Therapeutic Inertia: prevalence, consequences and solutions

Kamlesh Khunti
University of Leicester, UK

Presenter Disclosure

Consultant: Amgen, Abbott, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Janssen, Lilly, MSD, Novartis, Novo Nordisk, Roche, Sanofi and Servier.

Research Support: AstraZeneca, Boehringer Ingelheim, Lilly, MSD, Novartis, Janssen, Novo Nordisk, Roche and Sanofi

Speaker’s Bureau: AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, MSD, Novartis, Novo Nordisk and Sanofi
Impact of intensive therapy for diabetes: summary of major clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>DCCT/EDIC³</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>←</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
</tbody>
</table>

³ In type 1 diabetes.

CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications.


Targeting: Achieving early glycaemic control which may generate a good legacy effect

![Graph showing legacy effect and HbA1c levels](image)

- Conventional
- Metformin

Legacy effect

- Median HbA1c (%)
- 0 6 7 8 9


Difference in HbA1c was lost after first year but patients in the initial intensive arm still had lower incidence of any complication:
- 24% reduction in microvascular complications
- 15% reduction in MI
- 13% reduction in all-cause mortality

MI, myocardial infarction


Early, combination therapy (EDICT Study): Initial triple therapy vs stepwise approach

EDICT study: drug-naive, newly-diagnosed T2DM patients randomized to MET/PIO/EXE BID (triple therapy, N=86) or an escalating dose of MET followed by sequential add-on of SU and insulin glargine (conventional therapy, N=89) to maintain HbA1c levels at <6.5% for 3 years.

Treatment failure defined as HbA1c > 6.5%; Despite lower HbA1c, subjects receiving Triple Therapy experienced 7-fold lower rate of hypoglycemia versus subjects receiving Conventional Therapy.

DeFronzo RA, et al. 52nd EASD Annual Meeting 2016, Munich, Germany; Abstract and poster presentation 794. Available at: www.easdvirtualmeeting.org, last accessed 01 March, 2017

ADA Standards of Care Treatment Algorithm 2018

Achievements of A1c in Europe: GUIDANCE Study

GUIDANCE study 7,597 patients with type 2 diabetes
Gap exists between checking HbA1c and achieving target HbA1c < 7.0%

GUIDANCE, Guideline Adherence to Enhance Care; HbA1c, glycated haemoglobin A1c.

Urgent need to overcome inertia

Therapeutic inertia

“failure to advance therapy or to de-intensify therapy when appropriate to do so”

Outline

Evidence for early tight glycaemic control

Therapeutic inertia
Definition
Extent of the problem
Reasons for inertia
Consequences of inertia
Potential solutions
Summary
Therapeutic Inertia in Stepwise Management of T2DM

- Diet and exercise
- Oral monotherapy
- Oral combination
- Oral plus insulin
- Insulin intensification

Main clinical hurdle?
Intensification inertia?

Treatment Inertia in T2DM over the lifecourse

81,573 people in the UK

Time to treatment intensification from first HbA$_1c$ ≥ 7.5% (58 mmol/mol) by number of OADs and type of intensification

- Intensification by one OAD
- Intensification by two OADs
- Intensification by three OADs

Median time to intensification from HbA$_1c$ cut-off ≥ 7.5%:
- >7.2 years
- 1.9 years
- >6.1 years

Data for a subgroup of more than 55,000 participants with HbA$_1c$ ≥ 7.5% (58 mmol/mol) having any intensification to their treatment at end of follow-up within a retrospective cohort of over 80,000 people

HbA$_1c$, glycated hemoglobin; OAD, oral antidiabetes drug

### Insulin initiation is delayed in clinical practice

**SOLVE**: 24-week observational study involving 10 countries that assessed safety and effectiveness of initiating QD insulin detemir in patients with T2DM treated with ≥1 OADs

<table>
<thead>
<tr>
<th>Country</th>
<th>Mean pre-insulin 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>

Patients remain poorly controlled on OAD treatment for prolonged periods of time.

At insulin initiation in SOLVE, mean pre-insulin HbA1c range was between 8.3% (China) and 9.8% (Turkey/UK).


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### Titration inertia: patients remain at low basal insulin dose

**SOLVE**: 24 week observational study of once-daily (QD) insulin detemir in patients with T2DM receiving OADs

Treat-to-target trials often report higher insulin doses compared to those recorded in observational trials, such as SOLVE.

In one treat-to-target trial, insulin-naive patients were titrated to receive insulin detemir QD or glargine QD

After 52 weeks, the mean daily insulin detemir dose (n=227) was 0.78 U/kg


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Earlier treatment intensification is associated with shorter time to subsequent glycaemic control

Patients do not reach individualised HbA1c targets in real world setting: DUNE Study
Prospective observational study of patients initiated on basal insulin in 28 countries

*Symptomatic
Meneghini L, et al. AhypoglycaemiaDA 77th Scientific Sessions 2017; Poster 990-P
EU5 and US real-world data in 40627 patients with type 2 diabetes initiating basal insulin 2008–2012

Target achievement at 3 months is predictive of target achievement at 24 months

Observational, retrospective analysis of electronic medical records from 5 EU countries and US to assess glycaemic control and hypoglycaemia in insulin-naive adults (≥30 years old) initiating basal insulin with or without OADs

<table>
<thead>
<tr>
<th>Country</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>France (N=2264)</td>
<td>5.04</td>
<td>3.53, 7.18</td>
</tr>
<tr>
<td>Germany (N=2330)</td>
<td>3.71</td>
<td>2.84, 4.85</td>
</tr>
<tr>
<td>Italy (N=1228)</td>
<td>5.22</td>
<td>3.19, 8.52</td>
</tr>
<tr>
<td>Spain (N=1117)</td>
<td>3.50</td>
<td>1.85, 6.62</td>
</tr>
<tr>
<td>UK (N=3468)</td>
<td>5.51</td>
<td>3.73, 8.13</td>
</tr>
<tr>
<td>USA (N=30,220)</td>
<td>3.51</td>
<td>3.21, 3.84</td>
</tr>
<tr>
<td><strong>Overall (N=40,627)</strong></td>
<td><strong>3.70</strong></td>
<td><strong>3.41, 4.00</strong></td>
</tr>
</tbody>
</table>
Post insulin Intensification Inertia

Time from initiation of basal insulin therapy to intensification with bolus or premix insulin or GLP-1 (n= 11,696)

Patients with HbA1c ≥ 7.5%<sup>a</sup>

Median time from initiation of basal insulin to intensification was 3.7 years [95% CI: 3.4;4.0]

<sup>a</sup> ≥ 6 months after starting basal insulin


Median time to treatment intensification
(after one HbA<sub>1c</sub> measurement above target – Selected studies)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Index treatment</th>
<th>Addition to index treatment</th>
<th>Hba&lt;sub&gt;1c&lt;/sub&gt; threshold</th>
<th>Median to treatment intensification, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fu, 2011</td>
<td>Metformin</td>
<td>OAD or injectable</td>
<td>≥7.0%</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.0–7.9%</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8.0–8.9%</td>
<td>0.4</td>
</tr>
<tr>
<td>Yu, 2016</td>
<td>Metformin</td>
<td>OAD or injectable</td>
<td>≥7.5%</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥7.0%</td>
<td>0.7</td>
</tr>
<tr>
<td>Conthe, 2011</td>
<td>1 OAD</td>
<td>OAD or injectable</td>
<td>≥6.5%</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥7.0%</td>
<td>1.0</td>
</tr>
<tr>
<td>Paul, 2015</td>
<td>1 OAD</td>
<td>OAD or insulin</td>
<td>≥7.0%</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥7.5%</td>
<td>1.3</td>
</tr>
<tr>
<td>Ajmera, 2015</td>
<td>2 OAD</td>
<td>OAD or insulin</td>
<td>≥8.0%</td>
<td>1.5</td>
</tr>
<tr>
<td>Khunti, 2016</td>
<td>Basal insulin</td>
<td>Bolus or premix insulin or GLP-1 RA</td>
<td>≥8.0%</td>
<td>3.7</td>
</tr>
</tbody>
</table>

GLP-1 RA, glucagon-like receptor agonist; HbA<sub>1c</sub>, glycated haemoglobin; OAD, oral antidiabetic drug

Khunti K et al. Diab Obes Metab (2017 online)
Overcome therapeutic inertia for quaternary prevention

Therapeutic inertia
“failure to advance therapy or to de-intensify therapy when appropriate to do so”

Quaternary Prevention: interventions that protect a group at risk of over-medicalisation

Potential overtreatment of T2DM in older adults

No statistical difference in achieved glycaemic control across health status (p 0.43)
Potential overtreatment of T2DM in older adults

No statistical difference in type of treatment across health status across health status (p 0.43)

Lipska KJ et al. JAMA Intern Med 2015;175(3):356-362

Overtreatment in UK

3862 patients with T2DM of whom 1379 (35.7%) prescribed SU or insulin therapies.
Median age 78 years; 48% CKD

Hambling C et al. Diab Med 2017;34:1219-1227
Outline

Evidence for early tight glycaemic control

Therapeutic inertia

Definition
Extent of the problem
Reasons for inertia
Consequences of inertia
Potential solutions
Summary

Clinical inertia: patient and physician barriers

- Clinical inertia: patient and physician barriers
- Patient perceptions of insulin treatment and outcomes
- 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
- Lack of appropriate education

Efficacy to effectiveness gap

RCTs are typically highly selective, often excluding:¹
- Elderly patients (aged 65 and older)
- Patients with comorbidities
- Patients taking other drugs

Patients seen in real-world practice may be:
- Mostly older than 65 years
- Suffering from several diseases
- Taking multiple drugs

“Diverse and complex”

- How can I be sure that RCT results are applicable to my patients?
- Does your drug work in the real world?

BP, blood pressure; CVD, cardiovascular disease; RCT, randomized controlled trial

Comorbidity of top 10 common conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage with both conditions</th>
<th>Percentage of people aged 65 years with condition</th>
<th>Mean No of conditions in people aged 65 years with condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>8.8</td>
<td>3.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.9</td>
<td>2.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.8</td>
<td>3.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Stroke/transient ischaemic attack</td>
<td>6.0</td>
<td>3.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6.5</td>
<td>3.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.6</td>
<td>2.9</td>
<td>6.5</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>14.3</td>
<td>2.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Painful condition</td>
<td>12.7</td>
<td>3.1</td>
<td>4.3</td>
</tr>
<tr>
<td>Depression</td>
<td>25.4</td>
<td>2.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Dementia</td>
<td>5.3</td>
<td>4.1</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*Percentage who do not have one of 39 other conditions in the full count*

Where are the barriers to insulin initiation: physicians or patients?

![Bar chart showing percentage of patients not treated with insulin due to various reasons.]

Earlier intensification by 6 months is associated with 18% higher odds of lowering HbA1c below 7% at 24 months.

Montvida O et al. Diab Obes Met 2016 (online)
Consequences of Inertia: Retinopathy

- Significantly shorter median time to progression of diabetic retinopathy
- The adjusted incidence rate for diabetic retinopathy progression in clinical inertia: 4.9 (95% CI; 1.1, 21.8)


Consequences of Inertia: Cardiovascular complications

- At 5.3 years, significantly increased risk of:
  - MI 67% (CI 39–101%)
  - Stroke 51% (CI 25–83%)
  - HF 64% (CI 40–91%)
  - Composite CVE 62% (CI 46–80%)

- Patients with HbA1c ≥7% not receiving IT within 1 year
- Patients with HbA1c <7% who received IT before 1 year of diagnosis

Dyglycaemic “legacy” 26%

CVE, cardiovascular endpoint; HF, heart failure; IT, treatment intensification; MI, myocardial infarction

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Interventions to overcome Inertia

Education (CME)
Motivating and supporting patients on self-management
Adherence to medications
Adherence to guidelines
Developing quality measures
Effective use of information systems
Personal feedback to HCPs

CME, continuing medical education.
Overcoming barriers to injectable therapies

Stepping Up trial: logic model

Aim: To test the effectiveness of the Stepping Up model of care compared to usual care for T2D in GP

- Education and training of PN, GP
  - Increased confidence and skills of PN
  - Improved capacity in practice to manage the clinical work of insulin initiation

- Increased numbers of people starting insulin

  **Secondary outcome:**
  Number of patients commencing insulin

- Improved glycaemic outcomes
  **Primary outcome:**
  Change in HbA1c

Other outcomes
- Proportion reaching HbA1c ≤ 7%
- Psychometric scores: PHQ-9, PAID, AQoL-8D
- Hypoglycaemia

Russell-Jones D. Pouwer F, Khunti K. Diab Obes Met 2017 (online)
Furler J et al. BMJ 2017;356:j783
Mixed effects multilevel regression with adjustment for clustering at the practice level indicated a **0.7% reduction in HbA1c** in the intervention group compared to the control group ($\beta = -0.7$, 95%CI -1.1, -0.4, $p<0.001$)
Multifactorial intervention in individuals with type 2 diabetes and microalbuminuria: MEMO study

Overall effect: −0.48 (−0.76 to −0.21), p = 0.001

Impact of education on hypoglycaemia

Grade 1 (minor) hypoglycaemia was defined as the presence of hypoglycaemic symptoms with a self-measured capillary blood glucose of 3.1 mmol/L and self-treated. Grade 2 (moderate) hypoglycaemia was defined as a self-measured plasma glucose of < 3.1 mmol/L and self-treated. Grade 3 (major) hypoglycaemia was defined as requiring the assistance of another person.

Access to structured education poor globally

Summary

T2DM Progressive disease
Tight glycaemic control early associated with longer term benefits
Therapeutic inertia across treatment paradigm common in practice
Many barriers to achieving tight glycaemic targets
Different solutions are needed for different settings
Key issue is INDIVIDUALISING therapies
Earlier and appropriate intervention may improve patients’ chances of reaching goal


OAD monotherapy
OAD dual combination
OAD triple combination
Insulin

8.4% 8.7% 8.8% 9.0%
8.5% 8.7% 9.1%
2.9 years 3.2 years 6.4 years

HbA1c

For all patients
For those with HbA1c ≥ 7%

2.9 years 7.2 years 6.7 years
8.4% 8.8% 9.0%

Time

Conventional stepwise treatment approach
Earlier and more aggressive intervention approach


Thank you

www.leicesterdietescentre.org.uk
www.facebook.com/LeicesterDiabetesCentre
@kamleshkhunti
@LDC_Tweets