.9 [15.6, 22.6]</td>
<td>11.8 [5.6, 21.3]</td>
</tr>
<tr>
<td>≥3 Oral therapies</td>
<td>8.2 [6.9, 9.7]</td>
<td>0.6 [0.1, 2.3]</td>
<td>2.2 [0.3, 7.7]</td>
<td>4.1 [2.6, 6.2]</td>
<td>2.6 [0.3, 9.2]</td>
</tr>
</tbody>
</table>
CREDIT Study – choice of insulin regime

A

Physical practice: rural vs. urban
Physician specialty: GP vs. specialist
Practice: office- and hospital-based vs. hospital-based
Practice: office-based vs. hospital
Physician gender: male vs. female
Region: E Europe vs. S Europe
Region: N America vs. S Europe
Region: N Europe vs. S Europe
HbA1c
Insulin secretagogues before insulin initiation: yes vs. no

OR (95% CI; p value)
3.66 (2.51, 5.35; < 0.001)
0.50 (0.31, 0.79; 0.003)
0.67 (0.50, 0.90; 0.008)
0.46 (0.33, 0.62; < 0.001)
0.60 (0.45, 0.81; 0.007)
2.81 (1.95, 4.07; < 0.001)
3.06 (2.11, 4.50; < 0.001)
1.63 (1.19, 2.24; 0.003)
1.17 (1.11, 1.24; < 0.001)
0.47 (0.32, 0.69; 0.001)

Odds ratio

Favours basal insulin

Favours premix insulin

Freemantle N et al DOM 2012;14:901-909
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Clinical inertia in type 2 diabetes in real-life clinical practice (at 24 weeks)

n = 17,374.

Mean HbA1c and mean insulin dose in the total SOLVE™ cohort

An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The A1chieve study

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b Internal Medicine, Hai Aljamea Hospital, Jeddah, Saudi Arabia
c Endocrine Research Center (Firouzgar), Institute of Endocrinology & Metabolism, Tehran University of Medical Sciences, Tehran, Iran
d Instituto Jalisciense de Investigacion en Diabetes y Obesidad, Guadalajara, Mexico
e Novo Nordisk International Operations A/S, Zürich, Switzerland
f China-Japan Friendship Hospital, Beijing, China
Impact and efficacy of insulin in the RW

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort</th>
<th>Insulin-naive</th>
<th>Prior insulin users</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>66,726 (100)</td>
<td>44,872 (67.2)</td>
<td>21,854 (32.8)</td>
</tr>
<tr>
<td>Sex, M/F (%)</td>
<td>55.6/44.4</td>
<td>57.3/42.7</td>
<td>51.9/48.1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.0 (12.0)</td>
<td>53.2 (11.6)</td>
<td>55.6 (12.5)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>72.9 (15.0)</td>
<td>71.7 (14.4)</td>
<td>75.3 (15.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1 (5.0)</td>
<td>26.7 (4.7)</td>
<td>27.9 (5.5)</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>8.0 (6.2)</td>
<td>6.6 (5.4)</td>
<td>10.8 (6.8)</td>
</tr>
<tr>
<td>HbA₁c (mmol/mol)</td>
<td>80 (19)</td>
<td>80 (19)</td>
<td>79 (20)</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>9.5 (1.7)</td>
<td>9.5 (1.7)</td>
<td>9.4 (1.8)</td>
</tr>
<tr>
<td>Prior OGLDs, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>44,801 (82.0)</td>
<td>32,006 (82.4)</td>
<td>12,795 (81.1)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>37,086 (67.9)</td>
<td>29,645 (76.3)</td>
<td>7441 (47.2)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>10,578 (19.4)</td>
<td>8087 (20.8)</td>
<td>2491 (15.8)</td>
</tr>
<tr>
<td>One/two/&gt;two</td>
<td>16,193 (29.6)/27,466</td>
<td>8519 (21.9)/21,372</td>
<td>7674 (48.6)/6094</td>
</tr>
<tr>
<td>(50.3)/10,981 (20.1)</td>
<td></td>
<td>(55.0)/8971 (23.1)</td>
<td>(38.6)/2010 (12.7)</td>
</tr>
<tr>
<td>Geographic region, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>11,020 (100)</td>
<td>8206 (74.4)</td>
<td>2814 (25.6)</td>
</tr>
<tr>
<td>East Asia</td>
<td>10,032 (100)</td>
<td>6594 (65.7)</td>
<td>3438 (34.3)</td>
</tr>
<tr>
<td>Latin America</td>
<td>1138 (100)</td>
<td>636 (55.9)</td>
<td>502 (44.1)</td>
</tr>
<tr>
<td>Middle East + Gulf</td>
<td>14,976 (100)</td>
<td>7501 (50.1)</td>
<td>7475 (49.9)</td>
</tr>
<tr>
<td>North Africa</td>
<td>4039 (100)</td>
<td>1969 (48.7)</td>
<td>2070 (51.3)</td>
</tr>
<tr>
<td>Russia</td>
<td>3074 (100)</td>
<td>1899 (61.8)</td>
<td>1175 (38.2)</td>
</tr>
<tr>
<td>South Asia</td>
<td>22,447 (100)</td>
<td>18,067 (80.5)</td>
<td>4380 (19.5)</td>
</tr>
</tbody>
</table>

Data are n (%), %, or mean (SD).
### Impact and efficacy of insulin in the RW

#### Table: HbA1c and Hypoglycaemia

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort</th>
<th>Insulin-naive</th>
<th>Prior insulin users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>24 weeks</td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>HbA1c mmol/mol (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>44,661</td>
<td>30,369</td>
<td>14,292</td>
</tr>
<tr>
<td>Baseline/24 weeks</td>
<td>80 (19)/9.5 (1.7)</td>
<td>57 (12)/7.4 (1.1)</td>
<td>79 (20)/9.4 (1.8)</td>
</tr>
<tr>
<td>Change, p</td>
<td>−23 (19)/−2.1 (1.7), &lt;0.001</td>
<td>−23 (19)/−2.2 (1.7), &lt;0.001</td>
<td>−19 (19)/−1.8 (1.7), &lt;0.001</td>
</tr>
</tbody>
</table>

#### Table: Hypoglycaemia (event per person-year/percent with event)

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort</th>
<th>Insulin-naive</th>
<th>Prior insulin users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline/24 weeks</td>
<td>Baseline/24 weeks</td>
<td>Baseline/24 weeks</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>&lt;0.0001</td>
<td>0.1713</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Minor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>&lt;0.0001</td>
<td>0.0056</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nocturnal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>&lt;0.0001</td>
<td>0.0012</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*P values indicate statistical significance.*

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Impact and efficacy of insulin in the RWE

ABSTRACT

Aim: The aim of achieving was to remedy the deficit of data on the efficacy and safety of insulin analogues in routine clinical care in less well-resourced/newly developed countries. 

Methods: A non-interventional, 6-month, observational study of 66,726 people with type 2 diabetes, both insulin users and non-insulin users, started on insulin detemir, insulin aspart or biphasic insulin aspart in 28 countries across four continents.

Results: Baseline HbA1c (±SD) was poor: 9.5 ± 1.8%. At 6 months, improvement was −2.1 ± 1.7% in the entire cohort, and −2.2 ± 1.7% and −1.8 ± 1.7% for prior non-insulin users and insulin users. All three analogue therapies gave similar results, again independently of prior insulin use, but also from seven pre-specified country groupings. Overall, hypoglycaemia did not increase in those new to insulin, and fell in those switching insulins.

There was no change in body weight (−0.1 ± 3.7 kg), while lipid profile and systolic blood pressure (−6.3 ± 17.1 mmHg) were improved.

Conclusions: Beginning insulin analogue therapy in people with type 2 diabetes and poor blood glucose control is associated with marked improvements in diverse aspects of vascular risk factor profile without evidence of clinically significant safety or tolerability problems.
Outline

- Guidelines for use of insulin
- Clinical inertia of initiation and intensification of insulin
- When is insulin started in the RW
- What regimens are chosen in the RW
- Impact and efficacy in the RW
- Rates of hypoglycaemia in the RW
- Summary
As beta-cell function declines, treatment intensification increases hypoglycaemia risk

Adapted from Lebovitz Diab Rev 1999;7:139–53; UK Hypoglycaemia Study Group Diabetologia 2007;50:1140–7
The glycaemic threshold for hypoglycaemia symptom response alters with age

- In young adult males awareness of symptoms occurred when blood glucose was 3.6 mmol/L, but impairment in cognitive function occurred at 2.6 mmol/L.
- In older males these thresholds are much closer together - awareness of symptoms occurred almost simultaneously with cognitive decline.

Glycaemic thresholds for subjective symptomatic awareness of hypoglycaemia and for the onset of cognitive dysfunction in young and elderly non-diabetic males:

- Younger men: n=7 (22-26 years)
- Older men: n=7 (60-70 years)

Blood glucose (mmol/L):
- Symptoms: 3.5
- Reaction time: 2.5

Reaction time (defined as 4-choice reaction time test)
Prevalence and Incidence of Hypoglycaemia in T2 DM - systematic review and meta-analysis of population based studies

• 46 studies involving 532,542 subjects

• Prevalence of mild/moderate hypoglycaemia in T2DM 45%

• Prevalence of severe hypoglycaemia in T2DM 6%

• On average an individual with T2DM has 19 mild/moderate episodes and 0.8 severe episodes per year
HAT is the largest real-world hypoglycaemia study conducted to date

- HiT: 10 EU countries, N=5843
- DIALOG: France, N=3132
- UK Hypoglycaemia Study Group: UK, N=319
- HAT: 24 countries, N=27,585

2. Cariou B et al. ADA 2013 Abstract 591;
4. Khunti K et al, DOM 2106;18:907-915
Global HAT: retrospective and prospective hypoglycaemia rates in T2D

**Hypoglycaemia prevalence, % of patients**

<table>
<thead>
<tr>
<th></th>
<th>Retrospective</th>
<th>Prospective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any (4 wks)</td>
<td>51%</td>
<td>47%</td>
</tr>
<tr>
<td>Nocturnal (4 wks)</td>
<td>22%</td>
<td>16%</td>
</tr>
<tr>
<td>Severe (6 mths/4 wks)</td>
<td>16%*</td>
<td>9%†</td>
</tr>
</tbody>
</table>

IRR 1.20
IRR 0.69
IRR 1.19

T2D (n=19,563)

Khunti K et al, DOM 2106; 18: 907-915
Hypoglycaemia rates vary by world region

- Overall hypoglycaemia rates for T1D and T2D are high in northern and eastern European (particularly Russian) populations, respectively.

- European populations also display high rates of nocturnal hypoglycaemia
  - T2D-associated nocturnal hypoglycaemia is most common in Russian patients.
Absolute number of admissions by age and year (2005-2014)

Patients increase blood glucose monitoring in response to hypoglycaemia - regional differences

A high proportion of patients in all countries increased monitoring following hypoglycaemia

Increased patient contact with medical personnel following hypoglycaemia

<table>
<thead>
<tr>
<th>Region</th>
<th>Type 2 diabetes</th>
<th>Type 1 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>6.8%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Latin America</td>
<td>5.7%</td>
<td>2.8%</td>
</tr>
<tr>
<td>SE Asia</td>
<td>5.7%</td>
<td>12.6%</td>
</tr>
<tr>
<td>Middle East</td>
<td>7.0%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Russia</td>
<td>12.3%</td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>5.1%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Northern Europe/Canada</td>
<td>3.2%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

% patients requiring extra clinic visits

<table>
<thead>
<tr>
<th>Region</th>
<th>Type 2 diabetes</th>
<th>Type 1 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>8.8%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Latin America</td>
<td>10.7%</td>
<td>21.4%</td>
</tr>
<tr>
<td>SE Asia</td>
<td>8.6%</td>
<td>22.3%</td>
</tr>
<tr>
<td>Middle East</td>
<td>11.7%</td>
<td>21.7%</td>
</tr>
<tr>
<td>Russia</td>
<td>17.3%</td>
<td>17.1%</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>9.2%</td>
<td>14.2%</td>
</tr>
<tr>
<td>Northern Europe/Canada</td>
<td>7.3%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

% patients requiring extra telephone contact with medical personnel

Incidence of CVD and mortality in patients experiencing hypoglycaemia

- CV, cardiovascular; CVD, cardiovascular disease; T1D, type 1 diabetes; T2D, type 2 diabetes

Khunti et al. Diabetes Care 2015;38:316–22
Outline

• Guidelines for use of insulin
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Summary

In the RW

• Clinical inertia is a major problem in insulin initiation and intensification
• Poor adherence and persistence with insulin is the norm
• Insulin is started very late with high HbA1c and regional variations
• Once initiated insulin works well
• Hypoglycaemia is more of a problem in the RWE than in RCTs
• RCTs may underestimate to benefits of newer approaches to insulin therapy in the RWE
Thank you

www.leicesterdiabetescentre.org.uk

www.facebook.com/LeicesterDiabetesCentre

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