Challenges in the management of Type 2 Diabetes: Insulin Therapy
Type 2 diabetes is a progressive condition with the majority of patients requiring insulin therapy in the longer term.

The rapidly rising diabetes prevalence means that insulin initiation will increasingly be undertaken in primary care.

There is currently no evidence-based consensus about how best to initiate insulin therapy, and in particular which insulin preparation should be advocated.
Type 2 DM: Insulin Initiation Therapy Strategies

Initiating Insulin Therapy - OPTIONS

- Basal insulin
- Prandial insulin
- Premixtures of insulins
- Basal plus bolus (prandial) insulin
  +/- Oral hypoglycaemic agents

TARGETS*: HbA1c<7% (<6.5%), FBG<5.6mM, PPBG<7.8mM * individualise
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes

_Holman et al for the 4-T Study Group_  

Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial

_Bretzel et al Lancet 2008;371:1073-84_
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study group)

Holman et al. NEJM 2007;357:1716-30
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)

Trial Design:

Three-arm trial in 708 patients with type 2 diabetes from 58 centres in UK and Ireland

Evaluating addition of three different analogue insulin regimens to dual oral hypoglycaemic therapy (sulphonylurea and metformin)

Open-label randomisation to:
1. Twice a day biphasic insulin (NovoMix 30) n=222 or
2. Three times a day prandial insulin (NovoRapid) n=222 or
3. Once a day basal insulin (detemir) before bed, with a morning injection added if necessary n=224

sc injections using 3 ml disposable-pen devices (FlexPen)
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)

**Year 1**
Comparison of three single insulin regimens, added to OHAs*

- Add biphasic insulin twice a day
- Add prandial insulin three times a day
- Add basal insulin once (or twice) daily

**Years 2 and 3**
If HbA1c > 6.5%, stop sulfonylurea and add a second insulin formulation

- Add prandial insulin at midday
- Add basal insulin before bed
- Add prandial insulin three times a day

708 T2DM on dual OAD

Male = [(FPG [mM]–5)x2] x weight [kg] ÷ (14.3x height [m]-height [m]); F*13.2

* Intensify to a combination insulin regimen in year one if unacceptable hyperglycaemia

Holman et al NEJM 2007;357:1716-30
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)

Sample Size

700 patients required to detect a 0.4% difference in achieved HbA$_{1c}$, allowing for 15% loss to follow up

Statistical Methods

Missing data handled by multiple imputation

Analyses by intention to treat (ITT)

Mixed-effect regression or logistic models used to compare treatment groups overall

Closed-test procedure allows pair wise comparisons when overall treatment effect was significant
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)

Primary at 1 year
To compare HbA$_{1c}$ levels achieved by the three regimens

Secondary outcomes at 1 year include:
Proportion achieving HbA$_{1c}$ $\leq$ 6.5% with or without ‘hypos’*
Proportion with unacceptable hyperglycaemia
i.e. HbA$_{1c}$ $>$ 10% or 2 successive values $>$ 8.5% at $\geq$ 24 wks
Rates of hypoglycaemic events
Eight-point self-measured capillary blood glucose (SMBG)
Proportion requiring twice daily basal insulin (detemir)
Impact on body weight
Quality of Life (EQ-5D) – EuroQol self-reported Q$nnaire$

* weeks 48-52

Holman et al NEJM 2007;357:1716-30
**Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)**

**Major Inclusion Criteria**
- Aged 18 years or more,
- Type 2 diabetes $\geq$ 1 years
- On maximal tolerated doses of metformin + sulfonylurea for $\geq$ 4 months
- HbA$_{1c}$ 7.0% to 10.0% inclusive
- Body mass index $\leq$ 40 kg/m$^2$
- Written informed consent

**Major Exclusion Criteria**
- Taking insulin therapy
- Taking TZD or triple oral antidiabetic agents within the previous 6 months
- Plasma creatinine $>130$ µmol/l
- ALT $\geq$2x upper limit of normal
- Life threatening CV Disease
- Lactating or potentially pregnant females, severe retinopathy

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Holman et al NEJM 2007;357:1716-30
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)

- **Hypoglycaemia**:
  - Grade 1: symptoms only (glucose 3.1 mmol/l or more)
  - Grade 2: symptoms with glucose <3.1 mmol/l
  - Grade 3: third party assistance required

- **Safety Measures**:
  - Unexpected and/or serious adverse events
  - Plasma ALT, creatinine and lipid levels
  - Blood pressure
  - Metformin discontinued if plasma creatinine ≥150 µmol/l on two successive occasions
  - Data Safety Monitoring Board
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)

**Insulin Initiation and Titration**

**Starting dose:**
- **Men**
  \[
  \text{Starting dose} = \left(\frac{(\text{fasting plasma glucose (mmol/l)} - 5) \times 2}{14.3 \times \text{height (m)} - \text{height (m)}}\right) \times \text{weight (kg)}
  \]
- **Women**
  \[
  \text{Starting dose} = \left(\frac{(\text{fasting plasma glucose (mmol/l)} - 5) \times 2}{13.2 \times \text{height (m)} - \text{height (m)}}\right) \times \text{weight (kg)}
  \]

**Clinic visits:**
- Scheduled at 2, 6, 12, 24, 38 and 52 weeks preceded by 3 capillary glucose profiles
  - **(i) Biphasic and basal insulin groups**
    - Pre-breakfast and pre-evening meal
  - **(ii) Prandial insulin group**
    - Pre-meals, 2 hr postprandial & bedtime

**Targets:**
- **Pre-meal** 72-99 mg/dl (4.0-5.5 mmol/l)
- **2 hour postprandial** 90-126 mg/dl (5.0-7.0 mmol/l)
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)

Insulin Dose Titration:

The online Trial Management System suggested dose adjustments using a common algorithm for all groups.

- Doses increased if 1/3 or more of glucose values were above target, and in proportion to the gap from target.
- Doses reduced in the presence of hypoglycaemia.
- Investigators encouraged to amend suggested doses, as necessary, on clinical grounds in consultation with patients.
- Patients also educated how to modify doses between visits.

Holman et al NEJM 2007;357:1716-30
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)

**Insulin Initiation and Titration**

**Insulin:** Morning basal-insulin introduce when FPG at target but not pre-evening meal PG and when nocturnal hypoglycaemia limited increases at bed time

**Hypoglycaemia:**
- Grade 1: symptoms with SMBG of 56 mg/dl (3 mmol/l)
- Grade 2: minor – symptoms plus SMBG < 56 mg/dl
- Grade 3; major – if third party assistance required

**Hyperglycaemia:** Unacceptable – HbA1c > 10% or 2 consecutive values ≥ 8% after 24 weeks, then second type of insulin added and sulfonylurea discontinued,
  (i) prandial insulin added mid-day to biphasic insulin or thrice pre-prandially to basal insulin
  (ii) add basal insulin to prandial insulin at bedtime

Holman et al NEJM 2007;357:1716-30
### Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)

#### Baseline Demography

<table>
<thead>
<tr>
<th></th>
<th>Biphasic n=235</th>
<th>Prandial n=239</th>
<th>Basal n=234</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>68%</td>
<td>64%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>White Caucasian</strong></td>
<td>94%</td>
<td>90%</td>
<td>93%</td>
</tr>
<tr>
<td><strong>Asian</strong></td>
<td>5%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Other or mixed</strong></td>
<td>&lt;1%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Biphasic n=235</th>
<th>Prandial n=239</th>
<th>Basal n=234</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retinopathy</strong></td>
<td>15%</td>
<td>19%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td>17%</td>
<td>23%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>Nephropathy</strong></td>
<td>9%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Macroangiopathy</strong></td>
<td>22%</td>
<td>18%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>On sulfonylurea</strong></td>
<td>98%</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td><strong>On metformin</strong></td>
<td>96%</td>
<td>95%</td>
<td>97%</td>
</tr>
</tbody>
</table>

*No significant differences between groups*
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)

<table>
<thead>
<tr>
<th>Baseline Demography</th>
<th>Biphasic n=235</th>
<th>Prandial n=239</th>
<th>Basal n=234</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.7 ±8.9</td>
<td>61.6 ±10.5</td>
<td>61.9±10.0</td>
</tr>
<tr>
<td>Diabetes duration (years)*</td>
<td>9 (6-2)</td>
<td>9 (6-4)</td>
<td>9 (6-12)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>86.9 ±16.8</td>
<td>84.9 ±14.4</td>
<td>85.5 ±16.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.2 ±4.8</td>
<td>29.6 ±4.5</td>
<td>29.7 ±4.6</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>8.6 ±0.8</td>
<td>8.6 ±0.8</td>
<td>8.4 ±0.8</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>9.7 ±2.8</td>
<td>9.6 ±2.7</td>
<td>9.5 ±2.6</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.5 ±0.7</td>
<td>2.4 ±0.7</td>
<td>2.3 ±0.7</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.0 ±0.3</td>
<td>1.0 ±0.2</td>
<td>1.0 ±0.3</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)*</td>
<td>1.6 (1.2-2.1)</td>
<td>1.5 (1.2-2.3)</td>
<td>1.5 (1.1-2.2)</td>
</tr>
</tbody>
</table>

*median interquartile range

No significant differences between groups
ONE YEAR RESULTS

TREATING TO TARGET IN TYPE 2 DIABETES
T2DM: Biphasic, Prandial or Basal Insulin (4-T)

<table>
<thead>
<tr>
<th></th>
<th>HbA1c (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1yr</td>
<td>delta</td>
</tr>
<tr>
<td>Biphasic</td>
<td>8.6</td>
<td>7.3</td>
<td>-1.3</td>
</tr>
<tr>
<td>Prandial</td>
<td>8.6</td>
<td>7.2</td>
<td>-1.4</td>
</tr>
<tr>
<td>Basal</td>
<td>8.4</td>
<td>7.6</td>
<td>-0.8*</td>
</tr>
</tbody>
</table>

At 52 weeks
Basal vs Biphasic, Prandial *p<0.001

<table>
<thead>
<tr>
<th></th>
<th>HbA1c % &lt;7.0</th>
<th>&lt;6.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prandial</td>
<td>49</td>
<td>24</td>
</tr>
<tr>
<td>Biphasic</td>
<td>42</td>
<td>17</td>
</tr>
<tr>
<td>Basal</td>
<td>28*</td>
<td>8*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Insulin dose U/d (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prandial</td>
<td>56</td>
</tr>
<tr>
<td>Biphasic</td>
<td>48</td>
</tr>
<tr>
<td>Basal</td>
<td>42</td>
</tr>
</tbody>
</table>

Holman et al NEJM 2007;357:1716-30
Results: Insulin doses (median) at 1 year

- **Biphasic**: 0.53 (0.36 to 0.70), p < 0.006 vs. biphasic
- **Prandial**: 0.61 (0.37 to 0.88), p < 0.02 vs. prandial
- **Basal**: 0.49 (0.34 to 0.73), p < 0.02 vs. prandial

**Total dose per day (U)**
- **Biphasic**: 48 (30 to 71)
- **Prandial**: 56 (34 to 78)
- **Basal**: 42 (28 to 72)
T2DM: Biphasic, Prandial or Basal Insulin (4-T)

Results: Insulin doses (median) at 1 year

Adherence to dose adjustment suggestions (±10%)
- Biphasic: 89.7%
- Prandial: 80.4%
- Basal: 90.2%

Graph showing the insulin dose (U/kg/day) over months since randomisation.
T2DM: Biphasic, Prandial or Basal Insulin (4-T)

<table>
<thead>
<tr>
<th></th>
<th>HbA1c (%)</th>
<th></th>
<th>delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic</td>
<td>8.6</td>
<td>7.3</td>
<td>-1.3</td>
</tr>
<tr>
<td>Prandial</td>
<td>8.6</td>
<td>7.2</td>
<td>-1.4</td>
</tr>
<tr>
<td>Basal</td>
<td>8.4</td>
<td>7.6</td>
<td>-0.8*</td>
</tr>
</tbody>
</table>

Need for 2\textsuperscript{nd} Insulin dose of ‘basal’ insulin 33.8%

Need for 2\textsuperscript{nd} type of Insulin at or after 24 weeks;
- biphasic 8.9%
- prandial 4.2%
- basal 17.9%

*p<0.001 for all comparisons

Holman et al NEJM 2007;357:1716-30
T2DM: Biphasic, Prandial or Basal Insulin (4-T)

Glucose (mmol/l)

Delta FPG (mmol/l)
- Basal: $-3.3 \pm 2.9$
- Biphasic: $-2.5 \pm 3.1$
- Prandial: $-1.3 \pm 2.7$

Delta PPG (mmol/l)
- Prandial: $-4.6 \pm 3.0$
- Biphasic: $-3.8 \pm 3.5$
- Basal: $-2.6 \pm 3.0$

Self-monitoring BG:
1. Fasting BG:
   Basal < Biphasic < Prandial
2. Postprandial BG:
   Prandial < Biphasic < Basal

Holman et al NEJM 2007;357:1716-30
**Results:** Hypoglycaemic Events Grade 2 or 3

- **Biphasic**
  - Mean at 1 year (events/patient/year): 5.7

- **Prandial**
  - 12.0, *p<0.002* vs. biphasic

- **Basal**
  - 2.3, *p=0.01* vs. biphasic, *p<0.001* vs. prandial

*Holman et al NEJM 2007;357:1716-30*
## Results: Haemoglobin A1c %

<table>
<thead>
<tr>
<th></th>
<th>Biphasic aspart insulin</th>
<th>Prandial aspart</th>
<th>Basal insulin detemir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre- and post-</td>
<td>Pre- and post-</td>
<td>Pre- and post-</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>8.6</td>
<td>8.6</td>
<td>8.4</td>
</tr>
<tr>
<td>&lt;7.0%</td>
<td>41.7</td>
<td>48.7</td>
<td>27.8*</td>
</tr>
<tr>
<td>&lt;6.5%</td>
<td>17.0</td>
<td>23.9</td>
<td>8.1*</td>
</tr>
<tr>
<td>+ no ‘hypos’</td>
<td>52.5</td>
<td>43.9</td>
<td>78.9*</td>
</tr>
</tbody>
</table>

HbA1c > 8.5%: biphasic, prandial more effective than basal
HbA1c < 8.5%: no diff. between insulins to achieve <6.5%
40% of basal insulin group required second dose

Holman et al NEJM 2007;357:1716-30
**T2DM**: Biphasic, Prandial or Basal Insulin (4-T)

**Results**: Body Weight

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline to 1 year (kg)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic</td>
<td>+4.7±4.0</td>
<td></td>
</tr>
<tr>
<td>Prandial</td>
<td>+5.7±4.6, <em>p&lt;0.005 vs. biphasic</em></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>+1.9±4.2, <em>p&lt;0.001 vs. biphasic or prandial</em></td>
<td></td>
</tr>
</tbody>
</table>

* p<0.001

**Holman et al NEJM 2007;357:1716-30**
**T2DM : Biphasic, Prandial or Basal Insulin (4-T)**

**HbA1c >8.5% basal less likely to achieve HbA1c ≤6.5%**

**HbA1c <8.5% no difference between insulins in achieving HbA1c ≤6.5%**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Biphasic</th>
<th>Prandial</th>
<th>Basal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c %</td>
<td>7.3</td>
<td>7.2</td>
<td>7.6</td>
</tr>
<tr>
<td>≤6.5%</td>
<td>17</td>
<td>23.9</td>
<td>8.1</td>
</tr>
<tr>
<td>Weight kg</td>
<td>+4.7</td>
<td>+5.7</td>
<td>+1.9</td>
</tr>
<tr>
<td>‘Hypos’</td>
<td>5.7</td>
<td>12</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Holman et al NEJM 2007;357:1716-30
Addition of Biphasic, Prandial or Basal Insulin to Oral Therapy in Type 2 Diabetes (4-T Study)

Conclusions from study

Addition of a single analogue insulin formulation to metformin and sulfonylurea can lower HbA$_1c$ by between 0.8 and 1.4%, and sustain these values over one year.

Regimens using biphasic or prandial insulin reduced HbA$_1c$ to a greater extent than basal, but were associated with greater risks of hypoglycemia and more weight gain.

The one-year results of the 4-T study suggest that similar patients are likely to need more than one type of insulin to achieve target glucose levels in the longer term.

The final two years of the trial will examine specifically the use of complex insulin regimens in these patients.

Holman et al NEJM 2007;357:1716-30
THE APOLLO CHALLENGE

APOLLO : Open Randomised Control Trial

Parallel design trial comparing an oral antidiabetic drug combination Rx with either antus once daily or ispro at mealtimes in T2DM persons failing oral treatment

Bretzel et al Lancet 2008;371:1073-84
Study objective and design:

Primary objective: to show non-inferiority of insulin glargine once-daily plus oral antidiabetic drugs (OADs) vs insulin lispro three-times daily plus OADs in terms of change in HbA$_1$c (baseline to endpoint)

Study design: 44 week, randomised, open-label, parallel, multinational, multi-centre (69) clinical trial in subjects with T2DM inadequately controlled on OADs

Bretzel et al Lancet 2008;371:1073-84
The APOLLO Trial

Participating countries: 69 centres

**AP** Parallel design comparing an **OAD** combination therapy with either **L** Antus once-daily or **L** Lispro at mealtimes in type 2 diabetic patients failing **Oral** treatment

Bretzel et al Lancet 2008;371:1073-84
The APOLLO Trial

Objectives

**Primary**
Change in HbA1c levels

**Secondary**
Proportion of subjects achieving target HbA1c ($\leq 7\%$)
Change in fasting blood glucose (FBG) levels
Proportion of subjects achieving target FBG ($\leq 100$ mg/dl)
Change in 8-point self-monitored blood glucose (SMBG)
Incidence of hypoglycemic events

**Safety**
Adverse events

Bretzel et al, Lancet 2008;371:1073-84
The APOLLO Trial

Study Location: Multicentre (69) Europe and Australia (1)
Duration: 44 weeks

Inclusion criteria: Aged 18-75 yrs; T2DM ≥ 1 yr; HbA1c 7.5-10.5% and on antidiabetic agents for 6m with stable doses for 3 m; FPG ≥ 6.7mM; BMI ≤ 35 kg.m², SMBG users

Exclusion criteria: insulin Rx in the past 4 weeks, GAD +ve, severe retinopathy, significant CVD, renal & hepatic disease, significant other co-morbidities and pregnancy

Procedure: Ethical approval and informed consent
        Open labelled RCT, randomisation centrally,
        Stratified by centre and co-Rx with metformin on a 1:1 basis

Medications: insulin glargine (205), insulin lispro (210)
SMBG: 8-point day profile monthly after 12 week forced titration phase up to 44 weeks

Bretzel et al Lancet 2008;371:1073-84
## The APOLLO trial

### Study Design

| Weeks | Pre-screening | -4 | -3 | -2 | -1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 10 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 |
|-------|---------------|----|----|----|----|---|---|---|---|---|---|---|---|---|-----|----|----|----|----|----|----|----|----|----|----|----|----|----|
|       | Screening Phase (4 weeks) | Entry criteria | Patient training | Start SMBG | Forced titration | Titration fine-tuning |
|       |                |               |                |             | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 10 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 |

**Screening Phase (4 weeks)**
- Entry criteria
- Patient training
- Start SMBG

**Treatment Phase (44 weeks)**
- OAD + insulin glargine (10 IU, once daily)
- OAD + insulin lispro (4 IU, 3x daily at mealtimes)

**Enrolment (n=477)**
- Patients with T2DM
- HbA1c ≥7.5% ≤10.5%
- FBG ≥ 6.7 mmol/L

**Treatment randomisation 1:1 (N=418)**
- Insulin titration regimen
- Target Blood Glucose (mmol/l)
  - FBG ≤5.5
  - Preprandial BG ≤5.5
  - Postprandial BG 2h ≤7.5

* Additional weekly calls to adjust insulin dose if HbA1c >7.0%

T2DM=type 2 diabetes mellitus; BG=blood glucose; SMBG=self-monitored BG; FBG=fasting BG

Bretzel et al Lancet 2008;371:1073-84
## Demographics and baseline characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Insulin glargine (186)</th>
<th>Insulin lispro (191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M(%)</td>
<td>55.0</td>
<td>59.0</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59.7 (9.0)</td>
<td>59.7 (9.0)</td>
</tr>
<tr>
<td>BMI (kg.m(^2))</td>
<td>29.2 (3.6)</td>
<td>29.3 (3.5)</td>
</tr>
<tr>
<td>DM duration (yrs)</td>
<td>9.1 (6.8)</td>
<td>8.6 (6.3)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.73 (0.97)</td>
<td>8.67 (0.97)</td>
</tr>
<tr>
<td>FBG (mmol/l)</td>
<td>10.40 (2.0)</td>
<td>9.80 (2.20)</td>
</tr>
<tr>
<td>Previous Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(%) metformin</td>
<td>78.0</td>
<td>77.0</td>
</tr>
<tr>
<td>alpha Gl</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>TZDs</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Current Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(%) metformin</td>
<td>76.0</td>
<td>75.0</td>
</tr>
<tr>
<td>glimepiride</td>
<td>94.0</td>
<td>93.0</td>
</tr>
</tbody>
</table>

* Per-protocol population

The APOLLO Trial

Bretzel et al Lancet 2008;371:1073-84
### The APOLOLO Trial

#### Demographics and baseline characteristics*

<table>
<thead>
<tr>
<th></th>
<th>Full analysis set (n=412)</th>
<th>Insulin glargine (n=204)</th>
<th>Insulin lispro (n=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td>60.0 ± 9.0</td>
<td>59.68 ± 9.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>29.2 ± 3.7</td>
<td>29.37 ± 3.51</td>
</tr>
<tr>
<td>male (n [%])</td>
<td></td>
<td>107 (52.5)</td>
<td>122 (58.7)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td></td>
<td>9.0 ± 6.8</td>
<td>8.5 ± 6.1</td>
</tr>
<tr>
<td>Duration of OAD treatment (years)</td>
<td></td>
<td>7.0 ± 5.8</td>
<td>7.0 ± 5.5</td>
</tr>
<tr>
<td>Taking metformin (n [%])</td>
<td></td>
<td>155 (76.0)</td>
<td>153 (73.6)</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td></td>
<td>8.7 ± 1.0</td>
<td>8.7 ± 1.0</td>
</tr>
<tr>
<td>FBG (mg/dL)</td>
<td></td>
<td>186 ± 36</td>
<td>178 ± 41</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td></td>
<td>10.3 ± 2.0</td>
<td>9.9 ± 2.3</td>
</tr>
<tr>
<td>Nocturnal BG (mg/dL)</td>
<td></td>
<td>177 ± 44</td>
<td>177 ± 53</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td></td>
<td>9.8 ± 2.5</td>
<td>9.8 ± 2.9</td>
</tr>
</tbody>
</table>

* Intension-to-treat population

Bretzel et al Lancet 2008;371:1073-84
## The APOLLOLO Trial

### Insulin Dose Titration algorithm and SMBG*

<table>
<thead>
<tr>
<th>Insulin glargine</th>
<th>Stating dose</th>
<th>Insulin lispro</th>
<th>PrePBG mmol/l</th>
<th>dose**</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 units</td>
<td></td>
<td></td>
<td>&gt;11.1</td>
<td>+3U</td>
</tr>
<tr>
<td>FBG mmol/l</td>
<td>dose</td>
<td></td>
<td>&gt;8.3 - ≤11.1</td>
<td>+2U</td>
</tr>
<tr>
<td>&gt;8.9</td>
<td>+8U</td>
<td></td>
<td>&gt; 5.5 - ≤ 8.3</td>
<td>+1U</td>
</tr>
<tr>
<td>&gt;7.8 - ≤8.9</td>
<td>+6U</td>
<td>Insulin dose</td>
<td>≤ 5.5</td>
<td>NIL</td>
</tr>
<tr>
<td>&gt;6.7 - ≤7.8</td>
<td>+4U</td>
<td>titration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 - ≤6.7</td>
<td>+2U</td>
<td>algorithm (weekly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5.5</td>
<td>NIL</td>
<td>in units/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Forced titration regimen – European Diabetes Policy Group**

*Self-Monitoring of BG : AccuCheck, Roche Diagnostics  
** Before main meal

TARGETS : FBG & preprandial BG < 5.5 mmol/l; Postprandial < 7.5 mmol/l

Bretzel et al Lancet 2008;371:1073-84
Results: Improvement in Haemoglobin A1c

<table>
<thead>
<tr>
<th></th>
<th>HbA1c (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Insulins</td>
<td>glargine</td>
<td>lispro</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.70</td>
<td>8.67</td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td>6.98</td>
<td>6.80</td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>-1.72</td>
<td>-1.87</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>0.157</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>0.008-0.322</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bretzel et al Lancet 2008;371:1073-84
Results: Improvement in Haemoglobin A1c

The APOLLO Trial

**Improvement in Haemoglobin A1c**

- **Insulins**
  - glargine
  - lispro

- **Baseline**
  - glargine: 8.70
  - lispro: 8.67

- **Endpoint**
  - glargine: 6.98
  - lispro: 6.80

- **delta**
  - glargine: -1.72*
  - lispro: -1.87*

* p<0.001

**Per-protocol analysis (n=377)**

**Adjusted mean (SE) values**

- Insulin glargine + OHAs
- Insulin lispro + OHAs

**Results:**

- Improvement in Haemoglobin A1c

Bretzel et al Lancet 2008;371:1073-84
The APOLLO Trial

Results: Patients reaching Haemoglobin A1c Targets

- HbA1c ≤ 7.0%
  - Insulin glargine + OHAs: 57%, 69%
  - Insulin lispro + OHAs: 30%, 38%

- HbA1c ≤ 6.5%
  - Insulin glargine + OHAs: 57%, 69%
  - Insulin lispro + OHAs: 30%, 38%

Bretzel et al. Lancet 2008;371:1073-84
The APOLLO Trial

Results: Patients reaching Haemoglobin A1c Targets

- HbA1c ≤ 7.0%
  - Insulin glargine + OHAs: 57%
  - Insulin lispro + OHAs: 69%

- HbA1c ≤ 6.5%
  - Insulin glargine + OHAs: 30%
  - Insulin lispro + OHAs: 38%

- FBG ≤ 5.5mM
  - Insulin glargine + OHAs: 38%
  - Insulin lispro + OHAs: 6%

Bretzel et al. Lancet 2008;371:1073-84
The APOLLOLO Trial

Results: Improvement in Fasting Blood Glucose

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Mean FBG (mmol/l)</th>
<th>Change from baseline*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.4</td>
<td>Insulin lispro -1.72 mmol/l</td>
</tr>
<tr>
<td>44</td>
<td>6.2</td>
<td>Insulin glargine -4.20 mmol/l</td>
</tr>
</tbody>
</table>

* * Calculated for the full analysis set (N=412)

Bretzel et al Lancet 2008;371:1073-84
The APOLLO Trial

Results: SMBG day profiles at baseline and endpoint

**Mean blood glucose (mmol/l)**

- **Baseline**
  - Bedtime 03:00: Mean blood glucose 6.0
  - Pre-Breakfast: Mean blood glucose 8.0
  - Pre-Lunch: Mean blood glucose 10.0
  - Pre-Dinner: Mean blood glucose 12.0

- **Endpoint**
  - Bedtime 03:00: Mean blood glucose
  - Pre-Breakfast: Mean blood glucose
  - Pre-Lunch: Mean blood glucose
  - Pre-Dinner: Mean blood glucose

**Significance Levels:**
- *p=0.0137
- **p<0.0041
- ***p<0.0001

**Comparison:**
- Insulin glargine + OHAs
- Insulin lispro + OHAs

* Bretzel et al. Lancet 2008;371:1073-84*
The APOLOLO Trial

Results: Blood Glucose at Baseline and Endpoint

![Blood glucose levels for fasting, nocturnal, and mean 8 point profile with IG and LP insulins.]

- Fasting (0600-0900h): IG -4.3, LP -1.8
- Nocturnal (0300h): IG -3.3, LP -2.6
- Mean 8 point profile: IG -3.4, LP -3.6

P value between groups: Fasting < 0.0001; Nocturnal 0.0041; Profile (8 point) 0.0147

Bretzel et al Lancet 2008;371:1073-84
The APOLLO Trial

Results: Incidence of hypoglycaemic events

Type of Hypoglycaemic Events
(Incidence per patient per year)

Safety analysis population (n=415)

Overall: 24.0
Symptomatic: 13.55
Nocturnal: 4.23
Severe: 2.3

Not on glimepiride:
- Insulin glargine + OHAs
- Insulin lispro + OHAs

Bretzel et al Lancet 2008;371:1073-84
The APOLOLO Trial

Results: Assessment of Treatment Satisfaction

<table>
<thead>
<tr>
<th>Treatment Satisfaction (187)</th>
<th>Perceived frequency of Hyperglycaemia (184)</th>
<th>Perceived frequency of Hypoglycaemia (187)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean DTSQ Score*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>+6.2</td>
<td>+0.95</td>
</tr>
<tr>
<td>Follow-up</td>
<td>+2.7</td>
<td>+0.24</td>
</tr>
</tbody>
</table>

*Scores: Sum of DTSQ items 1, 4-8; at Baseline and visit 15 or visit 21 (endpoint)

Bretzel et al Lancet 2008;371:1073-84
‘Basal’ insulin glargine like ‘prandial’ insulin lispro lower HbA1c equally to target HbA1c ≤7.0%, but with fewer hypoglycaemic events and greater treatment satisfaction.
The APOLLO Trial

Addition of insulin glargine to therapies with oral hypoglycaemic agents can be regarded as a first-line insulin initiation approach in type 2 diabetes mellitus.

See Articles page 1073

Bretzel et al Lancet 2008;371:1073-84
The APOLLO Trial

Annual Treatment Costs in T2DM on OHAs and either Basal Insulin Glargine or Prandial Insulin Lispro

<table>
<thead>
<tr>
<th>Item</th>
<th>GLARGINE (€ per Yr)</th>
<th>LISPRO (€ per Yr)</th>
<th>Δ Costs (€ per Yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>693.09</td>
<td>655.74</td>
<td>+37.35</td>
</tr>
<tr>
<td>Needles</td>
<td>98.22</td>
<td>294.66</td>
<td>-196.44</td>
</tr>
<tr>
<td>BG test strips</td>
<td>240.17</td>
<td>720.51</td>
<td>-480.34</td>
</tr>
<tr>
<td>Lancets</td>
<td>41.15</td>
<td>123.46</td>
<td>-82.31</td>
</tr>
<tr>
<td>Total costs</td>
<td>1,072.63</td>
<td>1,794.37</td>
<td>-721.74</td>
</tr>
</tbody>
</table>

A basal strategy with Insulin Glargine is 40% cost saving!

Bretzel et al Personal communication
## Initial Insulin Therapy in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Main outcomes</th>
<th>APOLLO Study</th>
<th>4T Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>basal</td>
<td>prandial</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at baseline</td>
<td>8.73</td>
<td>8.67</td>
</tr>
<tr>
<td>at endpoint</td>
<td>6.98</td>
<td>6.80</td>
</tr>
<tr>
<td>Δ (change)</td>
<td>-1.75</td>
<td>-1.87</td>
</tr>
<tr>
<td><strong>Responder Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% pts. achieving HbA1c target)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 7.0 %</td>
<td>57</td>
<td>69</td>
</tr>
<tr>
<td>≤ 6.5 %</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td><strong>Responder Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% pat. achieving FBG target)</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td><strong>Insulin-Dose (IU/d) (at endpoint)</strong></td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td><strong>Treatment Satisfaction Score</strong></td>
<td>+6.23</td>
<td>+2.74</td>
</tr>
<tr>
<td>(DTSQ-APOLLO; EuroQol5-D-4T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. of overall hypoglycemic</strong></td>
<td>5.2</td>
<td>24.0</td>
</tr>
<tr>
<td>events per patient-year</td>
<td>(x4.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Change in body weight (kg)</strong></td>
<td>+3.0</td>
<td>+3.5</td>
</tr>
</tbody>
</table>

*Mod. from Bretzel RG et al., Diabetes Care 2009 (in press)
Challenges in the management of T2DM

Summary

T2 Diabetes is a progressive disease

Oral Hypoglycaemic agents (OHA) are ‘temporarily’ effective

Fasting hyperglycaemia is a key component in OHA failures

Basal insulin is FIRST LINE THERAPY (ADA/EASD Consensus)

Ensure adequate dose titration
Treat-To-Target safely
Not all basal insulins are the same

Basal insulins when HbA1c ≤ 8.5% offers benefits of

SIMPLICITY – one injection with flexible timing, one SMBG,
PATIENT FRIENDLY – convenient with less ‘hypos’
and suitable for Primary Care