Diabetes Management – insights from epidemiology and clinical trials

Glucose control – outcomes; therapies for type 1 and type 2 diabetes

Hypertension

DCCT (6.5 yrs) and UKDS – 10% lowering of HbA1c reduces incidence of microvascular complications by 25 to 37%

DCCT research group Diabetes 1997; 46: 271
UKPDS Stratton et al. BMJ 2000;321:405
Steno study – intensive multifactorial intervention in T2D with microalbuminuria

<table>
<thead>
<tr>
<th></th>
<th>Standard (n = 80)</th>
<th>Intensive (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>&lt; 160</td>
<td>&lt; 140</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>&lt; 95</td>
<td>&lt; 85</td>
</tr>
<tr>
<td>HbA1c</td>
<td>&lt; 7.5</td>
<td>&lt; 6.5</td>
</tr>
<tr>
<td>TG</td>
<td>&lt; 200</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>CHL</td>
<td>&lt; 250</td>
<td>&lt; 200</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&gt; 35</td>
<td>&gt; 42</td>
</tr>
<tr>
<td>ACE (nl BP)</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Aspirin (CAD)</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Aspirin (PVD)</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

Intensive group treated by study team; standard group by GP.
Glucose control with metformin, sulfonylurea, insulin. Exercise.
Fat and cholesterol restrictions; Statins or fibrates; smoking cessation;
vitamin C and E

Gaede et al. Lancet 1999; 353:620

Steno study – Kaplan-Meier estimates of the primary composite end point
44% vs 24% (mean followup 7.8 yr)

Gaede et al. NEJM 2003;348:383
<table>
<thead>
<tr>
<th>Observational followup after end of interventional component of study</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCCT/EDIC up to 7 year followup (HbA1c difference 0.4% at 1 yr and not different at 5 yrs)</td>
<td>Progression of retinopathy in intensively treated group was 66 to 77% less after mean followup of 4 yrs <em>(JAMA 2002; 287:2563)</em></td>
</tr>
<tr>
<td>DCCT/EDIC 30 yr followup <em>(Diabetes Care Feb 2016)</em></td>
<td>Intensive Rx reduced cardiovascular events by 30% [149 events in 82 vs 217 events in 102] after mean followup of 26 yrs. Can mostly be explained by albuminuria</td>
</tr>
<tr>
<td>UKPDS 10 yr followup (HbA1c difference lost after 1 yr) <em>(NEJM 2008; 359:1577)</em></td>
<td>Intensive Rx group - 24% risk reduction in microvascular event rate and 15 % risk reduction in MI after mean followup of ~ 8.5 yrs</td>
</tr>
<tr>
<td>Steno study mean 5.5 yr observational followup <em>(NEJM 2008; 358:580)</em></td>
<td>20% reduction in mortality in intensively treated group compared to control group</td>
</tr>
</tbody>
</table>


Gregg et al NEJM 370:1514 (2014)
Age standardized rates of DM complications in 2010

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate in DM pop</th>
<th>Rate in non DM pop</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>45.5</td>
<td>25.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>52.9</td>
<td>34.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Amputation</td>
<td>28.4</td>
<td>2.7</td>
<td>10.5</td>
</tr>
<tr>
<td>ESRD</td>
<td>20.0</td>
<td>3.3</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Gregg et al NEJM 370:1514 (2014)

Ethnic disparities persist even with uniform health coverage (reference, whites)

Excess mortality in patients with T2D – Swedish diabetes registry
Study – mean followup ~ 4.6 yrs

<table>
<thead>
<tr>
<th></th>
<th>DM n=435,368</th>
<th>Controls n=2,117,483</th>
<th>Adjusted Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>17.7 %</td>
<td>14.5 %</td>
<td>1.15</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>7.9%</td>
<td>6.1%</td>
<td>1.14</td>
</tr>
</tbody>
</table>

Increased all cause mortality & cardiovascular death increased with younger age, worse glycemic control and renal disease


Improved life expectancy in newer cohorts of type 1 diabetes – Pittsburgh cohort

Miller et al Diabetes 61:2987 (2012)
Life expectancy in Scottish cohort with T1D – death rates from 2008 to 2010

Lose 11 years for men and 13 years for women


20 yr mortality risk in T1D comparable to general population (Pittsburgh Study)

MA = microalbuminuria
ON = overt nephropathy
ESRD

Orchard et al. Diabetologia 53:2312 (2010)
Younger T2D patients may have worse outcomes compared to T1D (median followup ~ 21 to 23 yrs)

<table>
<thead>
<tr>
<th></th>
<th>T2D (15-30)</th>
<th>T1D (15-30)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>mortality</td>
<td>11%</td>
<td>6.8%</td>
<td>2.0</td>
</tr>
</tbody>
</table>

T2D patients – higher BMI, nephropathy; stroke, CAD, hypertensive, hyperlipidemia

Death in T2D occurred after shorter disease duration 26.9 yrs vs 36.5 yrs

Constantino et al Diabetes Care 36:3863 (2013)

Summary

The DCCT, UKPDS and Steno studies showed that glycemic control and multifactorial intervention reduces microvascular and macrovascular complications associated with diabetes.

Patients with history of severe hypoglycemia & advanced atherosclerosis should not aim for < 7%

Recent epidemiological data show an improvement in outcomes of both type 2 and type 1 diabetes

Good glucose control early during disease course can lead to long term benefits even if control deteriorates subsequently

Development of renal disease is an important negative prognostic factor

Younger type 2 patients may have worse outcomes
Glucose control in type 1 diabetes
Rapidly acting human insulin analogs

- Insulin lispro (Humalog, Lilly) - U100 and U200 preparations
- Insulin aspart (Novolog, Novo Nordisk)
- Insulin glulisine (Apidra, Sanofi Aventis)

Short-acting regular insulin

- Regular insulin (Lilly, Novo Nordisk); Regular insulin (U500)
- Technosphere inhaled regular insulin (Afrezza)

Intermediate-acting insulins

- NPH insulin (Lilly, Novo Nordisk)

Premixed insulins

- 70% NPH/30% regular (70/30 insulin—Lilly, Novo Nordisk)
- 70% NPL/25% insulin lispro (Humalog Mix 75/25—Lilly)
- 50% NPL/50% insulin lispro (Humalog Mix 50/50—Lilly)
- 70% insulin aspart protamine/30% insulin aspart (Novolog Mix 70/30—Novo Nordisk)
- 70% insulin degludec/30 insulin aspart (Ryzodeg, Novo Nordisk)

Long-acting human insulin analogs

- Insulin glargine (Lantus (U100), Toujeo (U300), Sanofi Aventis; Basaglar (U100), Lilly)
- Insulin detemir (Levemir, Novo Nordisk)
- Insulin degludec (Tresiba, Novo Nordisk) – U100 and U200 preparations

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A letter to the Lancet re: clinical reports on insulin degludec

What are editors for?

The two trials of insulin degludec share characteristics we think worthy of notice. Each... recruits fewer than ten patients per centre... a good means to get a large number of units used to prescribing new drugs. Both trials produce the same finding: ...not a big difference in glycaemic control achieved by insulin degludec compared with insulin glargine. Each focuses its main conclusion not on this primary outcome, but on one of several secondary measurements: nocturnal hypoglycaemia in the first paper and overall hypoglycaemia in the second. In both, the difference was of marginal significance and no mention is made of adjustment for multiple testing. ..... The papers focus on these secondary outcomes in such a way as to encourage clinicians to believe they warrant the selection of insulin degludec over alternatives.

John Yudkin and colleagues, June 2012
Adjunctive treatment T1D

Metformin

GLP1 receptor agonists

SGLT2 inhibitors

Pramlintide

Libman et al. JAMA 2015; 314:2241

Adolescents (12 to 20 yrs) with T1D. Metformin for 6 months; no improvement in HbA1c but less weight gain and lower insulin doses

Vella et al. Diabetologia 2010

Standardized mean Difference of HbA1c with and without metformin
Liraglutide does not improve glucose control in overweight adults with T1D but did lower body wt

-6.8 kg difference between groups

Dejgaard et al Lancet Diabetes Endocrinol Dec 2015

A cautionary case: SGLT2 inhibitor use in type 1 diabetes

23 year old Caucasian woman with T1D since age 8 – on injections

HbA1c around 8 %

Started on canagliflozin

Glucose levels dropped and so insulin doses were gradually decreased

Insulin glargine dose reduced from 30 to 10 to 8 to 2; also significant reduction in bolus insulin doses

Admitted to hospital with nausea, vomiting, dehydration and ketoacidosis about a month after starting canagliflozin
FDA Drug Safety Communication

73 cases of DKA reported associated with SGLT2 inhibitor Rx
16 cases in patients with type 1 diabetes

http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm

Pramlintide (IAPP analog) + Insulin
Lowers A1C in Type 1 & type 2 Diabetes

Summary

Most proposed adjunctive therapies have modest benefit in T1D and are not recommended. The exception might be pramlintide in a few select patients.

A programmable syringe pump & a plastic cannula inserted into SC tissue
Meta-analyses – T1D patients on average have HbA1c improvement by ~ 0.3 %

T1D ~ 19 yrs; on NPH based regimen

24 pumps

26 insulin glargine/ lispro

Visits at 0, 2, 8, 16, 24 weeks

HbA1c fell by ~ 0.7 % in both groups

Hypoglycemia rates ~ same

Cost €3020 vs 778

REPOSE TRIAL - COMPARE INSULIN PUMP THERAPY TO MULTIPLE INSULIN INJECTIONS WHEN EDUCATION WAS EQUIVALENT IN T1D (n=267)

Primary endpoint – HbA1c change at 24 months was the same -0.5% from baseline

Heller et al. Oral presentation World Diabetes Congress 2015
Clarke error grid analysis for one of the current generation of sensors

75% of sensor data are within 20% of reference glucose (Zone A)  
20% of sensor data are outside the 20% range but would not lead to inappropriate Rx (Zone B)  
4% of sensor data indicate clinically important with failure to detect hypoglycemia or hyperglycemia (zone D)


Cgm use in adults with T1D improves HbA1c (injections or pumps)

Artificial Pancreas

Overnight Closed-Loop Insulin Delivery in Young People With Type 1 Diabetes: A Free-Living, Randomized Clinical Trial,
Closed loop increased time in target range
By ~ 15%
Reduced mean overnight glucose
By 14 mg/dl

Summary

The newer longer acting insulins have not been shown to have clinically significant benefits

Insulin pumps per se do not dramatically improve glucose control in the well educated patient

CGM is a major advance in Mx of T1D with improved HbA1c without increasing rates of hypoglycemia

CGM data automatically adjusting insulin delivery (artificial pancreas) does improve glucose control
Glucose control in type 2 diabetes

ADA/EASD algorithm 2015

6 classes of drugs:

Metformin
GLP1 receptor agonists/DPP 4 inhibitors
Sulfonylureas (+other secretagogues)
Pioglitazone
SGLT2 inhibitors
Insulin

In making therapeutic decision take into account efficacy; hypoglycemia risk; effect on weight; major side effects; cost

Inzucchi et al. Diabetes Care 2015;38:140–149
Randomized controlled study of gastric banding vs lifestyle weight loss in 60 obese patients (BMI 30 to 40) with DM < 2 years


Case 1

UCSF 2013 – 66 yr old Caucasian man. BMI 39.5 (290lb). DM since age 56. On metformin for 5yrs. Stopped and placed on insulin. 50 units of glargine; 20 to 30 units insulin aspart premeals (total insulin ~ 125 units daily). Peripheral neuropathy; nephropathy with urine albumin 3.1 g/g creatinine . Normal creatinine. HbA1c 8.1 %

Started metformin and titrated down insulin doses and added glimepiride

Summer 2015 started exenatide with further reduction in insulin doses

Jan 2016 weight 274 pounds. Hba1c 5.8% on combination of metformin, exenatide and glimepiride 2mg daily
<table>
<thead>
<tr>
<th>Combination</th>
<th>Improvement in HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin vs metformin + sulfonylurea</td>
<td>-0.6%</td>
</tr>
<tr>
<td>Metformin vs metformin + thiazolidinedione</td>
<td>-0.5%</td>
</tr>
<tr>
<td>Metformin vs metformin + DPP4 inhibitor</td>
<td>-0.4%</td>
</tr>
<tr>
<td>Metformin vs metformin + GLP1 receptor agonist</td>
<td>-0.9%</td>
</tr>
<tr>
<td>Metformin vs metformin + SGLT2 inhibitors</td>
<td>-0.6%</td>
</tr>
<tr>
<td>Metformin vs metformin + insulin</td>
<td>-0.5%</td>
</tr>
</tbody>
</table>

**GLP1 receptor agonist vs GLP1 receptor agonist + insulin**
-1.0%  
*(Levin et al. Endo Prac 18: 17 (2012))*

**GLP1 receptor agonist vs GLP1 receptor agonist + SGLT2 inhibitor**
-0.8%  
*(Fulcher et al. Diab Obesity Metab 18:82 (2016))*

**DPP4 inhibitor vs DPP4 inhibitor + SGLT2 inhibitor**
-0.5%  
*(Fulcher et al. Diab Obesity Metab 18:82 (2016))*
Adding a DPP4 inhibitor to high efficacy Rx has modest benefit

<table>
<thead>
<tr>
<th>Combination</th>
<th>~ Improvement in HbA1c with combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIP1 receptor agonist + metformin vs DPP4 inhibitor + GLP1 receptor agonist + metformin</td>
<td>-0.3% ( \text{(Violante et al. Diab Med 2012 1464.)} )</td>
</tr>
<tr>
<td>SGLT2 inhibitor + metformin vs DPP4 + SGLT2 + metformin</td>
<td>-0.3% ( \text{(Rosenstock et al Diabetes Care 2015. 38:376)} )</td>
</tr>
</tbody>
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<tr>
<td>DPP4 inhibitor vs DPP4 inhibitor + pioglitazone</td>
<td>- 0.5 %</td>
</tr>
<tr>
<td>Metformin + thiazolidinedione vs GLP1 receptor agonist + metformin + thiazolidinedione</td>
<td>-1.0% ( \text{FDA briefing document on Liraglutide} )</td>
</tr>
<tr>
<td></td>
<td>GLP-1 receptor agonists</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>HbA1c lowering with monotherapy</td>
<td>0.5 to 1.5 %</td>
</tr>
<tr>
<td>Weight</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

These drugs have glucose dependent insulin release and have low risk for hypoglycemia.

U500 insulin – no randomized studies and its PK profile is similar to NPH insulin.
Summary

Metformin + a GLP1 receptor agonist is the most efficacious combination

The agents are additive and not synergistic in terms of HbA1c lowering

The DPP4 inhibitors have modest efficacy either alone or in combination

Overlap of phenotypes

Type 1

Type 2

Genetic
- 80 YO Hispanic woman
- Diagnosed 4 yrs ago routine testing
- HbA1 deteriorated from 7.4 % to 13 % within a year

On Metformin 1 gm BID
Glyburide 5 mg daily

- GAD Ab >30 (1 or < U/mL)
- ICA 512 Ab 3.7 (<0.8 U/mL)

Ethnic differences in the relationship between BMI and diabetes prevalence

Ma & Chan Ann NY Acad Sci 2013; 1281:64
Asians have higher prevalence of diabetes at same waist circumference as caucasians

![Graph showing diabetes prevalence vs waist hip ratio for Europeans and South Asians.](image)


5 day high fat diet high calorie diet causes development of insulin resistance in Asians but not Caucasians (regular diet supplemented with 375 mLs cream/day; BMI 22, waist 81 cm Caucasians; BMI 21, waist 80 cm Asians)

![Bar graph showing Rd/insulin before and after the diet for Caucasians and Asians.](image)

* P <0.05

Bakker et al Diabetes 2014; 63: 248
In clinical trials, the studies with higher percentage Asian participants DPP4 Rx had greater lowering in HbA1c

Kim et al. Diabetologia 2013; 56: 696

Hypertension
ADA recommends systolic BP < 140; diastolic BP < 90

ACCORD STUDY

Intensive BP treatment 119/64 (on 3.4 medicines) did not improve primary outcome (non fatal MI, nonfatal stroke, cardiovascular death) compared to standard blood pressure control – 143/70 (on 2.1 medicines)

ADVANCE STUDY

Lowering BP to 136/73 (baseline BP was 145/81) with perindopril/indapamide compared to placebo reduced risk of primary end point (major macrovascular or microvascular event)

SPRINT trial – in nondiabetic subjects with systolic B >130; lowering systolic BP to 121.4 (compared to 136.2) reduced cardiovascular mortality and all cause mortality

Primary outcome – MI, acute coronary syndrome, stroke, heart failure; death cardiovascular causes.

Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses
Mattias Brunström, Bo Carlberg

49 trials; 73, 738 participants

If baseline systolic BP > 150; Rx reduced all cause mortality, cardiovascular mortality, MI, stroke, ESRD

If baseline systolic BP 140 – 150; Rx reduced all cause mortality
MI, heart failure

If baseline systolic BP < 140; Rx increased cardiovascular mortality; trend increase all cause mortality.

NB. Majority of trials included subjects with known cardiovascular disease

BMJ 352:i717 (2016)