Type 2 diabetes is a progressive disease with modifiable risk factors. While some patients may initially be managed with diet and exercise, about 50% will require drug therapy within 1 year. For optimal glycemic control, many patients will eventually need oral combination and/or insulin therapy. Since diabetes is a multifactorial disease, optimal care must also emphasize control of blood pressure, lipids, etc.

KEY FINDINGS FROM THE UKPDS

- The UKPDS-33 showed that intensive blood-glucose-control reduced the 10 year risk of microvascular endpoints by ~25% compared to patients allocated to the conventional treatment group. Intensive glycemic control did not have a significant impact on macrovascular endpoints (e.g., risk of stroke or myocardial infarction), diabetes related mortality or all cause mortality. However, tight blood pressure control (UKPDS-38) reduced some macrovascular endpoints.

- The UKPDS-34 studied treatment of obese Type 2 patients with diabetes followed for a mean of 10 years. Metformin GLUCOPHAGE showed the following benefits compared to conventional (primarily diet) therapy [reductions based on # of patients with endpoint]:
  - 38% ↓ risk of stroke; (absolute risk reduction: ARR=2.1%)
  - 32% ↓ risk of any diabetes related endpoint (ARR=10.2%)
  - 33% ↓ in all-cause mortality (ARR=7.1%)

Treatment with sulfonylureas (SU) and insulin did not confer the same benefits. The authors postulated that since HbA1c was similar in both metformin and SU/insulin groups, glycemic control alone could not explain the risk reduction. The UKPDS had many factors that limit interpretation of the data.

CHOOSING AN ORAL HYPOGLYCEMIC

Obese Versus Non-obese
- In non-obese patients, metformin or sulfonylureas (SU) are usually considered first-choice agents.
- In obese patients (BMI ≥30kg/m²), metformin should be considered for first-line therapy. As noted above, it was the only agent to reduce overall mortality in the UKPDS.

Metformin should be avoided in patients with impaired renal function, hepatic disease, alcoholism, symptomatic CHF, and those undergoing intravascular radiocontrast study who are at risk of lactic acidosis. Dosage adjustment may be required in the elderly (due to declining renal function; see Table 2).

Predominant Elevation in PPBG
- Patients who have an elevated postprandial blood glucose (PPBG) >10mmol/L and whose fasting plasma glucose (FPG) is <7 may be considered for agents such as acarbose PRANDASE whose main effect is on PPBG. Repaglinide GLUCONORM and insulin lispro HUMALOG may be considered in patients who have suboptimal control of both PPBG and FPG. PPBG may be elevated early in the course of disease and there is some evidence it is related to poor macrovascular outcomes.

Table 1: Tx GOALS – ADULT DIABETES

<table>
<thead>
<tr>
<th>GLUCOSE CONTROL</th>
<th><strong>OPTIMAL</strong></th>
<th>SUBOPTIMAL</th>
<th>INADEQUATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>&lt; 7.0</td>
<td>7.0-8.4</td>
<td>&gt; 8.4</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>4.0-7.0</td>
<td>7.1-10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>PPBG (mmol/L)</td>
<td>5.0-11.0</td>
<td>11.1-14.0</td>
<td>&gt; 14</td>
</tr>
</tbody>
</table>

Table 2: Metformin Dosing In The Elderly

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Maximum Metformin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>1,700 mg/day*</td>
</tr>
<tr>
<td>30</td>
<td>850 mg/day*</td>
</tr>
<tr>
<td>&lt;30</td>
<td>contraindicated</td>
</tr>
</tbody>
</table>

*There are varying opinions regarding the safety of metformin in those with reduced renal function. Some specialists are more cautious and avoid any use. The “Glitazones” are an alternative in overcoming insulin resistance.

**Target treatment goals need to be individualized with consideration given to life expectancy, co-morbidity and risk of hypoglycemic side effects.
Combination Oral Therapy

- Combination therapy will be required in most Type 2 patients to maintain glycemic control. Many combinations have been studied in terms of their effects on glucose control. Other effects such as weight gain, changes in lipid profile, and additive risk of hypoglycemia have also been evaluated.
- A variety of patient factors should be considered in agent selection. (see Table 6 – Individualization of Therapy).
- Some dual combination regimens have been studied (see Table 7: Combination Therapy). Combinations of more than 2 agents may also be used, but data on these combinations is not available.
- The combination of repaglinide & sulfonylureas is not recommended.16

Insulin in Type 2 Diabetes

- Most current guidelines suggest that when diet, exercise and oral agents fail to provide glycemic control, insulin is indicated. Evidence regarding this is currently limited to studies evaluating glycemic control. Studies on the effects of insulin on clinical outcomes such as morbidity and mortality have not been done. The UKPDS found that insulin therapy was often eventually necessary for glycemic control. It found that tight glycemic control reduced the risk of microvascular complications. Hyperinsulinemia did not appear to contribute to cardiovascular risk, an issue that is still under some debate. Drawbacks to insulin therapy include the side effects of weight gain, hypoglycemia and patient reluctance to use insulin.
- Combinations of oral hypoglycemics and insulin are likely preferable to treatment with insulin alone. A combination approach has an insulin sparing effect and usually leads to improved glycemic control. Some combinations are associated with less hypoglycemia and less weight gain.17 Inclusion of metformin in the regimen minimizes the problems of weight gain and hypoglycemia. The FINFAT study compared different agents combined with bedtime insulin and found that a reduction in HbA1c of 2.5% was greater for metformin than for other studied combinations (SU, SU+metformin, morning insulin).18
- Adding bedtime insulin to oral hypoglycemics is commonly recommended. This approach allows lower doses of insulin to be used, and keeps the insulin regimen simple. (See page 3 – Approach … Add Insulin Therapy.)

Thiazolidinediones (TZDs)

- Agents: rosiglitazone AVANDIA and pioglitazone ACTOS
- TZDs are insulin sensitizers and are moderately effective in controlling hyperglycemia. Adverse effects include weight gain and edema (~4.8% versus 1.2% for placebo); caution in patients with heart failure/hypertension. Incidence of edema was higher in patients also on insulin.
- Patients on TZDs require monitoring of liver function tests (e.g. ALT) at baseline, q2 months during the 1st year of therapy and periodically thereafter. Therapy should not be initiated in patients whose ALT is >2.5x the upper limit of normal and should be discontinued in patients whose ALT rises >3x upper limit of normal. (Troglitazone, the first agent in this class was withdrawn from the market due to severe hepatotoxicity and ≥ 60 deaths.)
- There is some hope that if TZDs are used early in the course of Type 2 diabetes, they may be able to alter the progression of the disease.
- Studies on morbidity/mortality outcomes not yet available
- Long-term safety remains to be established

Acarbose PRANDASE

- Acarbose is useful in reducing peak postprandial blood glucose (PPBG) concentrations.
- Side effects of flatulence, abdominal discomfort and diarrhea limit patient acceptance of this agent. These side effects can be minimized by starting with low dosages (e.g. 25mg with each meal) & titrating up over several months.
- Safety advantages: it does not cause hypoglycemia
- Studies on morbidity/mortality outcomes not yet available
- Long-term safety remains to be established

Repaglinide GLUCONORM

- Repaglinide is rapid but short acting and is useful in lowering PPBG and HbA1c. It has a lower risk of hypoglycemia than sulfonylureas and appears to be well tolerated. It may be especially useful in individuals with irregular eating habits.
- Studies on morbidity/mortality outcomes not yet available
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We would like to acknowledge the following reviewers: Dr. S. Juta (SDH-Diabetes Clinic), Dr. T. Laubscher (CCFP (SDH-FM), Dr. J. Dillon (Internal Med, Iowa), L. Guirguis (Dove Project, Edmonton) M. Zwack (Pharmacist, Prince Albert) & the RxFiles Advisory Committee: Loren Regier RSP BA

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Table 3: NOTES ON NEWER AGENTS (see also Table 8)

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Table 5: APPROACH TO MANAGEMENT OF TYPE 2 DIABETES

Nonpharmacologic Therapy

- **Lifestyle Modifications & Patient Education** are important at all levels!!!

If individualized goals for glucose are not achieved in 2-4 months, 
→ reassess; advance to next level of therapy

See Health Canada’s Food & Fitness Guides

Oral Hypoglycemic Monotherapy

- **If obese (BMI ≥30)**
  - MF target dose in UKPDS (age ≥65): 1700mg am + 850mg @ supper
  - start metformin (MF) 500mg po OD or BID
  - (†dose over 3-4 weeks; usual ≤2,000mg/day; lower doses in elderly-see Table 2)
  - alternative agents used if metformin contraindicated/not tolerated (e.g., acarbose, sulfonylureas, repaglinide, “glitazones”; see chart)

- **If non-obese**
  - start sulfonylurea (SU) or metformin (†dose over 3-4 weeks)
  - consider acarbose or repaglinide if main target is PPBG
  - alternative agents such as “glitazones” may also be considered (note these agents can take a long time before effect seen (8-16 weeks). There are theoretical advantages to early use, but await studies on morbidity and mortality outcomes

Repeat HbA1c: Reassess lifestyle modifications in 2-4 months,
→ If targets for glucose control not achieved, advance combination therapy (Combination therapy will be required in most Type 2 patients)

Oral Combination Therapy

- a variety of 2-drug ( & sometimes 3 drug) combinations may be considered
- combination of repaglinide and sulfonylureas not usually recommended

Repeat HbA1c: Reassess lifestyle modifications in 2-4 months,
→ If targets for glucose control not achieved, advance to next level of therapy

Add Insulin Therapy +/- Oral Agents

- **Option 1:** Bedtime insulin (e.g. Humulin N/Novolin N) + daytime oral hypoglycemics
  → if on SU + other oral agent, may consider discontinuing / reducing the SU
  - add intermediate acting insulin, 10-15units at HS (initial max 0.25units/kg)
  - † insulin dose by 2 units every 3-4 days until fasting glucose of 4 -7
  - if result in better control, lower insulin dose, less weight gain than insulin alone
  - if target BG not achieved at 30units/day, or if daytime BG rises, may switch to split-mixed insulin or a more intensive regimen (usual range: 0.25-1unit/kg/d)

- **Option 2:** Switch to insulin therapy 1-4x/day
  → may discontinue oral hypoglycemic agents
  - adjust insulin dose and frequency to achieve target levels
  - e.g. Split-mixed insulin regimen
  - estimate total starting daily dose (0.3-0.6 units/kg)
  - divide daily dose: 2/3 in morning before breakfast; 1/3 in evening before supper
  - divide each dose: 2/3 intermediate-acting & 1/3 short-acting insulin (or 30/70 mix)
  - (Note: insulin temporarily indicated in any patient with metabolic decompensation, severe fasting hyperglycemia, or severe illness.)

Some patients may eventually require very high doses of insulin due to insulin resistance (max 400U/day in UKPDS)

Table 6: Individualization of Drug Therapy: Special Considerations

<table>
<thead>
<tr>
<th>Patient Factor</th>
<th>Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td>“Glitazones”, Repaglinide; also tolbutamide or gliclazide</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Metformin, “Glitazones”, Acarbose; also Repaglinide</td>
</tr>
<tr>
<td>Obese</td>
<td>Metformin; Acarbose; also “Glitazones”</td>
</tr>
<tr>
<td>Irregular meals</td>
<td>Repaglinide (may be preferred over SU)</td>
</tr>
<tr>
<td>PPBG &gt;10mmol/l</td>
<td>Repaglinide or Acarbose</td>
</tr>
<tr>
<td>&amp; FPG minimally ↑ ↑</td>
<td>Insulin lispro HUMALOG (if PPBG very high)</td>
</tr>
</tbody>
</table>

Table 7: Combination Therapy/Insulin Therapy in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>↓↓↓ HbA1c</th>
<th>↑↑ hypoglyc.</th>
<th>↓↓↑ WT</th>
<th>Comments (long-term outcomes not well studied!)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU + MF</td>
<td>↓↓↓</td>
<td>↑↑</td>
<td>↑</td>
<td>• if SU initial agent, may add MF or a TZD; (SU+MF may ↓ HbA1c by additional 1.7%; one study found ↓ mortality with combination)</td>
</tr>
<tr>
<td>SU + TZD 35</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑↑</td>
<td>• if SU initial agent, may add SU or repaglinide</td>
</tr>
<tr>
<td>SU + acarbose</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑</td>
<td>• MF combos generally result in less weight gain than SU combinations; • MF+pioglitazone had positive lipid effects; • MF+acarbose: ↓ weight / PPBG but ↑ GI SEs; • for hypoglyc. on acarbose: must treat with lunch CHO; may also ↓ weight &amp; triglycerides</td>
</tr>
<tr>
<td>MF+ repaglinide  36</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑</td>
<td>• may improve glycemic control over insulin alone; caution in elderly due to hypoglycemia</td>
</tr>
<tr>
<td>MF+ TZD 35,38</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑</td>
<td>• overcomes insulin resistance; MF has positive effect on wt &amp; lipids; preferred in obese patient; superior to insulin+SU; insulin sparing ~20-25%</td>
</tr>
<tr>
<td>MF+ acarbose 39</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>• tight BG control but hypoglycemia/weight gain</td>
</tr>
<tr>
<td>TZD + acarbose</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑</td>
<td>• may improve glycemic control over insulin alone; caution in elderly due to hypoglycemia</td>
</tr>
<tr>
<td>Insulin monotherapy</td>
<td>↓↓↓↓</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>• tight BG control but hypoglycemia/weight gain</td>
</tr>
<tr>
<td>Insulin + SU</td>
<td>↓↓</td>
<td>↑↑</td>
<td>↑</td>
<td>• may improve glycemic control over insulin alone; caution in elderly due to hypoglycemia</td>
</tr>
<tr>
<td>Insulin + MF (FINFAT STUDY36)</td>
<td>↓↓↓↓</td>
<td>↑↓</td>
<td>↑</td>
<td>• overcomes insulin resistance; effective but more study needed (e.g. ↑ risk of edema/HF)</td>
</tr>
<tr>
<td>Insulin+ pioglitazone or rosiglitazone*</td>
<td>↓↓↓↓↓</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
<td>• overcomes insulin resistance; effective but more study needed (e.g. ↑ risk of edema/HF)</td>
</tr>
<tr>
<td>Insulin+ repaglinide</td>
<td>↓↓↓</td>
<td>↑↑</td>
<td>↑</td>
<td>• option to ↓ PPBG</td>
</tr>
<tr>
<td>Insulin + acarbose</td>
<td>↓↓↓</td>
<td>↑↑</td>
<td>↑</td>
<td>• recommended to ↓ PPBG when diet high in CHO; may also ↓ weight &amp; triglycerides</td>
</tr>
</tbody>
</table>

BG= blood glucose CHO= carbohydrate  FF= fasting plasma glucose HbA1c = glycosylated hemoglobin HF= heart failure MF= metformin PPBG = postprandial blood glucose SE= side effects SU= sulfonylurea TZD= pioglitazone & rosiglitazone WT= weight *official labeling: “not indicated”
### HYPOGLYCEMIC AGENTS - COMPARISON CHART

**KINETICS**

<table>
<thead>
<tr>
<th>NAME / DOSAGE FORMS</th>
<th>EFFECTS ON</th>
<th>DRUG INTERACTION</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| SULFONYLUREAS (SU) – stimulate insulin release from β cell; increase peripheral glucose utilization (↑/#sensitivity of insulin receptors)? reduce hepatic glucoseogenesis | **Cloropropamide**
(100, 230mg scored tab)
| P = 5-6h
D = 24-72h | chloropropamide not recommended due to ↑BP & ↑retinopathy (UKPDS-33) | Does not correct impaired 1st phase insulin response; many (−75%) require 2nd agent for adequate control (e.g., metformin or TZD). | **Hypoglycemia**
most with chloropropamide & glyburide (see note below); least with tolbutamide & glipizide.
Caution in elderly (hypoglycemia risk) & obese (wt gain). |

| **Gliclazide**
DIAMICRON 80mg tab
DIAMICRON MR 30mg | P = 4-6h
D = 10-24h | Does not by itself cause hypoglycemia
Possible wt loss vs wt gain; → DOC for OBESITY. |

| **Glyburide**
(2.5, 5mg scored tab) | O=15-60min
P=2-4h
D=≤12-24h | Require dose titration q1-2 weeks |

| **Tolbutamide**
(500mg scored tab) | P = 3h
D = 6-12h | GI hypoglycemia (850mg tid) |

| BIGUANIDES – increase insulin sensitivity and cellular glucose uptake; reduce hepatic glucose production; ↓ morbidity & mortality in obese patients (UKPDS-34) | **Metformin**
(MF)
GLUCOPHAGE
(500, 850mg tab) | P = 3h
D = 8-12h | +ve effect on lipids & weight |

| Acarbose
PRANDASE
(50,100mg scored tab) | Meal-time dosing; may take several weeks for max. effect | acarbose minimally absorbed; monitor 2hr PPBG |

| Miglitol
GLYSET (25.50,100mg tab) | P = 3h
Available in Can. | miglitol well absorbed |

| THIAZOLIDINEDIONES (TZDs) or “GLITAZONES” – insulin sensitizers: ↓ hepatic output of glucose & peripheral insulin uptake; ~ 4+ weeks before effect (adj dose at ~3 months) | **Pioglitazone**
ACTOS
(15, 30, 45 mg tab) | Delayed action. Onset ~3wks | More effective in obese or hyperinsulinemia patients |

| Rosiglitazone
AVANDIA
(2, 4, 8mg tab) | Max effect in 8-16w | More effective in obese or hyperinsulinemia patients |

| CARBAMOYL BENZOIC ACID DERIVATIVES (CMbas) – short-acting insulin secretagogues; bind to β cell to stimulate insulin release at different site than SUs; (adj dose at ~7days) | **Repaglinide**
GLUCONORM
(0.5, 1, 2mg tab) | O = <10min
P=50-90min
D = 2-4h | Restores 1st phase insulin release (↓ PPBG) |

---

$ Retail Cost to Consumer based on acquisition cost, markup & dispensing fee in SK. Lowest generic price where available. Exception Drug Status in SK. Non-formulary in SK; ‘*’ denotes combination options BP= blood pressure DOC= drug of choice dysfx= dysfunction ETOH= alcohol FPG= fasting plasma glucose HbA1c= glycated Hemoglobin A1c (reflects glycemic control over prior 8-10 weeks) LDL= low density lipoprotein HF= heart failure Ins.= Insulin KINETICS: O= onset P= peak D= duration; LDL= low density lipoprotein PPBG= postprandial blood glucose SE= side effects Wt= weight

---

* **Drugs that may cause hyperglycemia** and loss of diabetic control: corticosteroids, diuretics (high-dose thiazides), estrogens, phenothiazines, phenytoin, sympathomimetics (decongestants) & thyroid products. Beta-blockers minimal risk of altering glucose control but may alter/mask hypoglycemic response. * Pregnancy Encourage diet, moderate exercise; Avoid oral hypoglycemics; Add insulin if FBG >5.3 & 2hr PPBG >8.9. Hypoglycemia risk: UKPDS risk of ≥1 MAJOR hypoglycemic events/yr (ITT); chloropropamide=1%, glyburide=1.4%, insulin 1.8%; risk of ANY hypoglycemic event/yr chlorop.= 16%, glyburide=21%, insulin 28%. Oral agents +/- Insulin: with progression of Type 2 diabetic disease, combination therapy with oral agents &/or addition of insulin to the regimen may eventually be required. PPBG may better reflect cardiovascular disease and all-cause mortality than FBG; FBG and HbA1c are greater predictors of microvascular complications. * Also consider: ASA, ACE Inhibitor, control of lipids/ hypertension, diet/exercise & DC smoking!
References: The RxFiles - Agents for Type 2 Diabetes (Oct/2001)

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