Μεταβλητότητα γλυκόζης και καρδιά

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Δήλωση συμφερόντων

• Associate Editor of *Angiology*
• Associate Editor of *Clinical Lipidology*
• Associate Editor of the Hellenic College of Treatment of Atherosclerosis for *The Open Cardiovascular Medicine Journal*
• Section Editor of *Archives of Medical Science*
• Book Review and News and Views Editor of *Current Vascular Pharmacology*
• Editorial Board Member of *Metabolism Clinical and Experimental* and *Current Medical Research and Opinion*

• NK has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra Zeneca, Boehringer Ingelheim, Galenica, MSD, Novartis, Novo Nordisk, Sanofi and WinMedica
Diabetes Is Associated With Significant Loss of Life Years

On average, a 50-year old with diabetes but no history of vascular disease is ~6 years younger at time of death than a counterpart without diabetes

Major Diabetes Complications in USA

Hyperglycaemic Deaths

CVD Admissions

Source: Gregg et al, The Lancet Diabetes & Endocrinology 2016 4, 537-547
Risk Factors for CVD in patients with T2DM

271,174 pts with T2DM matched to 1,355,870 controls
Median F/U = 5.7 years with 175,345 deaths

Death From Any Cause

Acute Myocardial Infarction

Stroke

Heart Failure

HbA₁c versus Glycemic Variability

**Patient 1:**
- HbA₁c = 7.1%
- Mean glucose: 143 mg/dl
- SD: 43 mg/dl

**Patient 2:**
- HbA₁c = 7.3%
- Mean glucose: 149 mg/dl
- SD: 94 mg/dl
Severe hypoglycemia and glucose variability are linked with CV outcomes.
Hypoglycemia and Cardiovascular Risk: Is There a Major Link?


<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Hypoglycemia-induced effect contributing to the risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal cardiac repolarization</td>
<td>QT interval prolongation, increased plasma epinephrine and norepinephrine concentrations, hypokalemia</td>
</tr>
<tr>
<td>Reduced myocardial perfusion</td>
<td>Hemodynamic changes with increase to cardiac workload and heart rate, fall in central arterial pressure and large vessel elasticity</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Increase of endothelial dysfunction and inflammation</td>
</tr>
<tr>
<td>Prothrombotic state</td>
<td>Increased platelet aggregation, increased coagulation</td>
</tr>
</tbody>
</table>
DEVOTE 3: temporal relationships between severe hypoglycaemia, cardiovascular outcomes and mortality

Thomas R. Pieber1 · Steven P. Marso2 · Darren K. McGuire3 · Bernard Zinman4 · Neil R. Poulter5 · Scott S. Emerson6 · Richard E. Pratley7,8 · Vincent Woo9 · Simon Heller10 · Martin Lange11 · Kirstine Brown-Fraden11 · Alan Moses11 · Jesper Barner Lekdorff1 · Lucine Lehmann11 · Kajsa Kvist11 · John B. Buse12 · on behalf of the DEVOTE Study Group


Fig. 3 Risk of all-cause death following a severe hypoglycaemic event by time period. n, number of patients; rate, events per 100 patient-years of observation.
DEVOTE 2: Day-to-day fasting glycemic variability and association with outcomes

- DEVOTE 2 was a prespecified secondary analysis of DEVOTE
- Associations of day-to-day fasting glycemic variability (based on the standard deviation of the pre-breakfast SMBG measurements) with severe hypoglycemia and outcomes were analyzed
- The effect of glycemic variability on outcomes was the same for Gla-100 and Deg-100 and data were pooled
- Day-to-day fasting glycemic variability was significantly associated with severe hypoglycemia and all-cause mortality
- The association between glycemic variability and MACE was not maintained after adjusting for baseline characteristics and the most recent HbA1c

<table>
<thead>
<tr>
<th>Severe hypoglycemia</th>
<th>Hazard ratio [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for HbA1c</td>
<td>4.11 [3.15; 5.35]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted for HbA1c, and BC</td>
<td>4.15 [3.17; 5.44]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MACE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.36 [1.12; 1.65]</td>
<td>0.0023</td>
</tr>
<tr>
<td>Adjusted for HbA1c</td>
<td>1.30 [1.06; 1.58]</td>
<td>0.0101</td>
</tr>
<tr>
<td>Adjusted for HbA1c, and BC</td>
<td>1.21 [0.98; 1.49]</td>
<td>0.0811</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.58 [1.23; 2.03]</td>
<td>0.0004</td>
</tr>
<tr>
<td>Adjusted for HbA1c</td>
<td>1.53 [1.19; 1.98]</td>
<td>0.0011</td>
</tr>
<tr>
<td>Adjusted for HbA1c, and BC</td>
<td>1.33 [1.01; 1.75]</td>
<td>0.0432</td>
</tr>
</tbody>
</table>

Variability was reported on a continuous scale. Adjusted for HbA1c: most recent HbA1c on a continuous scale. Adjusted for HbA1c and BC: most recent HbA1c on a continuous scale and BC (investigational product, sex, region, age at baseline, smoking status at baseline, diabetes duration at baseline, CV risk group inclusion criteria, insulin-naïve at baseline and renal function [eGFR] at baseline). BC, baseline characteristics; SMBG, self-measured blood glucose.

Zinman B et al. Diabetologia. 2017 Sep 15. doi: 10.1007/s00125-017-4423-z. [Epub ahead of print]
Glycemic Variability in Insulin-Treated Patients: Independent Risk Factor for Mortality

Coefficient of Variability of FPG and 10-year CV Mortality

Survival Probability

Time (years)

P < 0.001

Muggeo M et al. Diabetes Care 2000;23:45–50
Visit-to-Visit Variability of Fasting Plasma Glucose and the Risk of Cardiovascular Disease and All-Cause Mortality in the General Population

Anxin Wang, PhD; Xiaoxue Liu, MD; Jie Xu, MD, PhD; Xiaochen Han, MD; Zhaoping Su, MS; Shuhua Chen, MD; Nan Zhang, BS; Shouling Wu, MD, PhD; Yongjun Wang, MD, PhD; Yilong Wang, MD, PhD

**Background**—The association of short-term variability of fasting plasma glucose (FPG) and mortality has been well investigated. However, the relationships between visit-to-visit variability of FPG over longer periods of follow-up and cardiovascular disease (CVD) and all-cause mortality are unclear. This study aimed to investigate these relationships.

**Methods and Results**—The current analysis included 53,607 Chinese participants (mean age, 49.10 years) who were free of CVD in the Kailuan study. Participants were divided into 4 categories by quartiles of visit-to-visit variability of FPG. Visit-to-visit variability of FPG was defined as the coefficient of variation of 3 values of FPG that were measured from the examination periods of 2006 to 2007, 2008 to 2009, and 2010 to 2011. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals for CVD and all-cause mortality. After a mean follow-up of 4.93 years, 4261 individuals developed CVD and 1545 individuals died. The incidence of CVD and all-cause mortality was 5.04 and 5.85 per 1000 person-years, respectively. After adjusting for mean FPG and other potential confounders, individuals in the highest quartile of variability of FPG compared with participants in the lowest quartile showed a 26% greater risk of developing CVD (hazard ratio, 1.26; 95% confidence interval, 1.08–1.47) and a 46% greater risk for all-cause mortality (hazard ratio, 1.46; 95% confidence interval, 1.25–1.70).

**Conclusions**—Independent of mean FPG and other baseline parameters, elevated visit-to-visit variability of FPG significantly increases the risk of CVD and all-cause mortality in the general population. Measuring long-term visit-to-visit variability of FPG is helpful for predicting the risk for CVD and all-cause mortality. ([J Am Heart Assoc. 2017;6:e006757. DOI: 10.1161/JAHA.117.006757.])
Visit-to-Visit Variability of Fasting Plasma Glucose and the Risk of Cardiovascular Disease and All-Cause Mortality in the General Population

Anxin Wang, PhD; Xiaoxue Liu, MD; Jie Xu, MD, PhD; Xiaochen Han, MD; Zhaoping Su, MS; Shuohua Chen, MD; Nan Zhang, BS; Shouling Wu, MD, PhD; Yongjun Wang, MD, PhD; Yilong Wang, MD, PhD

J Am Heart Assoc. 2017;6:e006757.
Glycemic Variation and Cardiovascular Risk in the Veteran’s Affairs Diabetes Trial

Objective
There is uncertainty about the importance of glycemic variability in cardiovascular complications in patients with type 2 diabetes. Using the Veteran Affairs Diabetes Trial (VADT), we investigated the association between variation in fasting glucose and glycated hemoglobin (HbA$_1c$) over time with the incidence of cardiovascular disease (CVD) and assessed whether this is influenced by intensive or standard glycemic control.

Research Design and Methods
During the VADT, fasting glucose and HbA$_1c$ were measured every 3 months for up to 84 months in 1,791 individuals. Variability measures included coefficient of variation (CV) and average real variability (ARV) for fasting glucose and HbA$_1c$. Overall mean glucose and HbA$_1c$ measures as well as their maximum and the most recent measurement were also examined.

Results
Variability measures (CV and ARV) of fasting glucose were significantly associated with CVD even after adjusting for other risk factors, including mean fasting glucose. When considering separately groups receiving intensive and standard glycemic control, this relationship was evident in the intensive treatment group but not in the standard group. Additional adjustment for severe hypoglycemic episodes did not alter the relationship between fasting glucose variability and CVD. Interestingly, no HbA$_1c$ measures were associated with CVD after adjusting for multiple baseline risk factors.

Conclusions
Our analysis indicates that in the VADT, variability of fasting glucose plays a role in the development of CVD complications beyond the influence of standard fasting glucose measures. The adverse consequences of fasting glucose variability on CVD appear greatest in those receiving intensive glucose control.
Glycemic variability is associated with myocardial damage in nondiabetic patients with ST-elevation myocardial infarction
Satoshi Oka, Juntaro Deyama, Ken Umetani, Tomoko Hara, Takuya Shimizu, Aritaka Makino, Keita Sano and Masahiko Nakamura

Background Glycemic variability (GV) induces coronary microcirculatory disturbance and myocardial damage in diabetic patients with acute myocardial infarction. However, in nondiabetic acute myocardial infarction patients, the relationship between GV and myocardial damage remains unclear.

Patients and methods We investigated GV with a continuous glucose monitoring system in nondiabetic ST-segment elevation myocardial infarction patients treated with emergent percutaneous coronary intervention. GV was expressed as the mean amplitude of glycemic excursions (MAGE). Myocardial damage was estimated by myocardial blush grade and ST-segment resolution (STRes). STRes was defined as complete (>70%), partial (30–70%), or none (<30%).

Results Consecutive patients (n = 73) were enrolled and classified into a lower or higher MAGE group on the basis of the median MAGE. The higher MAGE group showed lower levels of myocardial blush grade (2.41 ± 0.76 vs. 1.72 ± 0.85, P = 0.001) and STRes (complete: 56.8 vs. 33.3%, P = 0.044; partial: 32.4 vs. 36.1%, P = 0.741; none: 10.8 vs. 30.6%, P = 0.037).

Conclusion GV was associated with myocardial damage after percutaneous coronary intervention in nondiabetic ST-segment elevation myocardial infarction patients.

Keywords: acute myocardial infarction, glycemic variability, myocardial damage

Department of Cardiology, Yamanashi Prefectural Central Hospital, Kofu, Yamanashi Prefecture, Japan

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Received 22 August 2017 Accepted 22 November 2017
Clinical Implications of Glucose Variability: Chronic Complications of Diabetes

Hye Seung Jung

Glucose variability has been identified as a potential risk factor for diabetic complications. Oxidative stress is widely regarded as the mechanism by which glycemic variability induces diabetic complications. However, there remains no generally accepted gold standard for assessing glucose variability. Representative indices for measuring intraday variability include calculation of the standard deviation along with the mean amplitude of glycemic excursions (MAGE). MAGE is used to measure major intraday excursions and is easily measured using continuous glucose monitoring systems. Despite a lack of randomized controlled trials, recent clinical data suggest that long-term glycemic variability, as determined by variability in hemoglobin A1c, may contribute to the development of microvascular complications. Intraday glycemic variability is also suggested to accelerate coronary artery disease in high-risk patients.
Glucose variability for cardiovascular risk factors in type 2 diabetes: a meta-analysis
Glucose variability for cardiovascular risk factors in type 2 diabetes: a meta-analysis

Abstract

Aims: It is consensus that glucose variability (GV) plays an important role in maccomplications of type 2 diabetes, but whether GV has a causal role is not yet clear for cardiovascular disease (CVD). This study sought to explore the effect on GV for CVD risk factors with type 2 diabetes.

Methods: The systematic literature search was performed to identify all GV and CVD risk factors, including total cholesterol (TC), LDL cholesterol (LDL-C), triglyceride (TG), HDL cholesterol (HDL-C), Body Mass Index (BMI), waist circumference (WC), High-Sensitivity C-reactive protein (Hs-CRP), Homeostasis model assessment (HOMA) and carotid intima-media thickness (IMT). Preferred Reporting Items was synthesized for Systematic reviews and Meta Analyses guideline. And the pooled analyses were undertaken using Review Manager 5.3.

Results: Twenty two studies were included with a total of 1143 patients in high glucose variability group (HGVG) and 1275 patients low glucose variability group (LVGG). Among these selected CVD risk factors, HOMA-IR and reduced IMT were affected by GV. HOMA-IR level was significantly lower in LGVG than in HGVG (MD = 0.58, 95% CI: 0.26 to 0.91, P = 0.0004), with evidence of heterogeneity between studies (I² = 0%; P = 0.47). Reduced IMT level was significantly lower in LGVG than in HGVG (SMD = 0.28, 95% CI: 0.09 to 0.47, P = 0.003), with evidence of heterogeneity between studies (I² = 0%; P = 0.48). However, the others were no significant statistical difference.

Conclusions: Among these selected CVD risk factors in type 2 diabetes, minimizing GV could improve insulin resistance and reduced IMT, consistent with a lowering in risk of CVD.
Long-term Glycemic Variability and Risk of Adverse Outcomes: A Systematic Review and Meta-analysis

Diabetes Care 2015;38:2354–2369 | DOI: 10.2337/dc15-1188

Catherine Gorst,¹ Chun Shing Kwok,²,³ Saadia Aslam,⁴ Iain Buchan,⁵ Evangelos Kontopantelis,⁶ Phyo K. Myint,⁶ Grant Heatlie,² Yoon Lake,⁷ Martin K. Rutter,⁸,⁹ and Mamas A. Mamas²,³,⁵

2372 studies found from MEDLINE and EMBASE search:

2307 studies were excluded since did not evaluate outcomes of interest or include HbA₁c variability or included participants without diabetes with gestational diabetes with prediabetes or were in vivo in vitro studies or incorrect study type or not available in English.

65 potentially relevant studies from titles and abstract screening.

45 studies were excluded since did not evaluate outcomes of interest or include HbA₁c variability or included participants without diabetes with gestational diabetes with prediabetes or were in vivo in vitro studies or incorrect study type or were not available in English or were not able to obtain full paper with insufficient details from the abstract to allow inclusion.

20 studies met the final inclusion criteria after reviewing full manuscripts.
Long-term Glycemic Variability and Risk of Adverse Outcomes: A Systematic Review and Meta-analysis

OBJECTIVE

Glycemic variability is emerging as a measure of glycemic control, which may be a reliable predictor of complications. This systematic review and meta-analysis evaluates the association between HbA1c variability and micro- and macrovascular complications and mortality in type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Medline and Embase were searched (2004-2015) for studies describing associations between HbA1c variability and adverse outcomes in patients with type 1 and type 2 diabetes. Data extraction was performed independently by two reviewers. Random-effects meta-analysis was performed with stratification according to the measure of HbA1c variability, method of analysis, and diabetes type.

RESULTS

Seven studies evaluated HbA1c variability among patients with type 1 diabetes and showed an association of HbA1c variability with renal disease (risk ratio 1.56 [95% CI 1.08-2.25], two studies), cardiovascular events (1.98 [1.39-2.82]), and retinopathy (2.11 [1.54-2.89]). Thirteen studies evaluated HbA1c variability among patients with type 2 diabetes. Higher HbA1c variability was associated with higher risk of renal disease (1.34 [1.15-1.57], two studies), macrovascular events (1.21 [1.06-1.38]), ulceration/gangrene (1.50 [1.06-2.12]), cardiovascular disease (1.27 [1.15-1.40]), and mortality (1.34 [1.18-1.53]). Most studies were retrospective with lack of adjustment for potential confounders, and inconsistency existed in the definition of HbA1c variability.

CONCLUSIONS

HbA1c variability was positively associated with micro- and macrovascular complications and mortality independently of the HbA1c level and might play a future role in clinical risk assessment.
Figure 1. The Triangle of Diabetes Care

- Improve glucose levels
- Limit glucose variability
- Avoid hypoglycaemia

BETTER OUTCOMES FOR PATIENTS
# Glycaemic variability in diabetes: clinical and therapeutic implications

Antonio Cariello, Louis Monnier, David Owens

<table>
<thead>
<tr>
<th>Computation</th>
<th>Interpretation</th>
<th>Advantages and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD of mean glucose concentration</td>
<td>Short-term within-day glucose variability</td>
<td>Traditional measure of dispersion for large quantities of data such as those recorded with CGM systems and directly calculated by devices</td>
</tr>
<tr>
<td>CV for glucose</td>
<td>Short-term within-day glucose variability</td>
<td>Adjusted on the mean glucose concentration and easily calculated from SD and mean glucose concentration.</td>
</tr>
<tr>
<td>MAGE</td>
<td>Short-term within-day glucose variability</td>
<td>Major glucose fluctuations; not directly reported by CGM devices but is simple to calculate.</td>
</tr>
<tr>
<td>MODD</td>
<td>Short-term between-day glucose variability</td>
<td>Not directly reported by CGM devices; requires additional computation, but is easy to interpret.</td>
</tr>
<tr>
<td>CONGA</td>
<td>Short-term within-day temporal glucose variability</td>
<td>Complex calculation.</td>
</tr>
<tr>
<td>ADRR</td>
<td>Composite of short-term within-day and between-day temporal glucose variability</td>
<td>Complex calculation.</td>
</tr>
<tr>
<td>LBG and HBGI</td>
<td>Risk indices for predicting hypoglycaemia (LBGI) or hyperglycaemia (HGBI)</td>
<td>Complex calculation; more oriented towards capturing the risk for severe hypoglycaemia and hyperglycaemia than assessing glycaemic variability.</td>
</tr>
<tr>
<td>MAG</td>
<td>Short-term within-day temporal variability</td>
<td>Fairly complex calculation.</td>
</tr>
<tr>
<td>IQR of AGP</td>
<td>Reflects the presence or absence of day-to-day synchrony in glucose patterns at a given time</td>
<td>Measure of dispersion for small amounts of data such as those recorded at a given time point over several days (directly reported by the Abbott FreeStyle Libre).</td>
</tr>
<tr>
<td>Visit-to-visit changes</td>
<td>Measures of variability (SD, CV) of HbA1c, FPG, etc between sequential visits</td>
<td>Measures that are very heterogeneous in design.</td>
</tr>
</tbody>
</table>

CGM=continuous glucose monitoring, CV=coefficient of variation, MAGE=mean amplitude of glycaemic excursions, MODD=mean of daily differences, CONGA=continuous overlapping net glycaemic action, ADRR=average daily risk range, LBGI=low blood glucose index, HBGI=high blood glucose index, MAG=mean absolute glucose variation, AGP=averaged glycaemic profile over several consecutive days (14 days with the Abbott FreeStyle Libre), FPG=fasting plasma glucose.

**Table:** Main metrics for assessment of glycaemic variability.
Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

https://doi.org/10.2337/dc18-0033
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHEDATHEROSCLEROTIC CARDIOVASCULAR DISEASE (ASCVD) OR CHRONIC KIDNEY DISEASE (CKD)

**Use metformin unless contraindicated or not tolerated**
- If not at HbA1c target:
  - Continue metformin unless contraindicated (remember to adjust dose to stop metformin with declining eGFR)
  - Add SGLT2i or GLP-1 RA with proven cardiovascular benefit (see below)
- If HbA1c target:
  - If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven cardiovascular benefit (see below)
  - OR reconsider/consider individualized target and introduce SGLT2i or GLP-1 RA
  - OR re-assess HbA1c at 3-month intervals and add SGLT2i or GLP-1 RA if HbA1c goes above target

**ASCVD predominates**

- GLP-1 RA with proven CVD benefit
- SGLT2i with proven CVD benefit, if eGFR adequate

**HF or CKD predominates**

- PREFERABLY: SGLT2i with evidence of reducing HF and/or CKD progression in CVD risk if eGFR adequate OR
- If HbA1c not tolerated or contraindicated or if eGFR less than adequate, add GLP-1 RA with proven CVD benefit

**If HbA1c above target**

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
  - DPP-4i if not on GLP-1 RA
  - Basal insulin
  - TZD
  - SGLT2i

1. Proven CVD benefit means it has licensed indication of reducing CVD events.
   - For GLP-1 RA: strongest evidence for liraglutide = semaglutide = exenatide extended release. For SGLT2i evidence mostly stronger for empagliflozin = canagliflozin
2. Be aware that SGLT2i vary by region and individual agent with regard to individual level of eGFR for indication and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CV events in CVD risk
4. Caution with GLP-1 RA in EDMD
5. Dipeptidyl peptidase-4 inhibitors have demonstrated CV safety
6. Long-term use may be better tolerated through less well studied for CV effects
7. Choose prior generation SU to lower risk of hypoglycemia

70 ΧΡΟΝΙΑ ΚΑΡΔΙΟΛΟΓΙΑΣ (EKE)
70 YEARS OF CARDIOLOGY (HSC)
ΠΑΝΕΛΛΗΝΙΟ ΚΑΡΔΙΟΛΟΓΙΚΟ ΣΥΝΕΔΡΙΟ
PANHellenic Congress of Cardiology

WWW.HCS.GR
Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

https://doi.org/10.2337/dc18-0033
Empagliflozin, CV Outcomes and Mortality in T2DM

Primary Outcome

- Placebo
- Empagliflozin

Death from Cardiovascular Causes

- Hazard ratio, 0.62 (95% CI, 0.49–0.77)
- P < 0.001

Death from Any Cause

- Hazard ratio, 0.68 (95% CI, 0.57–0.82)
- P < 0.001

Hospitalization for Heart Failure

- Hazard ratio, 0.65 (95% CI, 0.50–0.85)
- P = 0.002

GLP1-RA: Liraglutide and CV Outcomes in T2DM - LEADER Trial

**Primary Outcome**
- HR 0.85
- P=0.02

**Death from Any Cause**
- HR 0.87
- P=0.01

New Diabetes Drugs and Patterns of CV Benefits in Patients With T2DM and CV Disease

- Atherogenesis
  - Volume overload
  - Myocardial fibrosis

Reduced stroke and MI risk

Possible lowered by GLP-1RA

? ↓ atherothrombosis ± avoidance of hypoglycaemia

Reduced CV-death Heart failure risk

Lowered by SGLT2 inhibitors

? Hemodynamic/metabolic mechanisms

Source: Sattar J Am Coll Cardiol 2017; 69: 2646–56


Novel ‘Diabetes’ Drugs: Unanswered Questions

- Are these drugs equally effective in patients without CVD or without DM (primary prevention)?
- Which patients benefit most from each drug? e.g. patients with HF or kidney disease
- Mechanisms by which drugs mediate CV benefit?

Heart failure
Diabetic nephropathy
Obesity

Future CVOTs
Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials

Table 2—Secondary outcomes

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin 2.5 mg</th>
<th>Empagliflozin 10 mg</th>
<th>Empagliflozin 25 mg</th>
<th>P value for differences vs. placebo</th>
</tr>
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<tbody>
<tr>
<td>Weight, kg</td>
<td></td>
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<tr>
<td>EASE-2 (26 weeks)</td>
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<tr>
<td>EASE-2 (52 weeks)*</td>
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<tr>
<td>EASE-3 (26 weeks)</td>
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<tr>
<td>CGM-derived time in glucose range of &gt;70 to ≤180 mg/dL, % (h/day)</td>
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<td>EASE-2 (26 weeks)</td>
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<td>EASE-2 (52 weeks)*</td>
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<tr>
<td>EASE-3 (26 weeks)†</td>
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<tr>
<td>CGM-derived IQR, mg/dL</td>
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</table>

Julio Rosenstock,¹ Jon Marquard,² Lori M. Laffel,³ Dietmar Neubacher,⁴ Stefan Kaspers,² David Z. Cherney,⁵ Bernard Zinman,⁶ Joy S. Skyler,⁷ Jytoshi George,² Nima Soleymanlou,⁸ and Bruce A. Perkins⁵

Diabetes Care Publish Ahead of Print, published online October 4, 2018

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70 ΧΡΟΝΙΑ ΚΑΡΔΙΟΛΟΓΙΑΣ (ΕΚΕ)  
70 YEARS OF CARDIOLOGY (HSC)  
ΠΑΝΕΛΛΗΝΙΟ ΚΑΡΔΙΟΛΟΓΙΚΟ ΣΥΝΕΔΡΙΟ  
PANHELLENIC CONGRESS OF CARDIOLOGY  
WWW.HCS.GR
24-Hour Glycemic Control of Dapagliflozin

- N=50, patients with type 2 diabetes
- Glucose concentration measured using a CGM system
- Effects of dapagliflozin 10 mg/d compared with placebo in patients taking doses of metformin ≥1500 mg/d alone or of insulin ≥30 units/d with or without up to 2 oral antihyperglycemic agents

Dapagliflozin Increased Time in Euglycemia

<table>
<thead>
<tr>
<th>Percentage of Time With Blood Glucose</th>
<th>≥70 mg/dL</th>
<th>≤180 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean (SD)</td>
<td>58.4 (24.08)</td>
<td>55 (22.22)</td>
</tr>
<tr>
<td>Adjusted mean (SE) change baseline to day 28</td>
<td>+12.2 (2.6)</td>
<td>-2.8 (2.55)</td>
</tr>
<tr>
<td>Adjusted mean (SE) difference vs placebo</td>
<td>+15 (3.65)</td>
<td></td>
</tr>
<tr>
<td>P value for treatment difference</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

- Small increase in hypoglycemia with dapagliflozin
- Most common adverse event = urinary tract infections

24-Hour Glycemic Control of Exenatide Once Weekly

- Exaggerated postprandial excursions and hypoglycemia can provide important, additional data to help manage type 2 diabetes
- Glucose concentration measured by using a CGM system
- Patients with type 2 diabetes inadequately controlled while taking metformin randomized to exenatide once weekly 2 mg (n=60) or placebo (n=56) for 10 wk
- Mean HbA$_{1c}$ and FPG in exenatide group: 8.2% and 178 mg/dL, respectively
- Mean HbA$_{1c}$ and FPG in placebo group: 8.0% and 168 mg/dL, respectively

Lowest Glucose Variability and Hypoglycemia Are Observed With the Combination of a GLP-1 Receptor Agonist and Basal Insulin (VARIATION Study)

OBJECTIVE
There is a dearth of published literature comparing glucose variability (GV) between different insulin regimens in type 2 diabetes. This cohort study compares GV using continuous glucose monitoring (CGM) in patients with well-controlled type 2 diabetes using four common insulin regimens: basal insulin + oral drugs (BO), basal insulin + glucagon-like peptide 1 receptor agonist (GLP-1 RA) (BGLP), premixed insulin (PM), and basal-bolus insulin (BB).

RESEARCH DESIGN AND METHODS
Consecutive patients from three endocrinology clinics who met study criteria—type 2 diabetes, age 18 to 80 years, BMI ≤ 45 kg/m², stable insulin regimen for a minimum of 6 months, and stable A1C value ≤7.5% (58 mmol/mol) before study enrollment—underwent 6-day masked CGM. Hypoglycemia was defined as a sensor glucose concentration <70 mg/dL on CGM.

RESULTS
A total of 160 patients with comparable baseline characteristics formed four equal insulin regimen cohorts. The daily glucose SD (the primary outcome) was significantly lower in the BGLP cohort versus the BO, PM, and BB cohorts (P = 0.03, P = 0.01, and P < 0.01, respectively), and remained so after adjusting for age, BMI, type 2 diabetes duration, and A1C. Similarly, daily hypoglycemia outcomes on CGM were least for the BGLP cohort.

CONCLUSIONS
The lowest GV and lowest hypoglycemia were observed in patients using the combination of basal insulin with a GLP-1 RA, supporting the complementary glycemic action of these agents in type 2 diabetes. These observed benefits in GV and hypoglycemia may contribute to the cardiovascular outcome reduction seen with GLP-1 RA therapy and should be investigated further.
Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial)

Marcus Lind,1,2 Irl B Hirsch,3 Jaakko Tuomilehto,4 Sofia Dahlqvist,2 Bo Ahrén,5 Ole Torffvit,5
Stig Attvall,4 Magnus Ekelund,5 Karin Filipsson,5 Bengt-Olov Tengmark,6 Stefan Sjöberg,7
Nils-Gunnar Pehrsson8

STUDY ANSWER AND LIMITATIONS
Liraglutide was associated with a significant reduction of 16.9 mmol/mol (1.5%) in HbA1c versus 4.6 mmol/mol (0.4%) for placebo, difference −12.3 mmol/mol (95% confidence interval −15.8 to −8.8 mmol/mol; −1.13%, −1.45 to −0.81 mmol/mol). Body weight was significantly reduced in participants in the liraglutide compared with placebo group (3.8 v 0.0 kg, difference −3.8, −4.9 to −2.8 kg), and total daily insulin doses were significantly reduced, by 18.1 units and 2.3 units (difference −15.8, −23.1 to −8.5 units). Reductions in mean and standard deviation of glucose levels estimated by masked continuous glucose monitoring were significantly greater in the liraglutide group than placebo group (−1.9 and −0.5 mmol/L). Neither group experienced severe hypoglycaemic events nor were there any significant differences in symptomatic or asymptomatic non-severe hypoglycaemia (<4.0 or <3.0 mmol/L). The mean number of non-severe symptomatic hypoglycaemic events (<4.0 mmol/L) during follow-up was 1.29 in the liraglutide group and 1.24 in the placebo group (P=0.96). One of the study’s limitations was its relatively short duration. Sustained effects of liraglutide have, however, been found over lengthier periods in connection with other treatment regimens. Cardiovascular safety and potential adverse events during longer exposure to liraglutide need to be evaluated. Nausea was experienced by 21 (32.8%) participants in the liraglutide group and 5 (7.8%) in the placebo group and 3 (5%) and 4 (7%) participants in these groups, respectively, had any serious adverse event.
Continuous Glucose Monitoring in Type 2 Diabetes Patients Treated with GLP-1 Receptor Agonist Dulaglutide in Combination with Prandial Insulin Lispro – An AWARD-4 Substudy

Johan Jendle¹, Marcia A. Testa², Sherry Martin³, Honghua Jiang³, Zvonko Milicevic⁴


• Παίζει ρόλο η διακύμανση της γλυκόζης στον καρδιαγγειακό κίνδυνο;
• Στην κλινική πράξη (κατευθυντήριες οδηγίες);
Management of Hyperglycemia in Type 2 Diabetes, 2018.
A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

https://doi.org/10.2337/dc18-0033
Cardiovascular disease prevention strategies for type 2 diabetes mellitus

Niki Katsiki, Francesco Purrello, Costas Tsioufis & Dimitri P Mikhailidis

Lifestyle and anti-obesity measures
- Diet
- Exercise
- Weight reducing drugs and bariatric surgery
- Smoking cessation

Hypolipidaemic treatment
Mainly statins. Ezetimibe and PCSK9 inhibitors may be used to reach LDL-C goals. Fibrates may be considered if triglyceride levels are considerably elevated (despite attempts to control glycaemic status).

Antihypertensive treatment
Although some drugs are insulin friendly and some not, the main target is to correct the blood pressure. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are an appropriate choice.

Antiplatelet treatment
Mainly aspirin and/or clopidogrel. Other agents are being investigated and may potentially prove to be superior.

Antidiabetic treatment
Note that recent trials have shown that some of these drugs significantly reduce the risk of vascular events (e.g. empagliflozin, canagliflozin, lixivatide, semaglutide).
Ευχαριστώ πολύ για την προσοχή σας!

Fluctuations In Blood Sugar Levels?