INDIVIDUALIZING CARE OF THE PATIENT WITH DIABETES MELLITUS

Douglas Nolan, D.O.
• I have no conflicts of interest to disclose
Objectives

- As a result of participating in this activity, the participant will be able to:
  - Discuss preventative and delay strategies for pre-diabetes management
  - Recognize insulin and non-insulin therapeutics available in treating diabetes mellitus and the impact they have on cardiovascular, cerebrovascular, and renovascular outcomes
  - Highlight the costs and adverse effects related to newer non-insulin anti-hyperglycemic medications
  - Understand the importance and essence of a multifaceted approach towards diabetes management
Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Main outcome measure Death or major trauma, defined as an injury severity score > 15.

Results We were unable to identify any randomised controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence-based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence-based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

accepted intervention was a fabric device, secured by strings to a harness worn by the participant and released (either automatically or manually) during free fall with the purpose of limiting the rate of descent. We excluded studies that had no control group.

Definition of outcomes

The major outcomes studied were death or major trauma, defined as an injury severity score greater than 15.8

Meta-analysis

Our statistical approach was to assess outcomes in parachute and control groups by odds ratios and quantified the precision of estimates by 95% confidence intervals. We chose the Mantel-Haenszel test to assess heterogeneity, and sensitivity and subgroup analyses and fixed effects weighted regression techniques to explore causes of heterogeneity. We selected a funnel plot to assess publication bias visually and Egger’s and Begg’s tests to test it quantitatively. Stata software, version 7.0, was the tool for all statistical analyses.

Results

Our search strategy did not find any randomised controlled trials of the parachute.
Common

- International Diabetes Federation
  - 463 million patients with DM in 2019
  - Projected to rise to 700 million by 2045
- In the US, > 9% have Type 2 DM
- About 90% receive care for DM2 from Primary Care
- Pre-diabetes
  - A1C between 5.7 – 6.4
  - A1C between 5.7 and 6, 5 year risk from 9-25%
  - A1C between 6 to 6.5, has a 5 year risk of 25-50%
- In the US, approximately 35% of overweight adults are pre-diabetic
Diabetes Prevention Program (DPP)

- Intensive, behavioral lifestyle intervention to achieve and maintain a 7% weight loss and 150 minutes of physical activity per week
  - 7% was selected because it is feasible and likely to lessen the risk of developing diabetes
  - Goal for physical activity was selected for at least 700 kcal/week expenditure
    - Moderate intensity similar to brisk walking at least 3 times per week
Does DPP work?

- Reduce the incidence of DM2 by 58% over three years
- Sustained reduction
  - DaQing study 39% reduction at 30 years
  - Finnish DPS study 43% reduction at 7 years
  - US Diabetes Prevention Program Outcomes Study 27% reduction at 15 years
Life Style Changes

- Weight loss and physical activity together have the potential to reduce the A1C by 1 – 2%
- A targeted weight loss goal of 5 – 7% and an exercise goal of 150 minutes of moderate intensity exercise per week, decreased the number of people going on to develop diabetes compared to usual care by about 2/3
- 2020 ADA Standard of Care - Metformin therapy for prevention of DM2 should be considered in those with pre-diabetes, especially for those with a BMI ≥ 35, those aged < 60 years, and women with prior history of gestational diabetes mellitus (A recommendation)
“Resistance training is just as important as cardio. Train yourself to resist chocolate, pastries, fried foods, beer, pizza...”
Historical Perspective

- Acute, severe vs Chronic, mild
  - Young, significant weight loss, death in a few years
  - Older, lived longer but had significant comorbidities
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- 1950’s Noticed enough differences
  - Juvenile vs Adult Onset
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• 1970’s Needed insulin to survive
  • Insulin dependent vs Non-insulin dependent
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• 1970’s Needed insulin to survive
  • Insulin dependent vs Non-insulin dependent
• 1990’s Autoimmune vs Insulin Resistance
  • Type 1 vs Type 2
Pretty Easy…

Type 1
- Children – Adolescents
- Caucasian
- Lean
- Insulin Requiring
  - DKA

Type 2
- Older
- Overweight/obese
- HTN, Dyslipidemia
  - Low HDL, High TG
- Ethnic minorities
Pretty Easy…Or Is It?

• 42% of Type 1 DM are diagnosed 31 – 60 years of age
• 1/3 of children diagnosed with diabetes are Type 2
• Different subtypes of Type 2
  • MODY
  • LADA
Latent Autoimmune Diabetes in Adults

• LADA
• Overlap of Type 2 and Type 1 (1 ½)
  • Resemble type 2 in that may not require insulin
  • Have autoimmune markers associated with type 1
• Diagnosis after 30 years of age
• Estimated to be 2 – 12% of all adult onset diabetes
LADA

- Diagnosis
  - Adult onset diabetes; > 30 years of age
  - Presence of diabetes associated autoantibodies
  - Absence of insulin requirement for at least 6 months after diagnosis
- There is a similar type of slowly progressive form of autoimmune diabetes called Latent Autoimmune Diabetes in the Young (LADY)
Which Test Is Specifically Diagnostic of Type 1 DM?

- GADA/GAD65 (Glutamic acid decarboxylase 65)
- Islet Cell Antibodies
- ZNT8
- Insulin Antibodies
- C-Peptide

- There is no specific “diagnostic” test
Which Test Is Specifically Diagnostic of Type 1 DM?

- GADA/GAD65
- Islet Cell Antibodies
- ZNT8
- Insulin Antibodies
- C-Peptide

- Diabetes Associated Autoantibodies
- Type 1, LADA
- Other antibodies exist
- The more positive, the more likely the diagnosis
- C-peptide should be interpreted with glucose level

There is no specific diagnostic test
“I try to eat healthy. I never sprinkle salt on ice cream, I only eat decaffeinated pizza and my beer is 100% fat free.”
Goals

• ADA “the goal for most adults is < 7%”
• AACE “≤ 6.5 for most”
• ACP recommend “treat to achieve a HbA1C level between 7% and 8%”
Goals

• Goals should be individualized
• Goals are difficult in the elderly
  • Older adults are excluded from 2/3 of trials
  • The risk of all-cause, cardiovascular, and cancer mortality appears to increase significantly among older adults with diabetes and HgbA1C > 8 (HbA1C and mortality in older adults with and without diabetes. Diabetes Care 2017, 40: 453-460 Palta et al)
  • “Better predictors both for the risk of and the risk from hypoglycemia for a given individual and should remind us to avoid agents likely to cause hypoglycemia” (Is HbA1C < 7 a marker of poor performance in individuals > 65 years old? Diabetes Care 2017; 40:526-528 Bloomgarden et al)
• Modify the goal if hypoglycemia, especially if unaware of hypoglycemia
Risk vs Benefit

- Kumamoto study and UK Prospective Diabetes Study (UKPD)
  - Intensive glycemic control significantly decreased rates of microvascular complications
  - UKPD showed enduring effects of early glycemic control on microvascular complications
- ACCORD, and ADVANCE studies
  - Lower A1C levels were associated with reduced onset or progression of microvascular complications
  - Did not show significant reduction in CVD outcomes in patients with more advanced DM2
  - ACCORD - after 5 years, the intensive treatment group had a 20% higher rate of mortality
- Veterans Affairs Diabetes Trial
  - Had a higher A1C target for intensive therapy
    - About 17% less likely to have a major cardiovascular event if received intensive therapy
    - Mortality risk was about the same
Patient and disease factors used to determine optimal glycemic targets.

### Approach to Individualization of Glycemic Targets

<table>
<thead>
<tr>
<th>Patient / Disease Features</th>
<th>More stringent ↔ A1C 7% ↔ Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia and other drug adverse effects</td>
<td>low → high</td>
</tr>
<tr>
<td>Disease duration</td>
<td>newly diagnosed → long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long → short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>absent → few / mild → severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent → few / mild → severe</td>
</tr>
<tr>
<td>Patient preference</td>
<td>highly motivated, excellent self-care capabilities → preference for less burdensome therapy</td>
</tr>
<tr>
<td>Resources and support system</td>
<td>readily available → limited</td>
</tr>
</tbody>
</table>

American Diabetes Association Dia Care 2021;44:S73-S84
“Pump vigorously if you feel a palpitation. We’re still battling with your insurance company for a better pacemaker.”
Metformin

- Low risk of hypoglycemia
- Can promote modest weight loss
- Robust cardiovascular safety
  - United Kingdom Prospective Diabetes Study
    - 32% reduction in any diabetes related end point
    - 42% reduction in diabetes related mortality
    - 36% reduction in all cause mortality
    - 39% reduction in myocardial infarction
    - 50% reduction in fatal myocardial infarction
- Can continue in patients with stable GFR > 30
- Up to 16% of patients may have B12 malabsorption or deficiency
After Metformin

- CKD
- CHF
- ASCVD
- NASH
- Obesity/Overweight
- Minimize hypoglycemia
- Cost
CKD

- **EMPA-REG**
  - Empagliflozin, Cardiovascular Outcomes and Mortality in DM2
  - Reduced secondary renal endpoints (reduced risk of doubling of Cr, ESRD, or death from ESRD by 39%)
- **CANVAS**
  - Canagliflozin Cardiovascular Assessment Study
  - Reduced secondary renal endpoints (reduced risk of doubling of Cr, ESRD, or death from ESRD by 40%)
  - Increased risk of amputation
- **CREDENCE**
  - Canagliflozin and Renal End points in Diabetes with Established Nephropathy Clinical Evaluation
  - Stopped early due to showing a 32% reduction for development of ESRD over control
Heart failure

• Approximately 50% of patients with DM2 may develop heart failure

• EMPA-REG
  • Empagliflozin, Cardiovascular Outcomes and Mortality in DM2
  • 35% reduction in hospitalization for HF vs placebo

• CREDENCE
  • Canagliflozin and Renal End points in Diabetes with Established Nephropathy Clinical Evaluation
  • 39% reduction in hospitalization for heart failure and 31% reduction in composite of cardiovascular death

• DECLARE-TIMI
  • Dapagliflozin Effect on Cardiovascular Events Thrombolysis in Myocardial Infarction
  • 35% reduction in hospitalization for HF vs placebo

• Studies show benefit in preventing hospitalization for heart failure
  • Suggest, but do not prove, may be beneficial in established heart failure
DAPA-HF Trial

- ADA 2020 Virtual Scientific Sessions in June; Dr Inzucchi
- “Effect of Dapagliflozin on the incidence of diabetes: A prespecified exploratory analysis from DAPA-HF”
  - Phase 3 placebo controlled international study
  - 4774 patients with average age of 66 followed for approximately 18 months
    - 2605 were not diabetic
- Risk of worsening HF or death from cardiovascular causes was lower with dapagliflozin
- Reduced new-onset DM by 32% (4.9% vs 7.1% of patients)
  - Additional analysis, those that did develop DM during the trial experienced a 70% increase in mortality
SGLT2

- Lower rates of all cause and cardiovascular death and lower risk of hospitalization for heart failure
- Reduction in renal endpoints
- Glucosuric effect
- Modest A1C lowering
- Weight loss and blood pressure lowering
- Increased risk of amputation
- Mycotic genital infections
- Important to monitor the GFR
  - May have decrease after initiating but continued use associated with reduced CVD and renal outcomes
- Low hypoglycemia risk
- Caution for dehydration
  - Syncope, hypotension, falls, acute renal impairment
ASCVD

- Defined as CAD, Cerebrovascular disease, or peripheral arterial disease presumed to be of atherosclerotic origin
- The leading cause of morbidity and mortality of patients with diabetes
- Estimated $37.3 billion in cardiovascular spending per year associated with diabetes
- 2008, the FDA issued a guidance that all new DM2 medications to perform cardiovascular outcomes trials
  - Previously approved medications were not subject
CVD

- LEADER – Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
  - 9340 patients
    - 81% established CVD
    - 24.7% ≥ stage 3 CKD
    - Both 15.8%
  - Deaths from cardiovascular causes were significantly reduced
  - Rates of non-fatal MI, non-fatal stroke, and hospitalization for HF lower but non-significant
- SUSTAIN-6 – Semaglutide in Subjects With Type 2 Diabetes
  - 2735 patients
    - 83% had established CVD, CKD, or both
  - Deaths from cardiovascular causes was consistent with the LEADER trial
  - Rates of non-fatal MI, non-fatal stroke was significantly lower
GLP-1 Receptor Agonists

- Reduction in deaths from cardiovascular causes
- Can be used with insulin but NOT in place of insulin
  - Many forms are injectable
- No benefit from combining with DPP-4
- Weight loss
  - Obesity (Saxenda, Wegovy)
- Caution in patients with GI disease, pancreatitis, gastroparesis, history of bowel obstruction, or Cr < 50 (don’t use if Cr < 30)
- Contraindicated if history of MEN2 syndrome or family history of medullary thyroid cancer
- If taking Warfarin, monitor INR more frequently until INR stable
GLP-1RA vs SGLT2

- Meta-analysis by T.A. Zilniker et al reviewed data from eight trials and 77,242 patients
  - 42,920 (55.6%) in GLP-1RA trials and 34,322 (44.4%) in SGLT2 trials
  - Both reduced the risk of MACE by 14% in patients with known ASCVD
    - Neither reduced the risk of MACE in patients without established ASCVD
  - SGLT2 reduced the relative risk of hospitalization for HF by 31%
    - GLP-1RA had a non-significant 7% relative risk reduction
  - SGLT2 showed relative risk reduction of 45% for the composite of reductions in eGFR, ESKD, and death due to renal causes
    - GLP-1RA reduced microalbuminuria but excluding microalbuminuria had a non-significant relative reduction of 8%
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- If CKD/CHF - SGLT2
- If contraindicated or not at goal, GLP1
- If ASCVD – GLP1
- If contraindicated or not at goal, SGLT2
Nephrolithiasis

- Active comparative new-user cohort study
  - Danish health registries from Nov 2012 to Dec 2018
- Compared SGLT2i to GLP1RA
  - Additional data added to include DDP4 as a second comparator
- SGLT2i reduced the risk by 50% with a risk reduction of 40% with recurrent nephrolithiasis
Nonalcoholic Steatohepatitis

- Insulin resistance is a shared characteristic of type 2 diabetes and obesity
  - Key driver of NASH
- Can be associated with
  - Fibrosis
  - Cirrhosis
  - Increased risk of hepatocellular carcinoma
PIVENS Trial

- Pioglitazone, Vit E, or Placebo for Nonalcoholic Steatohepatitis
- 247 patients w/NASH and without DM followed for 96 weeks
  - Pioglitazone 30mg daily
  - Vitamin E 800 IU daily
  - Placebo
PIVENS Trial

- Both Vitamin E and Pioglitazone did show a reduction in hepatic steatosis, lobular inflammation, and activity score for nonalcoholic fatty liver disease
  - Vit E did reach level of significance for improvement of NASH (43% vs 19%)
  - Pioglitazone did not reach level of significance for improvement of NASH (34% VS 19%)
- Neither showed improvement in fibrosis scores
- Pioglitazone had a higher weight gain
GLP-1RA

- 320 patients with NASH and liver fibrosis
- Semaglutide 0.1mg, 0.2mg, or 0.4mg daily injection
- Placebo
- 72 weeks
- Primary endpoint – resolution of NASH w/no worsening of fibrosis
- Secondary endpoint – improvement of fibrosis stage with no worsening of NASH
GLP-1RA

• Resolution of NASH w/out worsening of fibrosis was significantly higher with semaglutide
  • 59% in 0.4mg semaglutide vs 17% Placebo
• No significant difference in decrease in fibrosis of at least 1 stage w/out worsening of NASH
  • 43% vs 33% Placebo
• Resolution of both NASH and improvement in fibrosis stage
  • 37% 0.4mg semaglutide vs 15% Placebo
ED

- Erectile Dysfunction affects nearly 2/3 of men with DM2
  - Severity increases with age, DM duration, poor glycemic control, and presence of micro/macrovascular complications

- REWIND Study
  - Men/Women > 50 years of age with previous cardiovascular event or risk factors
  - Weekly dulaglutide injections vs placebo
  - Part of the study involved periodic assessments of ED
Erectile Dysfunction affects nearly 2/3 of men with DM2

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REWIND Study

- Men/Women > 50 years of age with previous cardiovascular event or risk factors
- Weekly dulaglutide injections vs placebo
- Part of the study involved periodic assessments of ED

- 8% reduction in ED w/dulaglutide (statistically significant)
- 19% reduction in those with previous cardiovascular disease
What Next?

- 15-20% of Diabetic Patients
  - ASCVD
  - Heart Failure
  - CKD
- What about the other 80 – 85%?
  - The efficacy, tolerability, and side effects are from average effects from clinical trials
    - May not be as helpful on what would be best for specific individuals that present to your clinic
DPP4 inhibitors

- Inhibits DPP4 which increases levels of GLP-1
  - Stimulates insulin secretion and suppresses glucagon secretion
- Modest A1C lowering
- Low risk of hypoglycemia
- Neutral weight change
- Renal dose adjustment
  - Except Linagliptin
- Do not achieve ASCVD results as with GLP1RA
- Potential risk of pancreatitis
- Arthralgia
- Possible slight increase in heart failure with saxagliptin and alogliptin
TZDs

Benefits

• Lowers A1C 0.5 – 1.4%
• May cause the resumption of ovulation in women who are anovulatory secondary to insulin resistance or PCOS (consider adding contraception if appropriate)
• Not contraindicated in renal dysfunction
• Improves histologic parameters in diabetic patients with NASH

Side effects

• Modest Weight gain
• Peripheral edema
  • May exacerbate CHF
  • Contraindicated in NYHA Class III/IV heart failure
• Increased risk of bone fractures
• Caution in Liver disease (primarily due to the first TZD marketed had issues)
<table>
<thead>
<tr>
<th>Benefits</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A1C reduction of 1-2%</td>
<td>• Weight gain</td>
</tr>
<tr>
<td>• Inexpensive</td>
<td>• Hypoglycemia</td>
</tr>
<tr>
<td>• Decreases microvascular risk</td>
<td>• Tolbutamide – first generation had increased risk of cardiac disease</td>
</tr>
<tr>
<td></td>
<td>• Meta-analysis of trials involving 2\textsuperscript{nd}-3\textsuperscript{rd} generation SU</td>
</tr>
<tr>
<td></td>
<td>• 47 RCTs involving 37,650 patients</td>
</tr>
<tr>
<td></td>
<td>• Glipizide, Glyburide, Glimeperide</td>
</tr>
<tr>
<td></td>
<td>• SU not associated with increased risk for all-cause mortality, cardiovascular mortality, MI, or stroke</td>
</tr>
</tbody>
</table>
Insulin

- UKPDS
  - No increased risk of MI or diabetes related death was observed
- ORIGIN Trial
  - 12,573 patients
  - Cardiovascular risk factors
  - Pre-diabetes or DM2
  - Insulin glargine or standard care (SU/metformin) or placebo
  - Glargine had neutral effect on cardiovascular outcomes
  - Increased hypoglycemia and modest weight gain
After Metformin, what works best?

• GRADE Study reported June 28, 2021 at ADA 81st Scientific Sessions

• GRADE: Glycemic Reduction Approaches in Diabetes: A Comparative Effectiveness Study
  • 5047 metformin treated subjects
  • < 10 years duration of diabetes
  • ≥ 30 years of age (mean 57 years)
  • A1C of 6.8 – 8.5 (mean 7.5)

• 2nd Line Therapy Added (Randomly Assigned) when not at target goal
  • SU
  • DDP4
  • GLP1RA
  • Insulin
GRADE Study

- Average Follow Up was 5 years
- Proportion of participants who developed A1C > 7%
  - Insulin Glargine 67%
  - Liraglutide 68%
  - Glimepiride 72%
  - Sitagliptin 77%
- Significantly lower risk for metabolic outcomes for Glargine and Liraglutide (compared to the other two)
- Glargine was most effective in keeping A1C < 7.5%
- Rates of Cardiovascular outcomes (preliminary findings and not powered for CV outcomes – still needs to be adjudicated)
  - Liraglutide (5.8%) Lowest
  - Glargine (7.6%)
  - Glimepiride (8%)
  - Sitagliptin (8.6%)
Basal Insulin

• ADA – consider
  • Hyperglycemia is severe, weight loss, ketosis
  • Glucose is > 300 and/or A1C > 10%
  • Dual therapy if A1C > 9% or not meeting goals after 3 months
Basal Insulin

• ADA – consider
  • Hyperglycemia is severe, weight loss, ketosis
  • Glucose is > 300 and/or A1C > 10%
  • Dual therapy if A1C > 9% or not meeting goals after 3 months
• About 25% of DM2 are currently receiving insulin
  • About 50% of those achieve a target A1C of < 7%
Basal Insulin

- In theory, the ideal dose should allow a DM2 patient to fast for 24 hours without hypoglycemia
- Efficient in controlling fasting hyperglycemia but little effect in postprandial glucose
  - Fasting glucose is dominant with higher A1C’s
  - Post prandial glucose is a larger contributor when A1C is closer to 7% (target)
- Ceiling effect when basal dose approaches 0.5 units/kg/day (leads to expert recommendation per ADA of when to initiate bolus insulin)
  - May occur as low as 0.3 units/kg/day in some
BEYOND Trial

- DM2 patients
  - >35 years of age
  - HbA1C > 7.5%
  - Current use of full Basal-Bolus Insulin (4 injections daily)
  - With/without metformin
  - Above for at least 6 months

- Assigned to 3 groups
  - Intensification of Basal-Bolus insulin regimen (101 participants)
  - Basal insulin + GLP1-RA (102 participants)
  - Basal insulin + SGLT2i (102 participants)

- Primary Outcome was change in baseline A1C at 6 months
- Secondary Outcomes were:
  - A1C ≤ 7.5 or ≤ 8 at 6 months
  - % of patients with a decrease of ≥ 0.5% at 6 months
  - Total daily insulin dosage and number of injections at 6 months
  - % of patients with hypoglycemia
  - Changes in body weight and fasting glucose at 6 months
  - Level of satisfaction in participants
BEYOND Trial

- Change in Baseline A1C (Primary Outcome)
  - Basal-Bolus Insulin – decrease 0.6%
  - Basal Insulin + GLP1RA – decrease 0.6%
  - Basal Insulin + SGLT2i – decrease 0.7%

- Non-inferior, p < 0.001 for both
BEYOND Trial – Secondary Outcomes

• A1C ≤ 7% and ≤ 8% at 6 months
  • No significant difference
• A1C change ≥ 0.5% from baseline at 6 months
  • Basal-Bolus 43%
  • Basal + GLP1 39%
  • Basal + SGLT2 44%
• Total insulin
  • Increased in Basal-Bolus
  • Decreased in other 2 groups
    • Basal dose did not change significantly over time
BEYOND Trial – Secondary Outcomes

- Fasting glucose improved with all groups
- Body weight significantly decreased in Basal + GLP1
- Hypoglycemia (FSBS < 70 w/signs or symptoms)
  - Basal-Bolus 17.8%
  - Basal + GLP1 7.8%
  - Basal + SGLT2 5.9%
- Satisfaction
  - Basal-Bolus - unchanged (16.3 → 15.7)
  - Basal + GLP1 - increased (17.4 → 34.2)
  - Basal + SGLT2 - increased (15.9 → 33.8)
LADA

- Diagnosis
  - Adult onset diabetes; > 30 years of age
  - Presence of diabetes associated autoantibodies
  - Absence of insulin requirement for at least 6 months after diagnosis
- GADA/GAD65 is considered the most sensitive marker for LADA
- Patients have functioning β-cells at diagnosis
- Therapy should improve control and preserve insulin secreting capacity
LADA – International Expert Panel

- **SU**
  - Not recommended
- **Metformin and Pioglitazone**
  - Limited evidence – efficacy inconclusive
- **DPP4i**
  - May improve glycemic control w/good safety profile
- **SGLT-2i**
  - Promising but no studies
- **GLP1**
  - Beneficial unless C-peptide levels are very low
LADA - Insulin

• Patients have functioning β-cells at diagnosis
  • Slow progression to insulin dependency
• Early insulin usage does not lead to preservation of β-cell function
• C-peptide w/glucose level guides usage
  • Glucose should be between 80 – 180 for accuracy
• C-peptide > 0.7
  • Treat as Type 2 but check repeated C-peptide if control worsens
• C-peptide between 0.3 and 0.7
  • “gray area” follow as Type 2 but avoid meds that could affect β-cell function
• C-peptide < 0.3
  • Multiple insulin regimen is recommended (Basal-Bolus)
  • If < 0.3 at diagnosis, could be considered Type 1
Precision Medicine

- The primary aim is lowering glucose/A1C
  - Excluding ASCVD, HF, CKD
- The goal would be to identify which individuals would have a greater response to one drug class over another
- U.K.’s Clinical Practice Research Datalink
  - Demographics
  - Clinical features
  - Diagnoses
  - Laboratory tests
  - Prescriptions
Individualized vs Subtypes

• Test head-head an individualized strategy vs Ahlqvist clusters strategy
  • Ad hoc analysis of data from two large clinical trials (ADOPT and RECORD) that clusters could be used to guide therapy
• Individualized Strategy utilized sex, BMI, A1C, and age at diagnosis
• SU, TZD, Metformin
Three-year glycemic response (change from baseline in HbA1c) with concordant and discordant subgroups using the subtypes strategy and the individualized prediction strategy in the RECORD trial independent validation set (n = 4,057).

John M. Dennis Diabetes 2020;69:2075-2085
Five-year glycemic response (change from baseline in HbA1c) with TZD and SU treatment in males without obesity (BMI <30) (A) and females with obesity (BMI ≥30) (B) subgroups in 1,232 participants in the ADOPT clinical trial (21).
Associations between baseline HbA1c and baseline eGFR (Chronic Kidney Disease Epidemiology Collaboration formula) and HbA1c response at 6 months (baseline HbA1c minus 6-month HbA1c) with SGLT2i and DPP-4i treatment in U.K. primary care data (Clinical Practice Research Datalink) (n = 20,965).
Trimaster

- Ongoing randomized trial due to report in May 2021
- Looking at subgroups by BMI and GFR
- DPP4i, SGLT2i, and TZD
Different Effects Depending on Race?

- 6 GLP1RA Trials analyzed
  - 4195 Asians and 37530 Whites
  - MACE benefits significantly better in Asians than in whites

- 5 SGLT2 Trials analyzed
  - 3980 Asians and 29007 Whites
  - 3 Trials found no significant reduction in MACE in Asians but possible low statistical power and underrepresentation of Asians
  - 2 Trials found potentially better in HF
Summary

• Individualize A1C based on patient’s characteristics
• Biomarkers – GADA, islet cell antibody, etc
• C-peptide can guide treatment in LADA
• Metformin remains first line
• CKD or CHF – SGLT2, GLP1
• CAD – GLP1, SGLT2
• Obesity – GLP1
• As the A1C approaches the target may need Basal Insulin + (Bolus, GLP1, SGLT2)
• New medications in development and studies are changing the playing field
  • Once weekly insulin – Icodec
  • Dual glucose-dependent insulinotrophic polypeptide and GLP1RA – Tirzepatide
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“I have a question about my medication. Why is the couple in the commercial sitting outdoors in separate bathtubs?”