Advances in Diabetes Treatment

New Drugs, Insulins, & Continuous Glucose Monitoring

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Objectives

- Discuss the new ADA/EASD guidelines and the impact upon diabetes treatment
- Review the most recently approved treatments for DM2 and safety concerns in older medications
- Explain the use of continuous glucose monitors in management of DM2
- Highlight promising experimental medication currently undergoing clinical trials

Diabetes Treatment Objectives

- Control Glucose/HbA1c to decrease complication rate and improve sense of well being
- Avoid hypoglycemia
- Limit weight gain, and promote weight loss
- If complications are already present, control glucose to slow their progression.

ADA Guidelines - HbA1c Goal

- The ADA recommends an HbA1c <7.0% in most nonpregnant patients
- A more stringent A1C goals (such as <6.5%) may be appropriate for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment.
  - Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant CVD.

- *Diabetes Care January 2012 vol. 35 no. Supplement 1 S11-S63*

ADA Guidelines - HbA1c Goal

- Less-stringent A1C goals (such as <8%) for patients with severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite self management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.

Diabetes Care January 2012 vol. 35 no. Supplement 1 S11-S63

ADA &EASD Position Statement

- The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) convened a joint task force to develop recommendations for anti-hyperglycemic therapy in non-pregnant adults with type 2 diabetes.
- An update was deemed necessary because:
  - New information on benefits/risks of glycemic control
  - Evidence concerning efficacy and safety of several drug classes
  - The withdrawal/restriction of some drugs
  - A move towards more patient-centered care

  - *S. E. Inzucchi et al. Diabetologia (2012) 55:1577–1596*

New Position Statement by the ADA and EASD

- They developed a patient-centered care approach and stated the recommendations should be considered within the context of the needs, preferences and tolerances of each patient; **individualization** of treatment is the cornerstone of success.

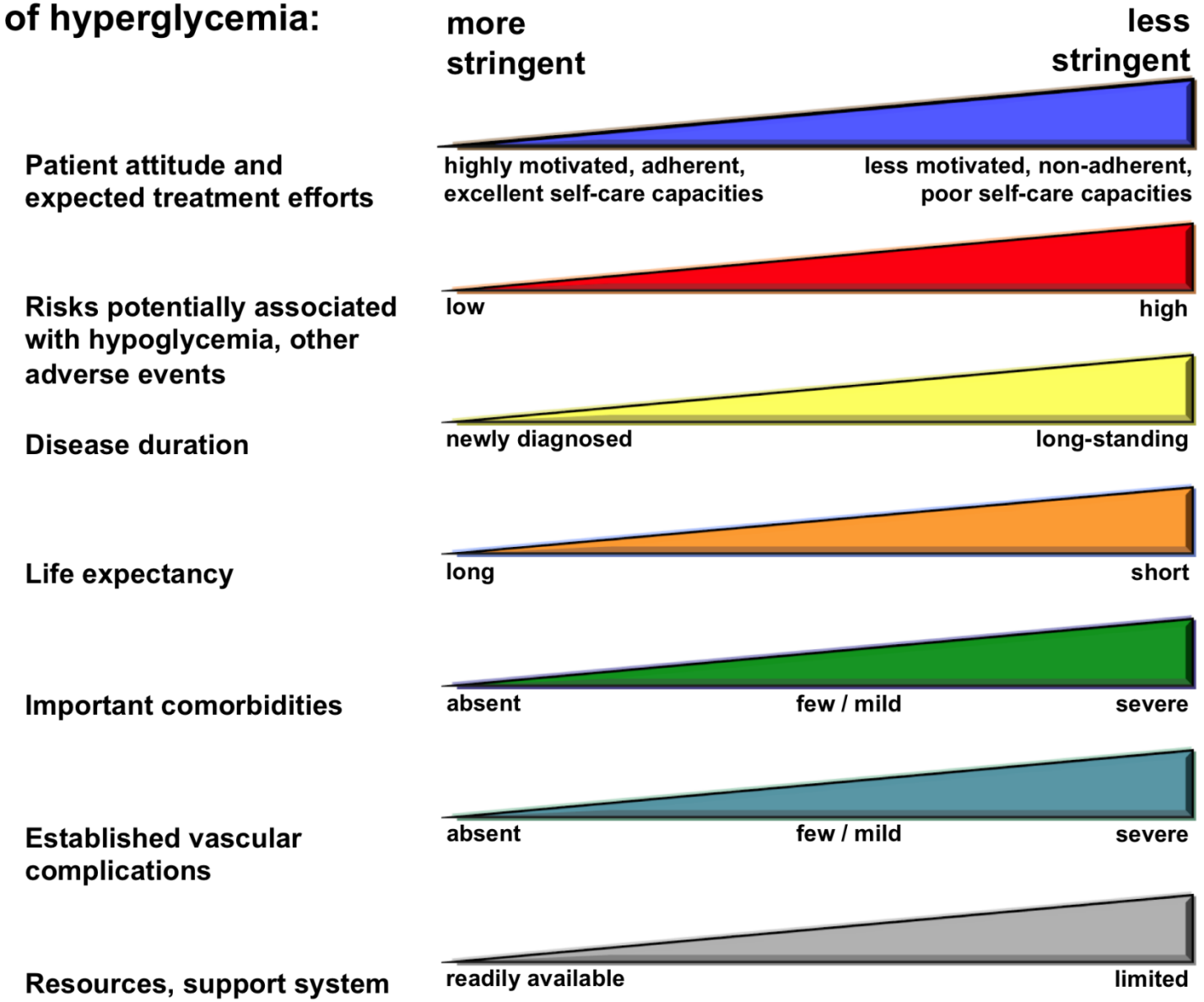
S. E. Inzucchi et al. Diabetologia (2012) 55:1577–1596

Benchmarks

- Utilizing the percentage of diabetic patients who are achieving an HbA1c <7.0% as a quality indicator, as promulgated by various healthcare organizations, is inconsistent with the emphasis on individualization of treatment goals.

- S. E. Inzucchi et al. Diabetologia (2012) 55:1577–1596

Approach to management of hyperglycemia:



Diabetes Care, Diabetologia. 19 April 2012 [Epub ahea

Key Points

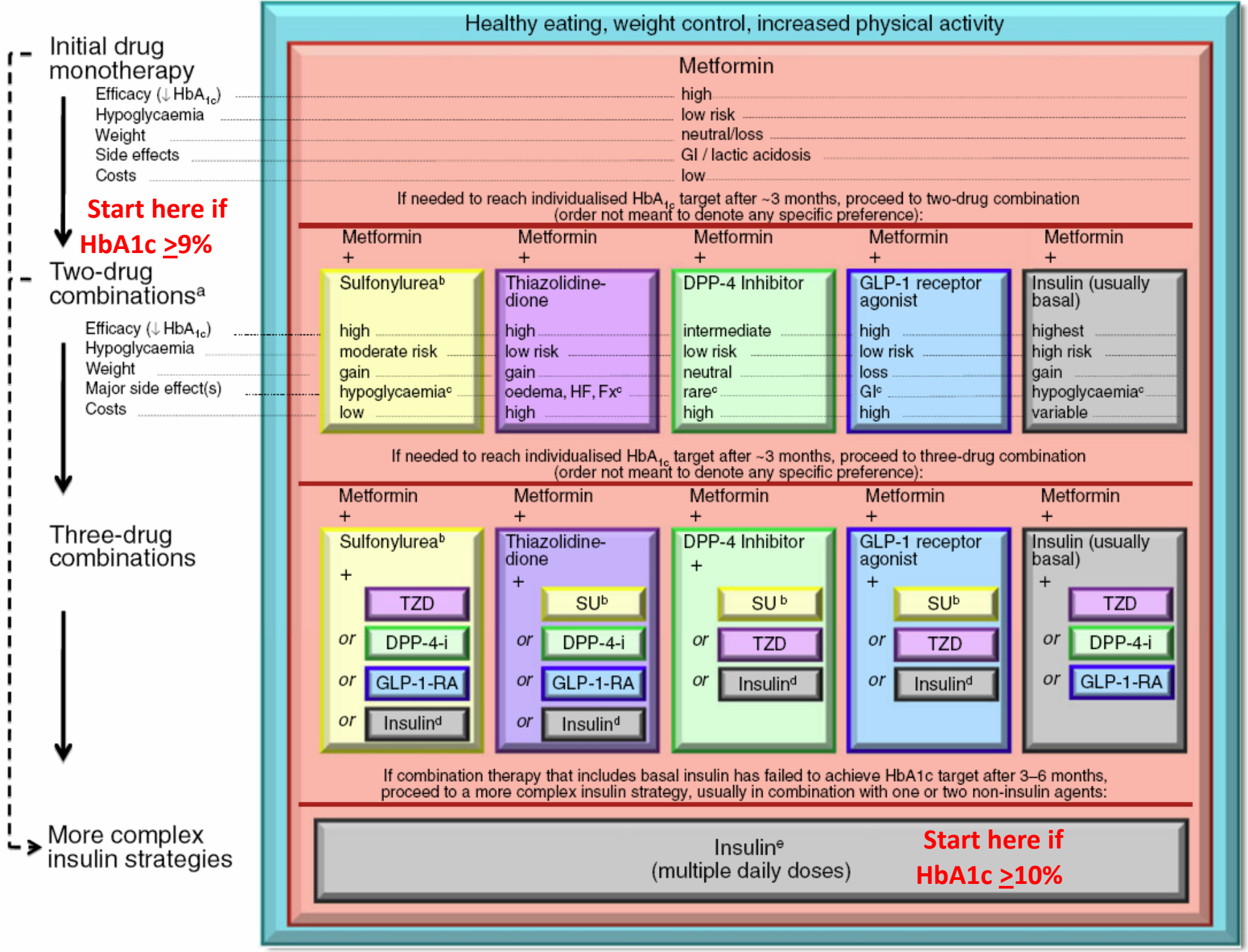
- Glycemic targets and glucose-lowering therapies must be **individualized**
- Diet, exercise and education remain the foundation of any type 2 diabetes treatment program
- Unless there are prevalent contraindications, metformin is the optimal first-line drug.
- After metformin, there are limited data to guide us.
- Combination therapy with an additional 1–2 oral or injectable agents is reasonable, aiming to minimize side effects where possible
- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control
- All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs and values
- Comprehensive cardiovascular risk reduction must be a major focus of therapy

What to do to control?

- In general <7% is appropriate
- Elderly, renal failure, or significant CAD start with 8-8.5% and decrease slowly, if feel is safe.
- Newly diagnosed DM without any of the above frequently can reach a normal HbA1c without hypoglycemia
- Use whatever it takes to get the patient to the appropriate individualized HbA1C goal

What medication to use?

- **Biguanide**
  - Metformin 1995
- **Sulfonylureas**
  - Glipizide
  - Glyburide
  - Glimepiride
- **Meglitinides**
  - Repaglinide
  - Nateglinide
- **Thiazolidinediones**
  - Rosiglitazone
  - Pioglitazone
- **A glucosidase inhibitors**
  - Acarbose
- **Bile acid sequestrant**
  - Colesevelam
- **Dopamine agonist**
  - Bromocriptine
- **Amylin Mimetic**
  - Pramlintide
- **DPP-4 Inhibitors**
  - Sitagliptin
  - Saxagliptin
  - Linagliptin
- **GLP-1 analogs**
  - Exenatide
  - Exenatide ER
  - Liraglutide
- **Insulin**
  - **Basal**
    - NPH
    - Glargine
    - Detemir
  - **Bolus**
    - Regular
    - Lispro
    - Aspart
    - Glulisine
  - **Pumps**


Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Efficacy (↓HbA1c)
Hypoglycaemia
Weight
Side effects
Costs
Start here if HbA1c ≥9%
Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low
If needed to reach individualised HbA1c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):
Two-drug combinations[a]
Efficacy (↓HbA1c)
Hypoglycaemia
Weight
Major side effect(s)
Costs
Metformin + Sulfonylurea[b]
high
moderate risk
gain
hypoglycaemia[c]
low
Metformin + Thiazolidine-dione
high
low risk
gain
oedema, HF, Fx[c]
high
Metformin + DPP-4 Inhibitor
intermediate
low risk
neutral
rare[c]
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI[c]
high
Metformin + Insulin (usually basal)
highest
high risk
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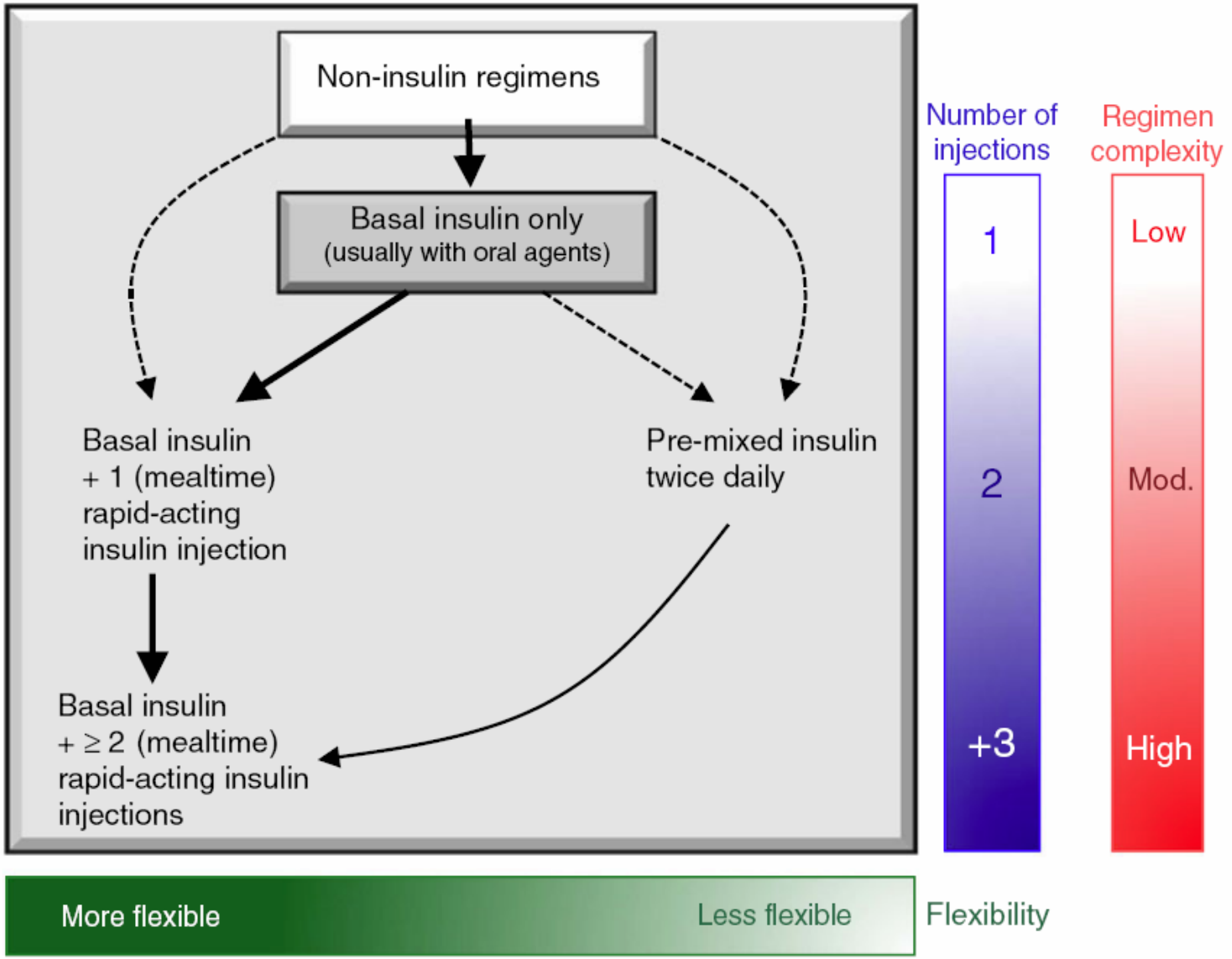
variable
If needed to reach individualised HbA1c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):
Three-drug combinations
Metformin + Sulfonylurea[b] + TZD or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + Thiazolidine-dione + SU[b] or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + DPP-4 Inhibitor + SU[b] or TZD or Insulin[d]
Metformin + GLP-1 receptor agonist + SU[b] or TZD or Insulin[d]
Metformin + Insulin (usually basal) + TZD or DPP-4-i or GLP-1-RA
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3–6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:
More complex insulin strategies
Insulin[e] (multiple daily doses)
Start here if HbA1c ≥10%

Sequential Insulin Strategies in T2DM



Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]

Why always Metformin first?

- At the end of 10 yr follow-up in the metformin group compared with the conventional therapy group in the UKPDS with only a 0.6% drop in the metformin arm (7.9% vs 7.3%):
  - There was a 32% risk reduction for any diabetes-related endpoint
  - There was a 39% risk reduction for myocardial infarction
  - There was a 36% risk reduction for death from any cause
  - 10 years after the study ended, these risk reductions continued despite the same Hba1c as the controls

UKPDS: 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. N Eng J Med 2008; 359

Metformin

- **May cause B12 deficiency**
- Decreases B12 absorption from the gut
- Monitor levels of B12 as if low leads to anemia and neuropathy

Therapies without changes

- Sulfonylureas
- Glinides
- Alpha glucosidase inhibitors
- Amylin analog
- Insulins

Thiazolidinediones (Glitazones)

- **Rosiglitazone**
- **Pioglitazone**
  - Contraindicated in liver dz, severe kidney dz, CHF
  - Increase risk of osteoporosis
  - Should check liver tests 2-3x/year

- Pioglitazone now has cancer risk
- Rosiglitazone has increased MI risk

Pioglitazone and Cancer

- Increase risk of bladder cancer with pioglitazone but not rosiglitazone
- Risk increases with >2yrs of therapy and greatest if >28,000mg total dosage
  - Usual dose is 15-30mg/day so if 30mg/day then 10,950mg/yr so 2.5 yrs
- Do not use in pt at risk for or with known bladder cancer

Rosiglitazone and increased MI

- The Risk Evaluation and Mitigation Strategy(REMS), called the Avandia-Rosiglitazone Medicines Access Program, limits the use of rosiglitazone medicines to:
  - Patients already being successfully treated with these medicines.
  - Patients whose blood sugar cannot be controlled with other anti-diabetic medicines and who, after consulting with their healthcare provider, do not wish to use pioglitazone-containing medicines
  - Prescriber enrolls himself online and each pt after counseling, then drug mailed to patient

Colesevelam

- Traditionally, a cholesterol lowering agent
- Unclear mechanism of glucose lowering
- Mean change in A1C from baseline to week 26 was –0.32% in the colesevelam group and +0.23% in the placebo group, resulting in a treatment difference of –0.54% ($P < 0.001$).

Fonseca: Diabetes Care August 2008 vol. 31 no. 8 1479-1484

Colesevelam

- Colesevelam 625mg 6 tablets daily or 3 tablets bid
- Can use in pt with hepatic dz or moderate renal dz, but not with CrCl <30
- Constipation, heartburn, nausea
- Must take other meds 4 hours before or 2 hours after or blocks absorption including warfarin, birth control pills, antibiotics, antiepileptics, antihypertensives etc.

Bromocriptine

- Dopamine agonist but unknown mechanism for lowering glucose – no change in insulin.
- Initial dose is one tablet (0.8 mg) daily within 2 hours of waking and increased weekly by one tablet until maximal tolerated daily dose of 1.6 to 4.8 mg is achieved
- Decreased HbA1c by 0.1-0.4% so when compared to placebo arm decreased 0.2-0.7%

Bromocriptine

- May exacerbate psychotic disorders or reduce the effectiveness of drugs that treat psychosis.
- Orthostatic hypotension and syncope
  - Use caution in patients taking anti-hypertensive medications.
- Nausea, HA, Dizziness, Rhinitis, Constipation
- Concern that may cause heart valve issues as seen with prolactinoma treatments.
- Can use in renal and liver disease pts

Colesevelam & Bromocriptine

- Most helpful in pts that are intolerant to or have contraindications to other treatments such as liver disease
- In the ADA/EADS Statement: May be used in selected pts but have modest efficacy and/or limiting side effects
  - Acarbose and Pramlintide also in this group

Dipeptidyl Peptidase 4 (DPP-4)

- Inhibiting DPP IV extends the half-life of native GLP-1
- Increased GLP-1 enhances insulin secretion, suppresses glucagon secretion, and slows gastric emptying all which lower glucose

- Modest HbA1c lowering about .6-.8%

DPP-4 Inhibitors

- Minimal side effects
  - Questionable risk of rare pancreatitis
  - Some studies yes, some no
  - 15 per 10,000 patient years versus 4 for comparator
- No issues with liver or cardiac patients
- No hypoglycemia or weight gain

  - Sitagliptin 25,50, 100mg qday
  - Saxagliptin 2.5, 5mg qday
  - **Linagliptin 5mg qday**
    - No dose adjustments with renal patients (others do)

GLP-1

- Analogs of glucagon-like peptide 1, but resistant to DPP-IV degradation
- Lower fasting and postprandial glucose
- Lowers postprandial triglyceride levels
- Suppresses appetite and decreases wt.
- May improves β cell function and proliferation

- Exenatide SC bid
- **Liraglutide SC qday**

GLP-I agonists

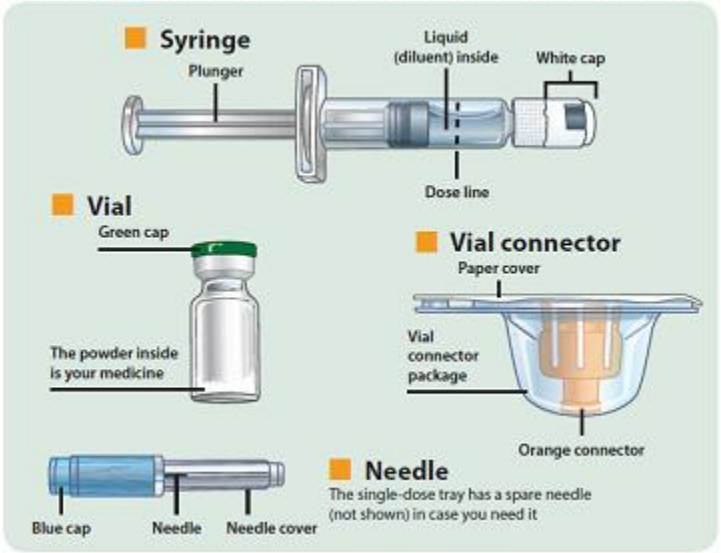
- Same concern about possible rare cases of pancreatitis.
- Concern re medullary thyroid cancer
- No differences were seen in calcitonin levels in subjects treated with **exenatide** vs. **liraglutide**
- Six cases of C-cell hyperplasia were identified, most with elevated baseline calcitonin levels, Liraglutide did not produce further increases in calcitonin levels even in subjects with baseline CT elevations.
- No cases of Medullary cancer (MCT) in GLP-1 pts but one case of MTC was described in a control pt.

Medullary Risk?

- Human **GLP-1** receptor has been found in subsets of thyroid tumor cells from patients with C cell hyperplasia, medullary cancer, and a smaller proportion of papillary thyroid cancers.
- So the GLP-1 receptor is not expressed in normal thyroid follicular cells but may be aberrantly present in a subset of thyroid cancer cells.
- Do not use GLP-1s in pts at risk for thyroid cancer or with known thyroid cancer

Exenatide ER

- 2mg SQ **qweek**
- HbA1c dropped 1.6% at 24wks and weight decreased 2.3kg (for comparison: Regular Exenatide HbA1c decreased 0.9% and wt 1.4 kg)
- Nausea (less than regular Exenatide), diarrhea, injection site nodules



Insulin Pumps

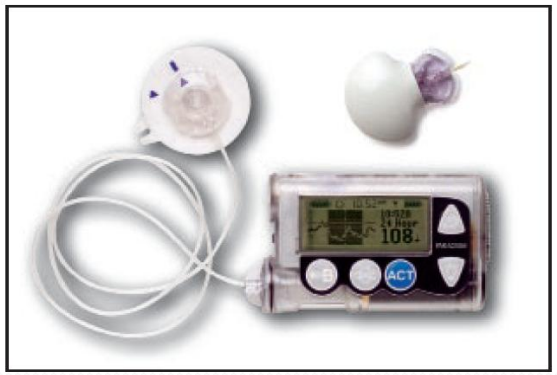
A

B

C

D

E



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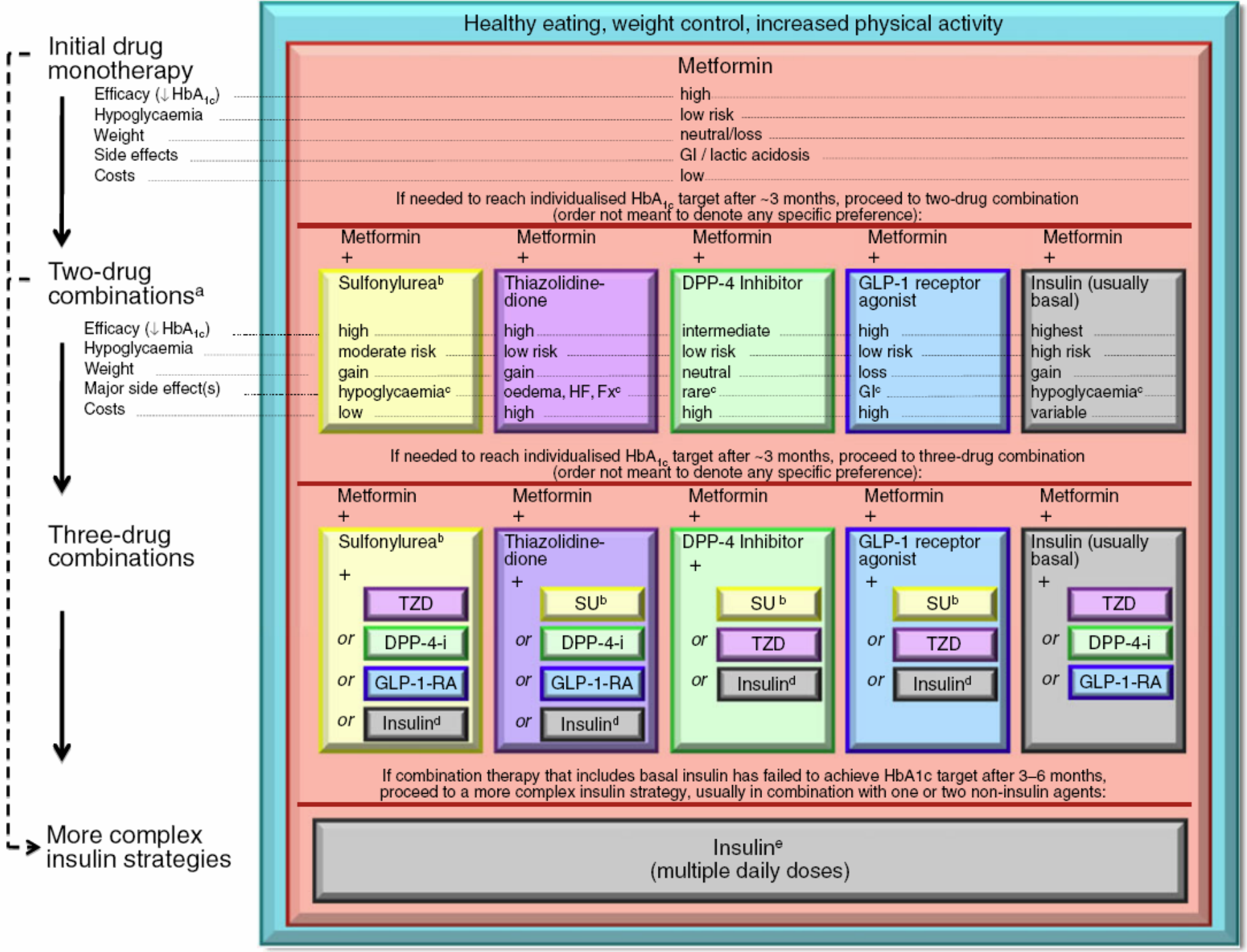
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More complex insulin strategies
Insulin[e] (multiple daily doses)

V-Go Insulin Delivery Device

- Approved for DM 2 patients
- Load with analog insulin using a fill device so no syringes
- Apply to skin and deploy needle, 4.6mm, 30 gauge
  - You never see the needle but stays in
- Spring activated and delivers set rate of insulin/hr for 24hrs, no batteries, no electronics
- Bolus insulin in 2unit increments

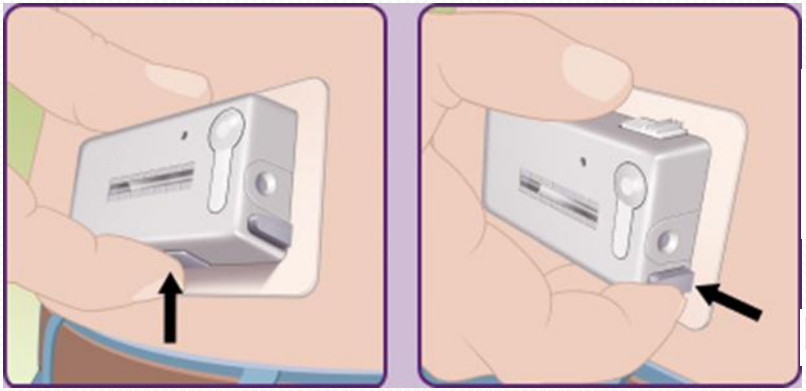
3 Sizes of Units

Preset basal rate	+	On-demand bolus dosing	=	Total available insulin
20 Units/24 hr (0.83 U/hr)	+	Up to 36 Units in 2-Unit increments*	=	56 Units
30 Units/24 hr (1.25 U/hr)	+	Up to 36 Units in 2-Unit increments*	=	66 Units
40 Units/24 hr (1.67 U/hr)	+	Up to 36 Units in 2-Unit increments*	=	76 Units

V-Go Unit and Fill Device

Needle Button

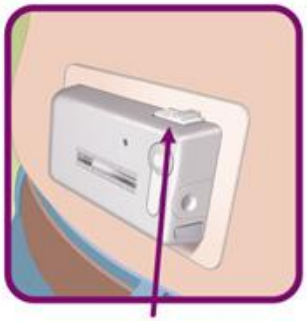
Press once to start the continuous preset basal rate of insulin



2 buttons for on-demand bolus dosing at meals (1 push = 2 Units)

Bolus Delivery Button

Bolus Ready Button



Slide and press once to stop the flow of insulin after 24 hours

Needle Release Button

V-Go

- Bolus button locks after 18 uses so can't bolus more but basal continues
- Throw away after 24hrs and replace at new site 1" away
- Can shower with it, swim up to 1 meter deep
- Covered by Medicare D and insurance plans as either a pharmacy benefit or a medical benefit.

Continuous Glucose Monitors

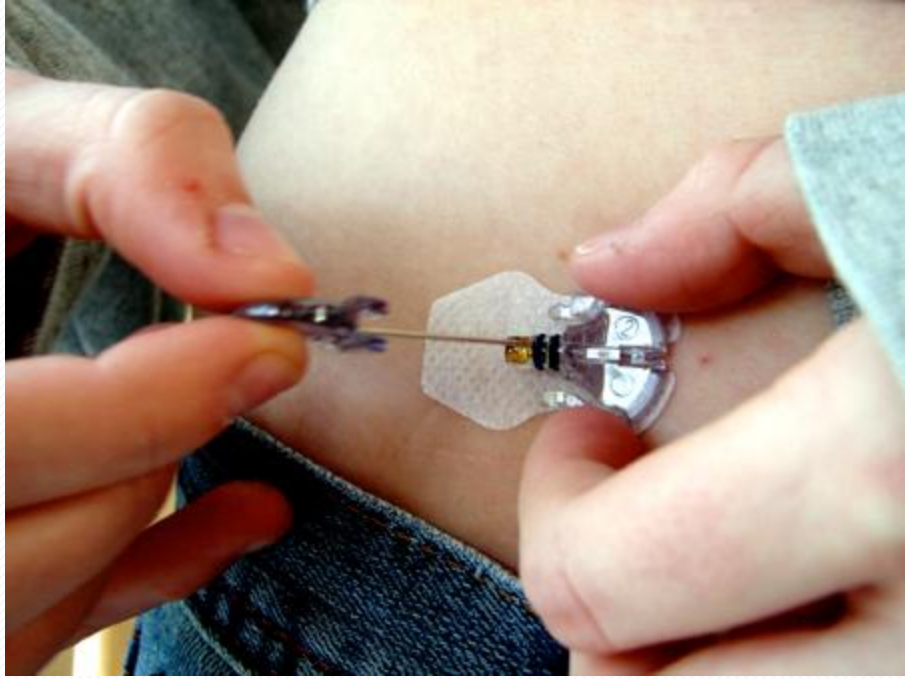
- Subcutaneous sensors measure glucose levels every 5 minutes, 24 hours a day for 3 or 7 days
- Fingersticks are required to calibrate the glucose sensor and before making treatment decisions
- Sensors are set with alarm parameters so pts alerted to high or low glucose
- Slight lag from blood glucose to subcutaneous fluid glucose
- Screens show graph of glucose changes

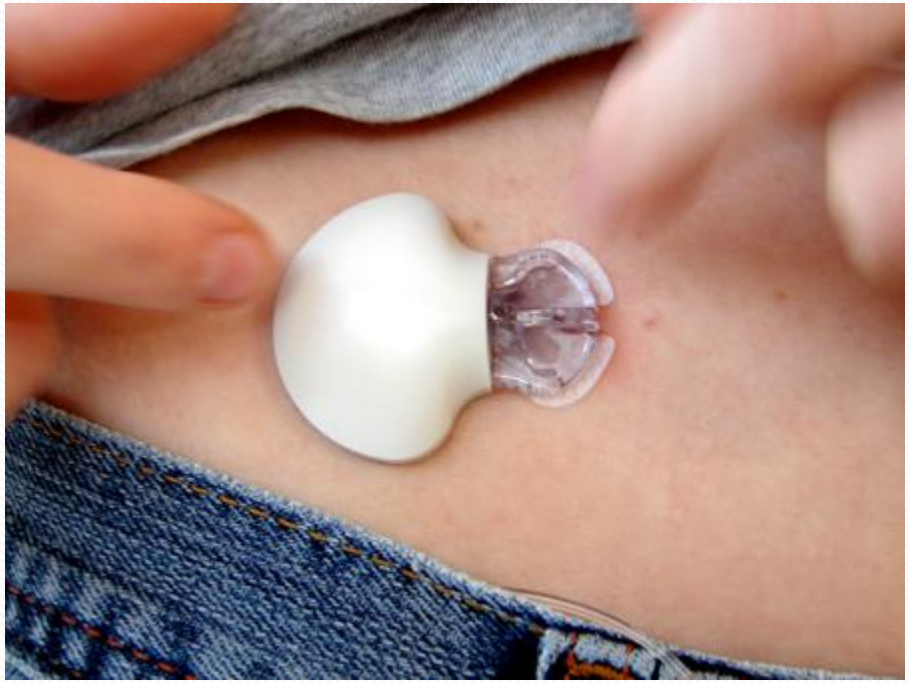
Worn for 7 days

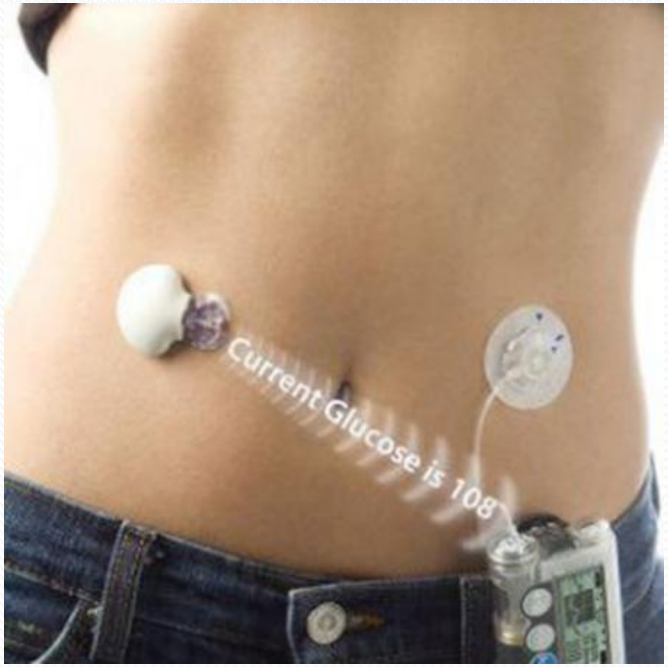
Worn for 3 days

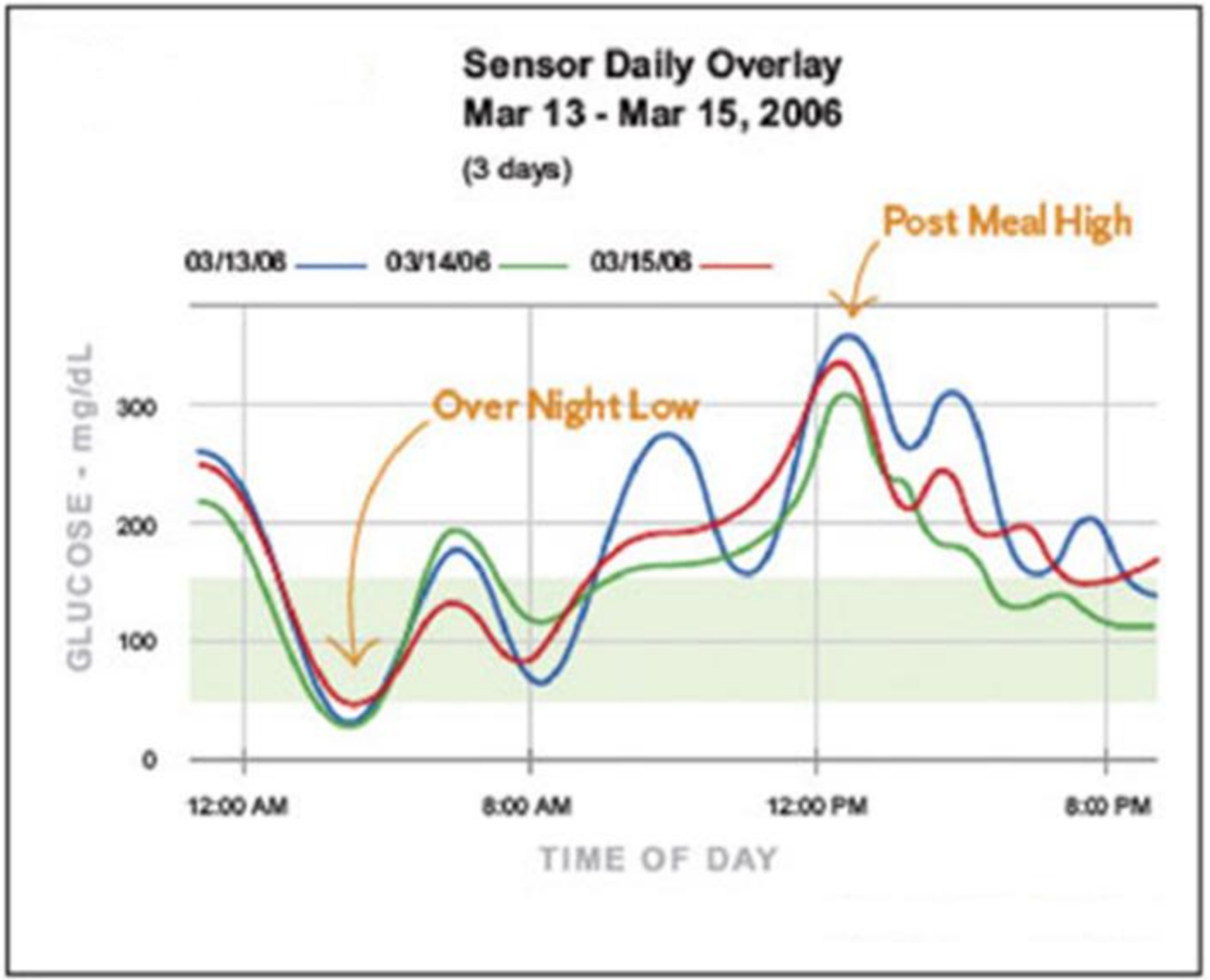

dexcom


DEXCOM

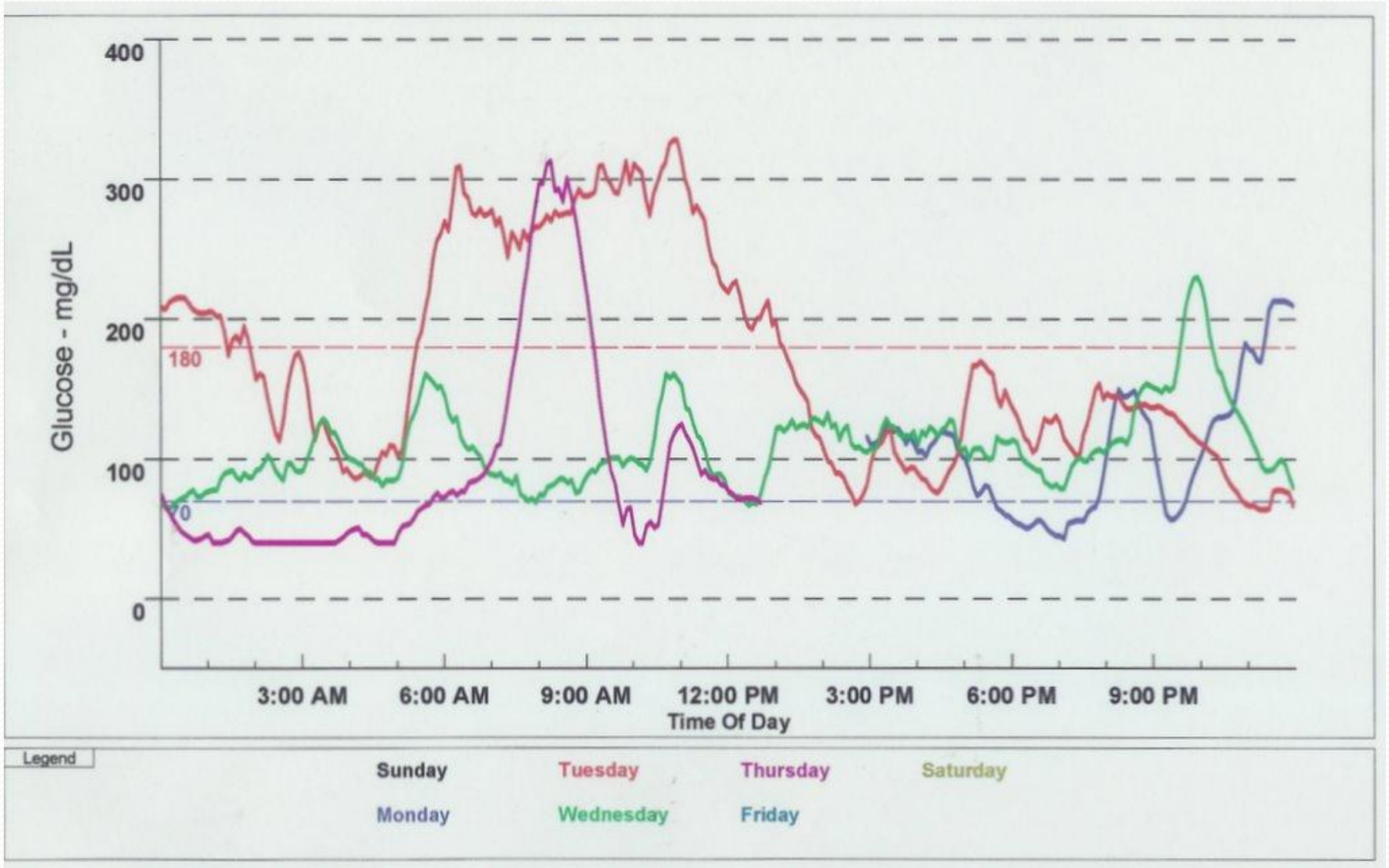





Current Glucose is 108



Data from monitor downloaded to computer and accessed by patients doctor/CDE from website.


400
300
200
180
100
70
0
Glucose - mg/dL
3:00 AM
6:00 AM
9:00 AM
12:00 PM
3:00 PM
6:00 PM
9:00 PM
Time Of Day
Legend
Sunday
Tuesday
Thursday
Saturday
Monday
Wednesday
Friday

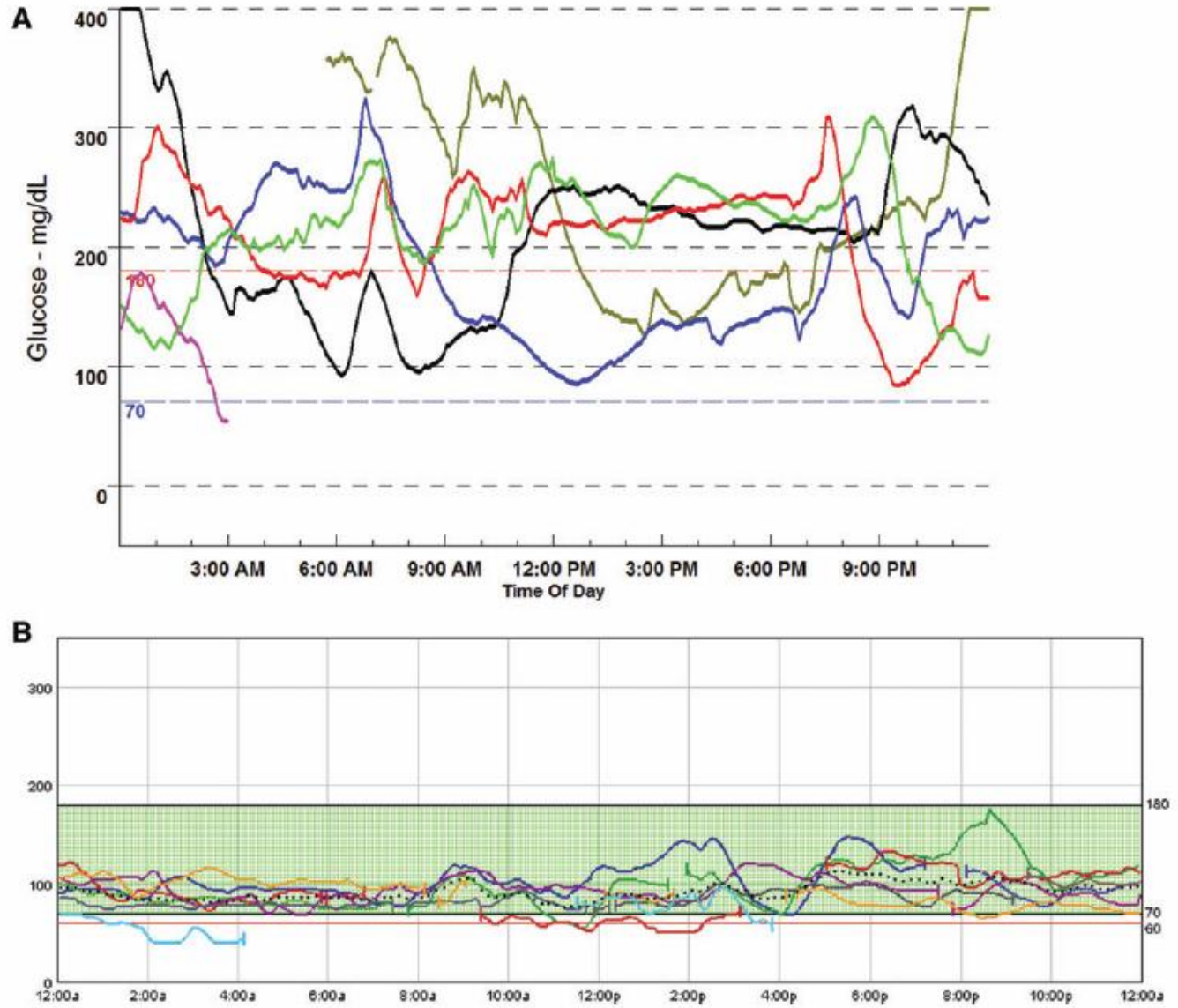


FIG. 3. Unpublished data from Medtronic Paradigm CGM tracings of the same patient (**A**) receiving multiple daily injections of insulin and (**B**) after 9 months of continuous sensor-augmented pump therapy. This research is supported by the Diabetes Research in Children Network and the Type 1 Diabetes TrialNet, which are both funded by grants from the National Institutes of Health. Color images available online at www.liebertonline.com/dia

Continuous Glucose Monitors

- Useful tool for 3-7day spot checks for patterns in pts that are difficult to control
  - Identifies unknown hypoglycemic episodes and frequently post prandial highs
- Very helpful worn continuously in pts with frequent hypoglycemia, nocturnal hypoglycemia, or hypoglycemic unawareness


3G
5:10 PM
138 mg/dL
Carbs
Insulin
138
mg/dL
Tues, Apr 3, 2012, 5:10 PM EDT
Pre-Dinner
Add Note
Home
Add
Data
Share
Info
138
04/03/12

Trend Chart

Plots glucose readings from the Scorecards over time.

Logbook

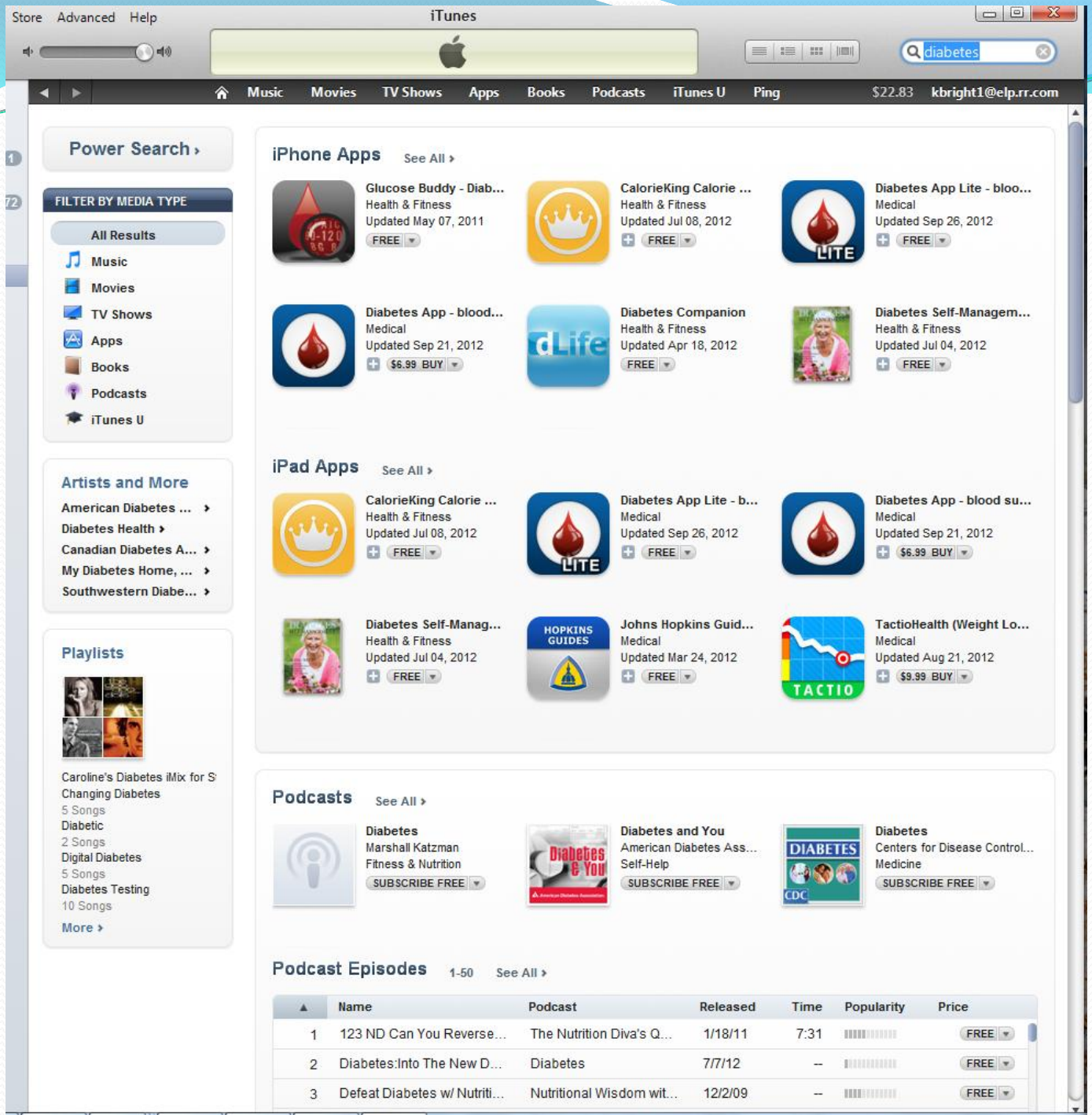
At-a-glance view of glucose readings from Scorecards.

Statistics

Displays averages, standard deviation, and total tests for glucose readings from Scorecards.

Alerts

Provides hypo and hyper alerts when glucose readings are out of the normal range.


Store Advanced Help
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Power Search ›
FILTER BY MEDIA TYPE
All Results
Music
Movies
TV Shows
Apps
Books
Podcasts
iTunes U
Artists and More
American Diabetes ... ›
Diabetes Health ›
Canadian Diabetes A... ›
My Diabetes Home, ... ›
Southwestern Diabe... ›
Playlists
Caroline's Diabetes iMix for S
Changing Diabetes
5 Songs
Diabetic
2 Songs
Digital Diabetes
5 Songs
Diabetes Testing
10 Songs
More ›
iPhone Apps See All ›
Glucose Buddy - Diab...
Health & Fitness
Updated May 07, 2011
FREE
CalorieKing Calorie ...
Health & Fitness
Updated Jul 08, 2012
FREE
Diabetes App Lite - bloo...
Medical
Updated Sep 26, 2012
FREE
Diabetes App - blood...
Medical
Updated Sep 21, 2012
$6.99 BUY
Diabetes Companion
Health & Fitness
Updated Apr 18, 2012
FREE
Diabetes Self-Managem...
Health & Fitness
Updated Jul 04, 2012
FREE
iPad Apps See All ›
CalorieKing Calorie ...
Health & Fitness
Updated Jul 08, 2012
FREE
Diabetes App Lite - b...
Medical
Updated Sep 26, 2012
FREE
Diabetes App - blood su...
Medical
Updated Sep 21, 2012
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Diabetes Self-Manag...
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Updated Jul 04, 2012
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Johns Hopkins Guid...
Medical
Updated Mar 24, 2012
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TactioHealth (Weight Lo...
Medical
Updated Aug 21, 2012
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Diabetes
Marshall Katzman
Fitness & Nutrition
SUBSCRIBE FREE
Diabetes and You
American Diabetes Ass...
Self-Help
SUBSCRIBE FREE
Diabetes
Centers for Disease Control...
Medicine
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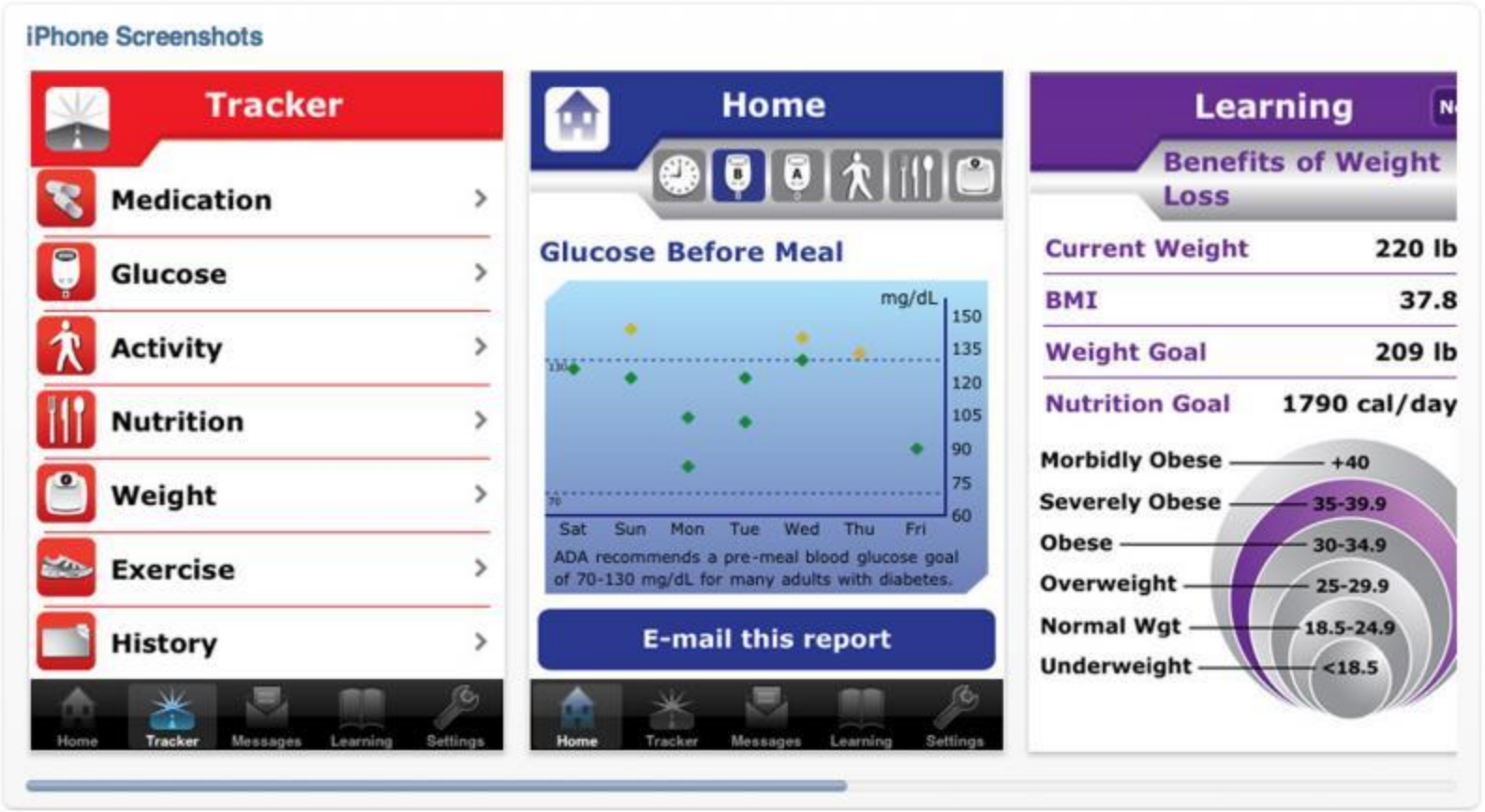
1 123 ND Can You Reverse... The Nutrition Diva's Q... 1/18/11 7:31 FREE
2 Diabetes:Into The New D... Diabetes 7/7/12 -- FREE
3 Defeat Diabetes w/ Nutriti... Nutritional Wisdom wit... 12/2/09 -- FREE

Phone Apps


iPhone Screenshots
Tracker
Medication
Glucose
Activity
Nutrition
Weight
Exercise
History
Home
Tracker
Messages
Learning
Settings
Home
Glucose Before Meal
mg/dL
150
135
120
105
90
75
60
Sat
Sun
Mon
Tue
Wed
Thu
Fri
ADA recommends a pre-meal blood glucose goal of 70-130 mg/dL for many adults with diabetes.
E-mail this report
Home
Tracker
Messages
Learning
Settings
Learning
Benefits of Weight Loss
Current Weight 220 lb
BMI 37.8
Weight Goal 209 lb
Nutrition Goal 1790 cal/day
Morbidly Obese +40
Severely Obese 35-39.9
Obese 30-34.9
Overweight 25-29.9
Normal Wgt 18.5-24.9
Underweight <18.5

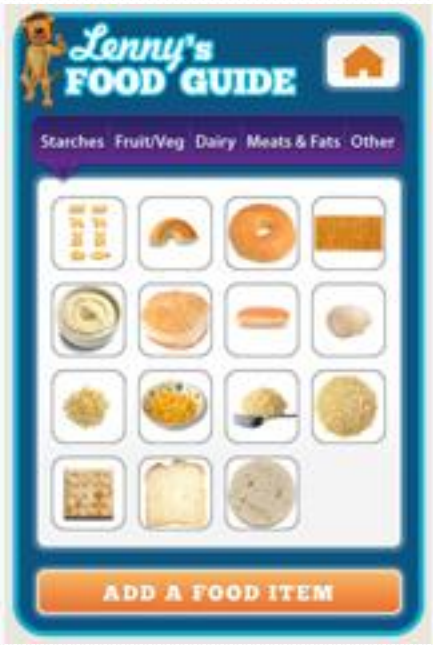
- Watch DM videos, look up foods and healthy diabetes-friendly recipes, and track and manage your blood glucose levels.

Manually enter glucose numbers, carbohydrate consumption, insulin dosages, and activities to track DM.

Nutrition

- Three applications: a database of nutritional values for foods and restaurant menu items, a food tracking tool to record your meals, and a restaurant locator

Carb Counting for Kids



Artificial Pancreas Project

- In 2006, JDRF established the Artificial Pancreas Consortium to fund doctors and researchers across the world to advance this revolutionary way to treat and manage type 1 diabetes.

Experimental Therapies

- The artificial pancreas, as closed-loop control of diabetes, is a system combining a glucose sensor, a control algorithm, and an insulin infusion device.
- The sensor transmits the glucose value to the insulin pump. The software in the pump determines the rate of insulin infusion. The rate changes continuously as the glucose goes up and down with activity and meals as a pancreas would do.
- Very small trials have shown it to be effective.

Experimental Therapies

- **Sodium-glucose cotransporter 2 (SGLT2) Inhibitors**
  - Empagliflozin
  - Canagliflozin
  - Dapagliflozin
  - Ipragliflozin

- These lower glucose by inhibiting the reuptake of glucose in the kidney and inducing glycosuria.
- Concerns of breast and bladder cancer, liver toxicity, and urinary and genital infections

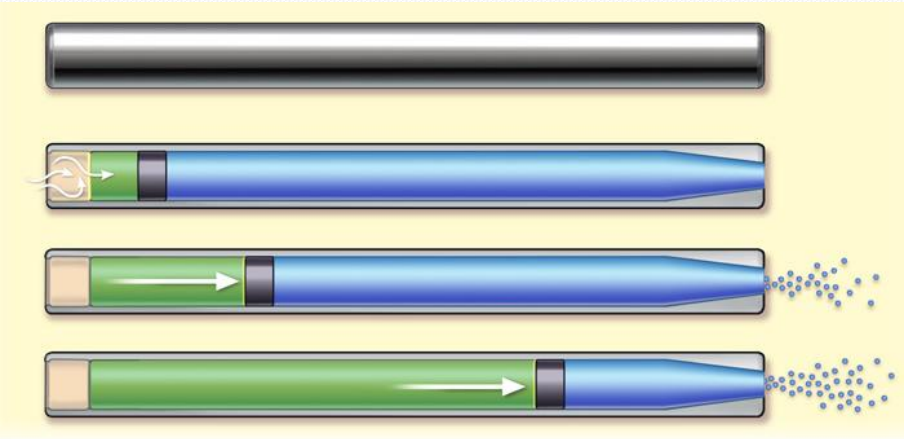
Experimental Medications

- **Insulin Secretagog and Insulin**
  - TAK-875
    - A oral selective GPR40 agonist.
    - Promotes glucose-induced insulin secretion
    - Acts like a sulfonylurea without the hypoglycemia
- **Basal daily SC Insulins**
  - Ly2963016 – once a day insulin
  - Degludec - very long half-life due to structural change that allows hexamers of insulin to form then hexamers associate into thousands stacked together in a row – disassociate at a very even rate to maintain even insulin release.

Experimental Medications

- **DPP4 Inhibitor**
  - Trelagliptin
    - advantage is once a week
- **GLP-1**
  - PB1023
    - SC once a week
  - Semaglutide
    - SC once a week
  - TTP054
    - oral GLP-1

Experimental Medications



- Implantable titanium osmotic pump with exenatide release for 1 year

Glucometer

- A non-invasive breath glucose detection device that measures the level of acetone in a patient's exhaled breath and correlates that acetone level to a measure of blood glucose – under study