8ème Congrès National de Médecine Vasculaire
Alger (hôtel Mercure) 29-30 Juin 2018

Au-delà de l'HbA1c: la Variabilité glycémique

Pr A Zaamouche

Plan

- Limites de l’HbA1c
- Définition de la variabilité glycémique et moyens de mesure
- Variabilité glycémique et complications du diabète
- Variabilité glycémique et hypoglycémie
- Conclusion

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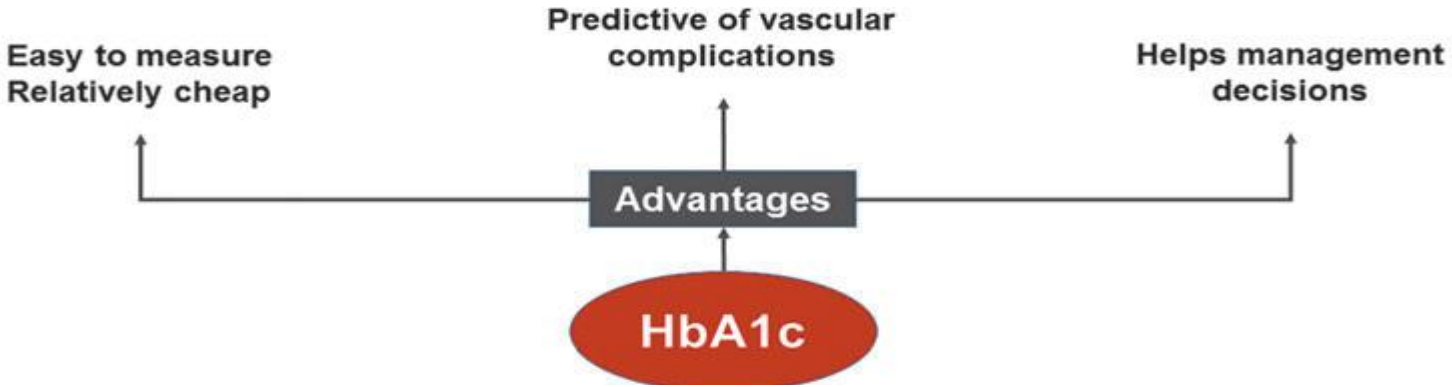
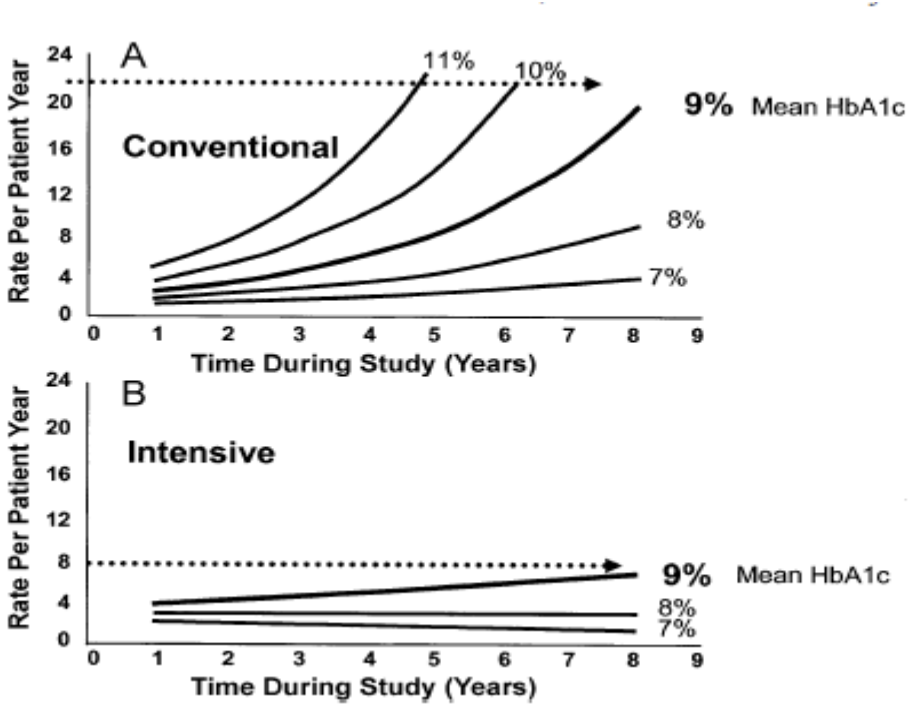
Avantages et limites de l’HbA1c



How Can We Realize the Clinical Benefits of Continuous Glucose Monitoring?Ramzi A and All , DIABETES TECHNOLOGY & THERAPEUTICSVolume 19, Supplement 2, 2017

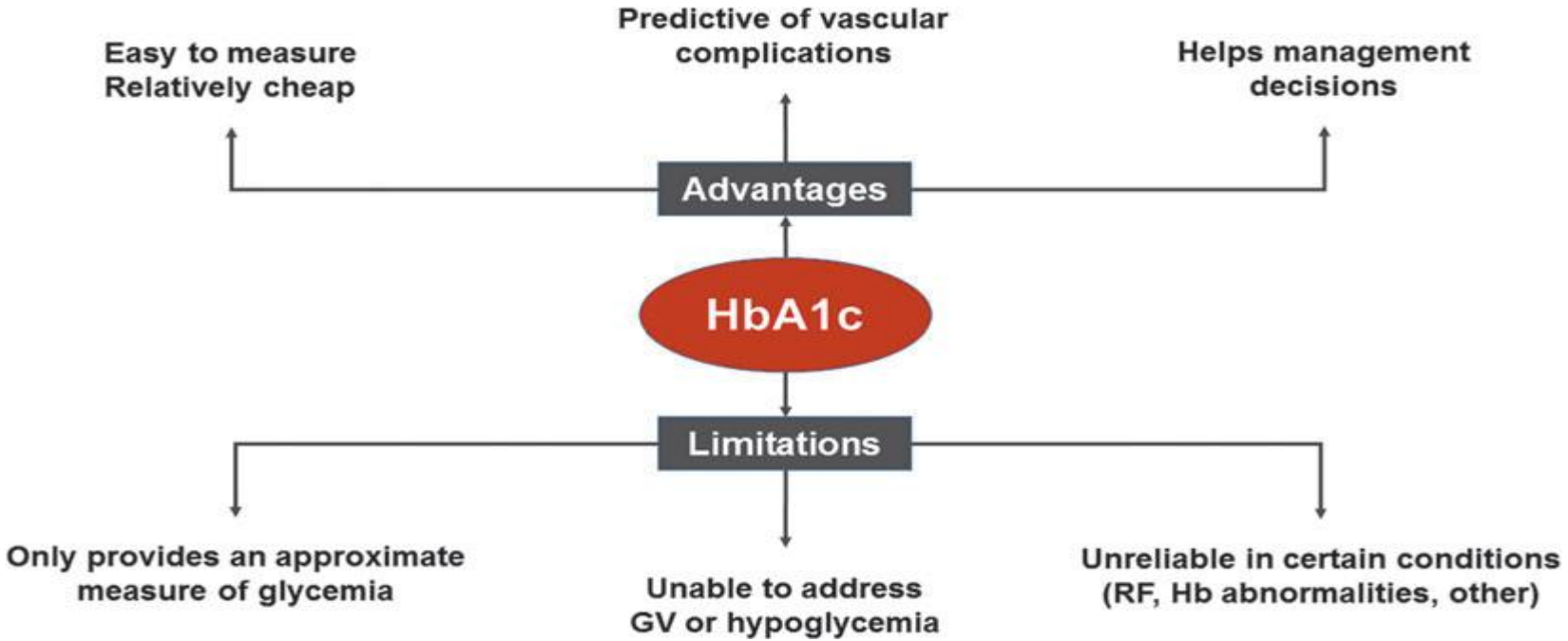
Avantages et limites de l'HbA1c



Absolute risk of sustained retinopathy progression as a function of updated mean A1C (percentage) during the DCCT and the time of follow-up during the study

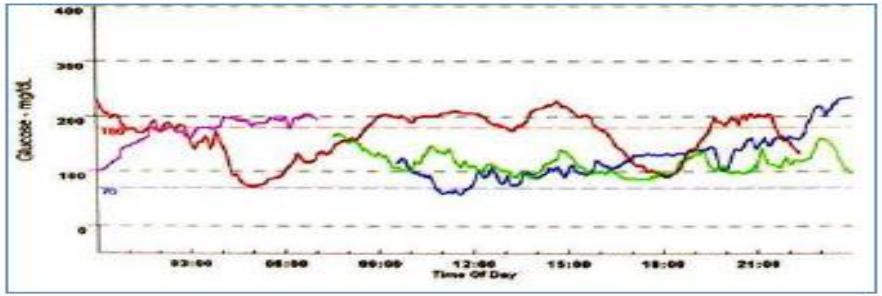
Irl B. Hirscha and All .Should minimal blood glucose variability become the gold standard of glycemic control?Journal of Diabetes and Its Complications 19 (2005) 178– 181

Avantages et limites de l'HbA1c

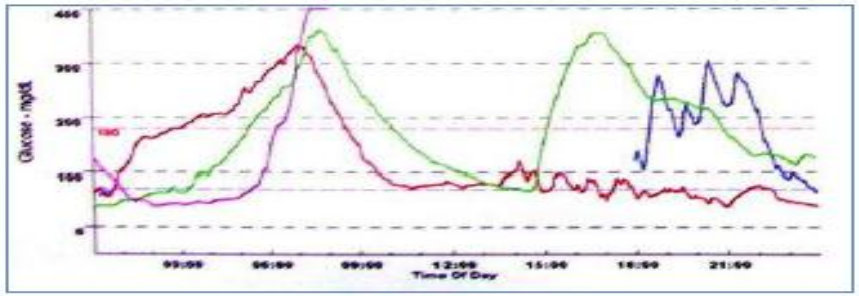


How Can We Realize the Clinical Benefits of Continuous Glucose Monitoring?Ramzi A and All , DIABETES TECHNOLOGY & THERAPEUTICSVolume 19, Supplement 2, 2017

Gestion de la variabilité glycémique ?
Excursions glycémiques non identifiées par HbA1c seule



Patient 1:
A1C = 7,1 %
Glycémie moyenne :
143 mg/dl
SD: 43 mg/dl



Patient 2:
A1C = 7,3 %
Glycémie moyenne :
149 mg/dl
SD: 94 mg/dl

Modified from A. Gelber et al., 44th Annual Meeting of EASD 2008 Rom, 1073,Diabetologia 2008;51 (Suppl. 1), S436-437

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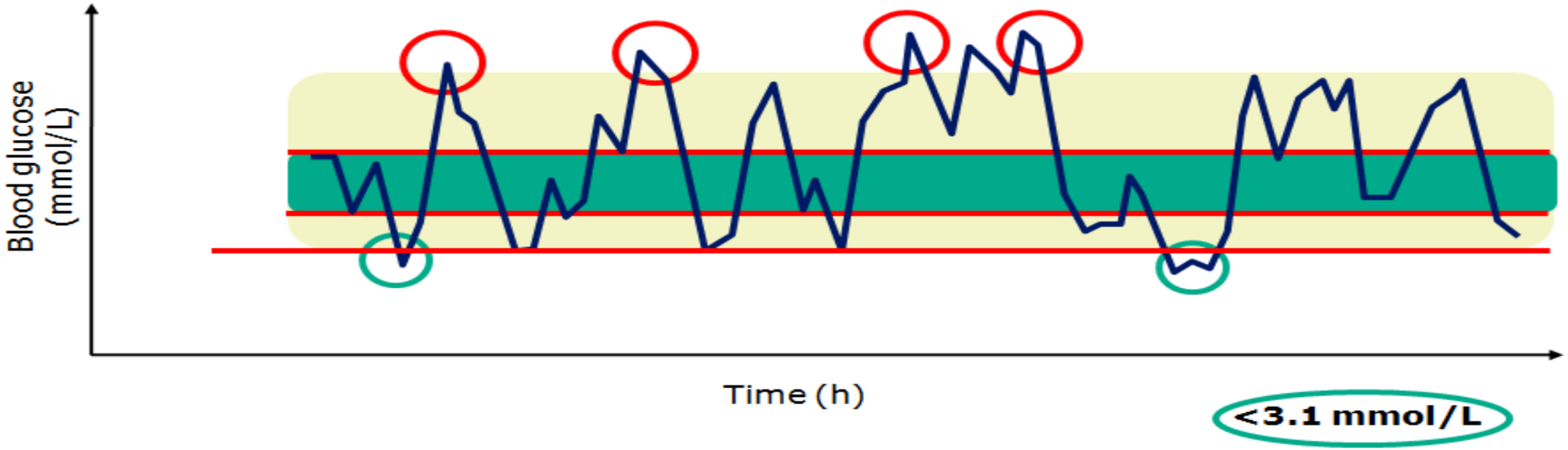
Defining glycemic variability

- Hypoglycaemic events
- Postprandial glucose excursions
- Minor fluctuations in blood glucose levels



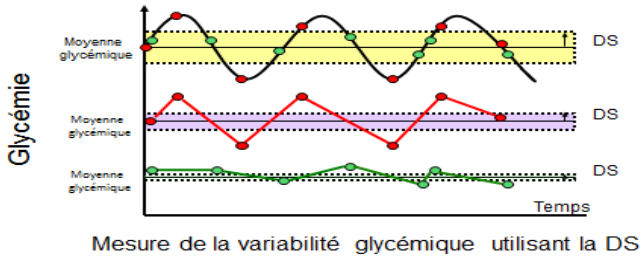
Monnier and Colette. Diabetes Care 2008;31(Suppl.2):S150–4

Figure 1. Carnet d'autosurveillance glycémique d'un patient avec diabète instable : Le patient est compliant (10-11 glycémies par jour) – Variabilité glycémique intra-journalière – Variabilité glycémique inter-journalière – Risque hypoglycémique (une voire deux hypoglycémies quotidiennes)

Jean-Pierre Riveline, Hélène Hanaire, Instabilité glycémique : démarche diagnostique et thérapeutique.MCED n°86 – Janvier 2017

Mesure de la variabilité glycémique

Variability measure	Formula	Explanation of symbols	Discriminating feature
SD	$\sqrt{\frac{\sum (x_i - \bar{x})^2}{k-1}}$	x_i = individual observation $\bar{x}$ = mean of observations k = number of observations	easy to determine, extensively used
CV	$\frac{s}{\bar{x}}$	s = standard deviation $\bar{x}$ = mean of observations	easy to determine, SD corrected for mean
adjusted M-value	$M_{GR} + M_W$ where $M_{GR} = \frac{\sum_{t=t_1}^{t} \left\lvert {}^{10}\log \frac{GR_t}{IGV} \right\rvert^3}{n}$ and $M_W = \frac{G_{max} - G_{min}}{20}$	M_{GR} = M-value for glucose readings M_W = correction factor for n <24 GR_t = glucose reading at time t IGV = ideal glucose value t_i = time in minutes after start of observations of the ith observation G_{max} = maximum glucose reading G_{min} = minimum glucose reading	not a pure variability measure
MAGE	$\sum \frac{\lambda}{n}$ if $\lambda \succ v$	λ = each blood glucose increase or decrease (nadir-peak or peak nadir) n = number of observations v = 1 SD of mean glucose for 24-hr period	used most extensively
CONGA	$\sqrt{\frac{\sum_{t=t_1}^{t_{k^*}} (D_t - \bar{D})^2}{k^* - 1}}$ where $D_t = GR_t - GR_{t-n}$ and $\bar{D} = \frac{\sum_{t=t_1}^{t_{k^*}} D_t}{k^*}$	k^* = number of observations where there is an observation n x 60 minutes ago $m = n \times 60$ D_t = difference between glucose reading at time t and t minus n hours ago	specifically developed for CGM
MODD	$\frac{\sum_{t=t_1}^{t_{k^*}} \lvert GR_1 - GR_{t-1440} \rvert}{k^*}$		inter-day variation



Mesure de la variabilité glycémique utilisant la DS

Siegelaar SE et al.
Endocrine Reviews 2010; 31: 171–82

Mesure de la variabilité glycémique

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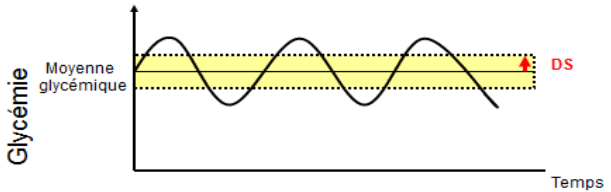

Mesure de la variabilité glycémique utilisant le CV% =
[DS / moyenne glycémique] x 100
Exemple : DS = 40 mg/dL et moyenne glycémique =160 mg/dL conduit à un CV = 25 %

Siegelaar SE et al.
Endocrine Reviews 2010; 31: 171–82

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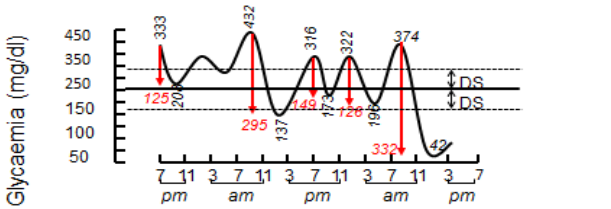

Principe de l'évaluation du MAGE (Mean of Amplitude Glycemic Excursions) pour une DS = 62 mg/dL

(d'après Molnar et Service)

Siegelaar SE et al.
Endocrine Reviews 2010; 31: 171–82

Mesure de la variabilité glycémique

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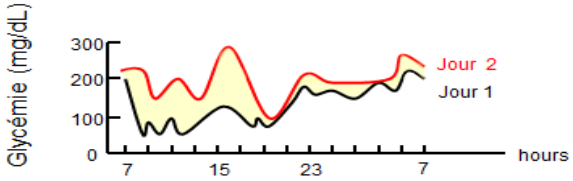

Principe de l'évaluation du
MODD = Mean Of Daily Differences

Siegelaar SE et al.
Endocrine Reviews 2010; 31: 171–82

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- **Conclusion**

Can glycaemic variability, as calculated from blood glucose self-monitoring, predict the development of complications in type 1 diabetes over a decade?

J. Bragd [a,*], U. Adamson [a], L.B. Bäcklund [b], P.E. Lins [a], E. Moberg [c], P. Oskarsson [c]

Mean SDBG and mean HbA_{1c} in 1990 patients with and without complications at baseline, and in those who developed complications, during study period 1990–2001

	Free of complications at baseline	With complications at baseline	Incidence of complications 1990–2001	
Unawareness SDBG	3.8 ± 1.0	4.3 ± 1.3	4.5 ± 0.8	$P = 0.028^*$
HbA_{1c}	7.9 ± 1.4	7.4 ± 0.6	7.6 ± 1.1	$P = 0.302$
Nephropathy SDBG	3.8 ± 0.8	4.6 ± 1.2	4.4 ± 1.6	$P = 0.022^*$
HbA_{1c}	7.6 ± 1.2	8.4 ± 1.1	8.5 ± 1.4	$P = 0.043^*$
Retinopathy SDBG	3.9 ± 1.0	–	4.2 ± 1.3	$P = 0.590$
HbA_{1c}	7.8 ± 1.3	–	8.0 ± 1.2	$P = 0.420$
Neuropathy SDBG	3.7 ± 0.9	4.4 ± 1.1	4.0 ± 0.8	$P = 0.034^*$
HbA_{1c}	7.5 ± 1.3	7.9 ± 1.0	8.2 ± 1.4	$P = 0.104$

* Within-group statistical significance.

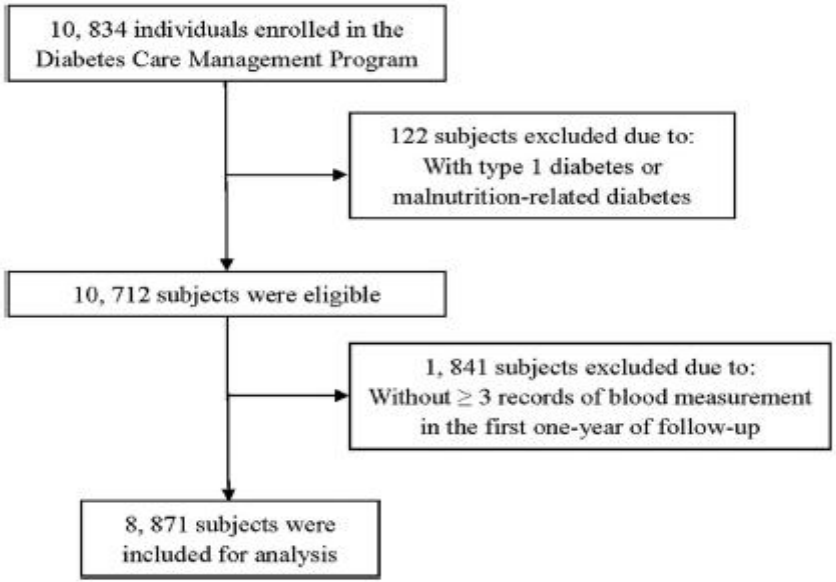
J. Bragd *and all* . Can glycaemic variability, as calculated from blood glucose self-monitoring, predict the development of complications in type 1 diabetes over a decade? Diabetes & Metabolism 34 (2008) 612–616

OPEN

Fasting plasma glucose variability and all-cause mortality among type 2 diabetes patients: a dynamic cohort study in Shanghai, China

Received: 06 June 2016
Accepted: 25 November 2016
Published: 22 December 2016

Dongli Xu[1], Hong Fang[1], Wanghong Xu[2], Yujie Yan[1], Yinan Liu[1] & Baodong Yao[1]



type 2 diabetes patients enrolled in the registry between 1 January 2007 and 31 December 2007

Until 31 December 2014

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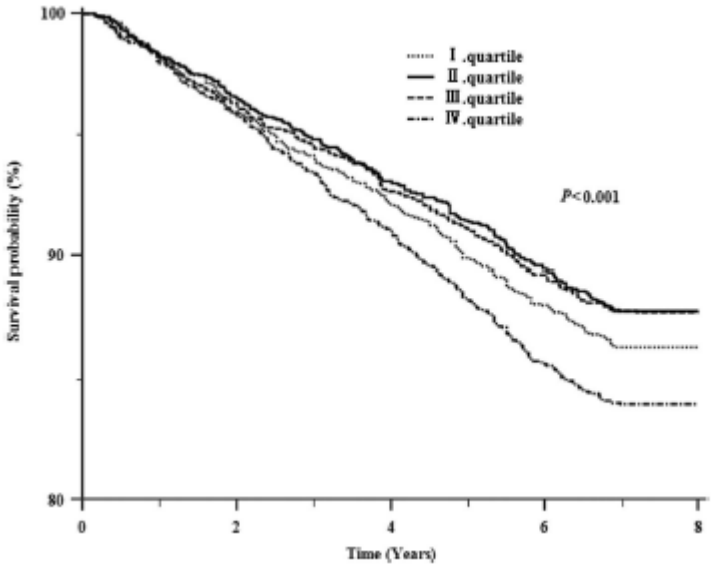


type 2 diabetes patients enrolled in the registry between 1 January 2007 and 31 December 2007

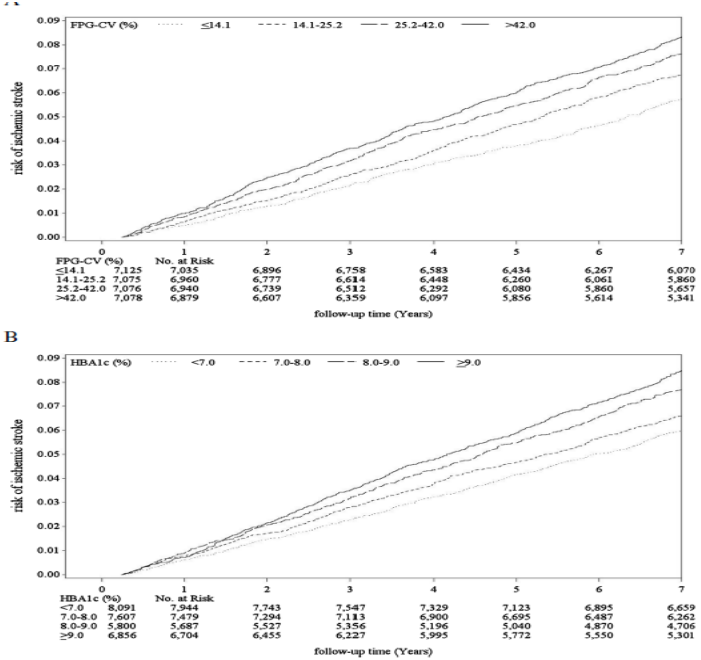
Until 31 December 2014

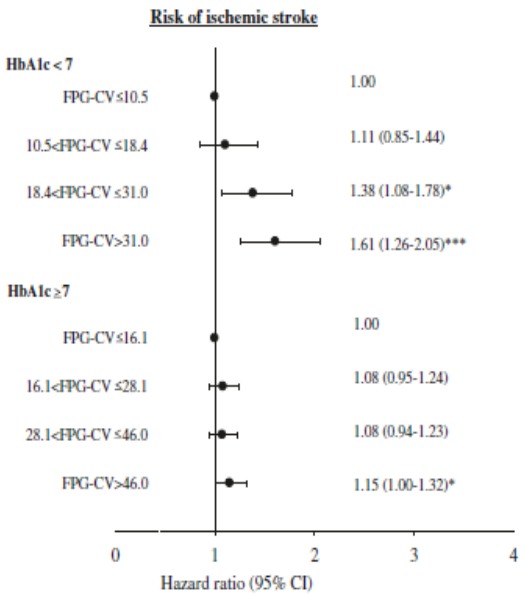
	Baseline quartiles of CV of FPG			
	1 (lowest)	2	3	4 (highest)
n	2215	2220	2218	2218
Deaths from all-causes, n (%)	285 (12.87)	254 (11.44)	257 (11.59)	340 (15.33)
Model 1	1.00	0.89 (0.75–1.05)	0.95 (0.81–1.13)	1.24 (1.06–1.45)**
Model 2	1.00	0.87 (0.73–1.03)	0.94 (0.79–1.11)	1.18 (1.01–1.39)*
Model 3	1.00	0.86 (0.73–1.02)	0.92 (0.78–1.09)	1.10 (0.93–1.31)

Model 1: adjusted for age and gender. Model 2: adjusted for age, gender, duration of diabetes, smoking, physical activity, methods of DM treatment, SBP, DBP, family history and BMI categories. Model 3: adjusted for variables in the model 2 plus baseline FPG. *$P < 0.05$; **$P < 0.001$.

Visit-to-visit variability of fasting plasma glucose as predictor of ischemic stroke: competing risk analysis in a national cohort of Taiwan Diabetes Study

Cheng-Chieh Lin[1,2,3†], Chun-Pai Yang[4,5,6†], Chia-Ing Li[2,3], Chiu-Shong Liu[1,2,3], Ching-Chu Chen[7,8], Wen-Yuan Lin[1,3], Kai-Lin Hwang[9], Sing-Yu Yang[10] and Tsai-Chung Li[10,11*]

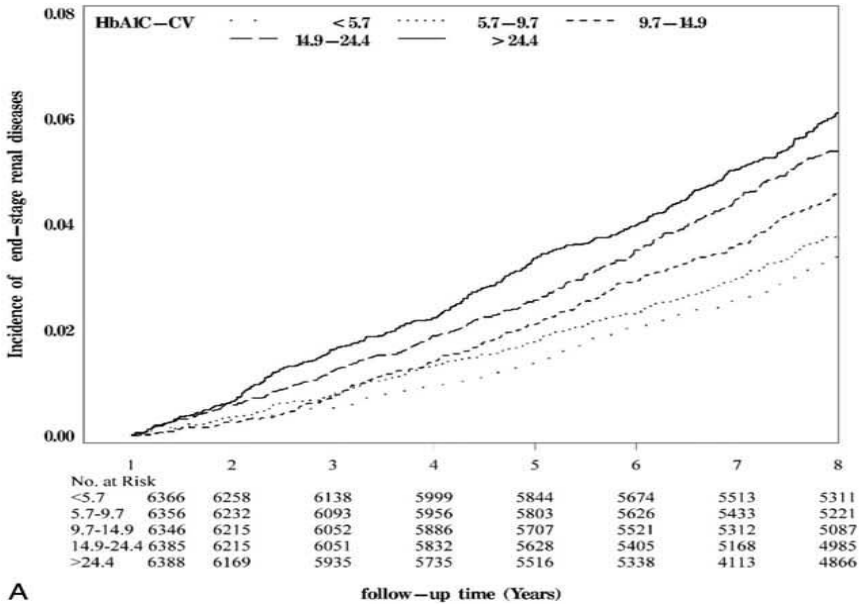


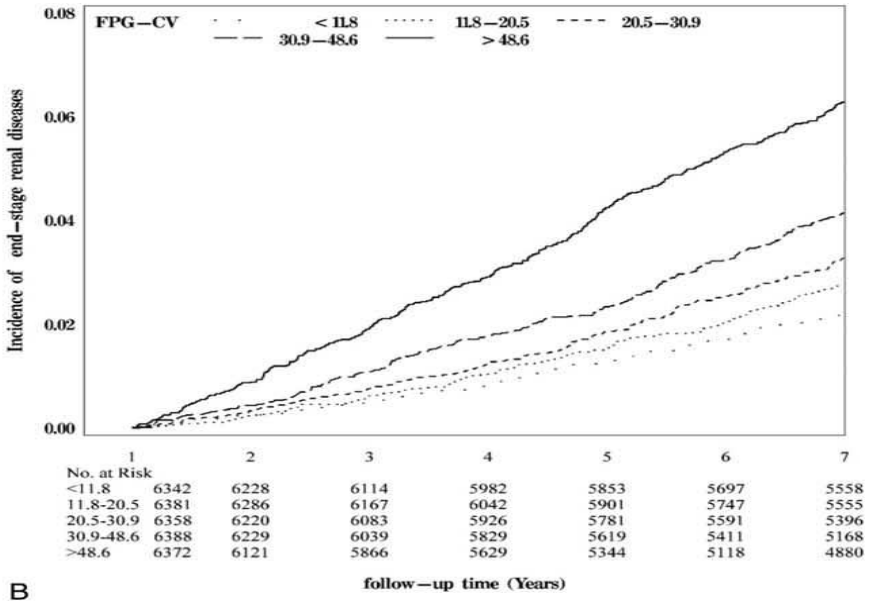


Cheng-Chieh Lin and All, Visit-to-visit variability of fasting plasma glucose as predictor of ischemic stroke: competing risk analysis in a national cohort of Taiwan Diabetes Study. BMC Medicine 2014, 12:165

Visit-to-Visit Glucose Variability Predicts the Development of End-Stage Renal Disease in Type 2 Diabetes

10-Year Follow-Up of Taiwan Diabetes Study



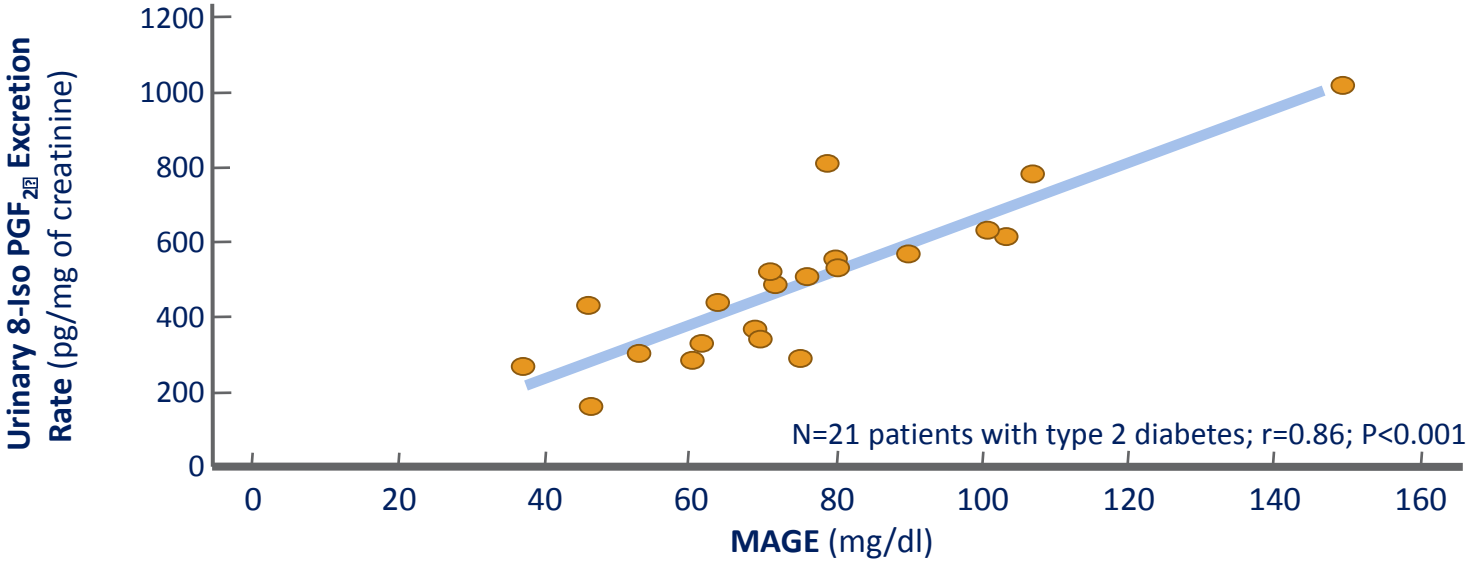


Risks of ESRD for (A) HbA1c-CV and (B) FPG-CV. Log-rank test, all P<0.001. ESRD¼end-stage renal diseases.

Ya-Fei Yang and All,Visit-to-Visit Glucose Variability Predicts the Development of End-Stage Renal Disease in Type 2 Diabetes 10-Year Follow-Up of Taiwan Diabetes Study. Medicine Volume 94, Number 44, November 2015

Correlation Between Glucose Excursions (MAGE) and Oxidative Stress in Type 2 Diabetes

24-Hour Urinary Excretion Rates of 8-Iso $PGF_{2\alpha}$ and MAGE in People with Type 2 Diabetes



Monnier L, et al. JAMA 2006; 295: 1681-7

Oscillating Glucose Is More Deleterious to Endothelial Function and Oxidative Stress Than Mean Glucose in Normal and Type 2 Diabetic Patients

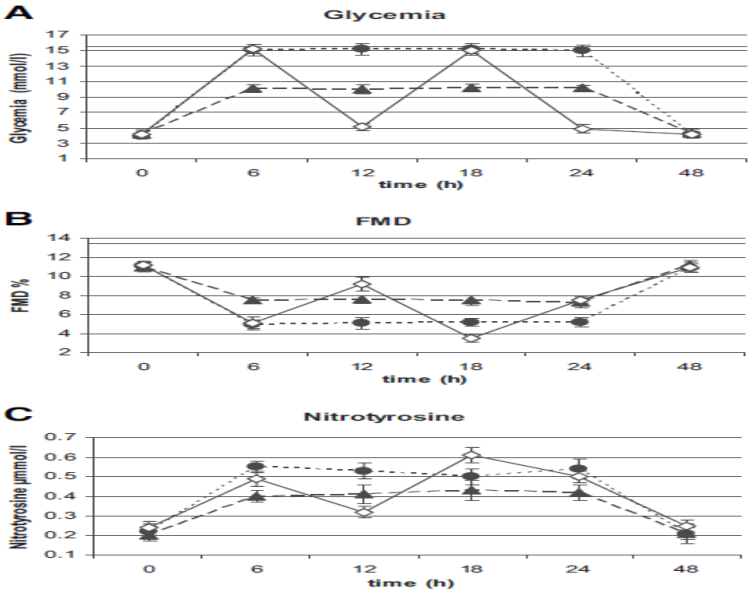


FIG. 1. *A*: Hyperglycemic clamps in normal subjects. For 24 h, glycemia *1*) was increased at 15 mmol/l every 6 h and normalized for the next 6 h (◇), *2*) maintained at 15 mmol/l (●) (peak value), and *3*) maintained at 10 mmol/l (▲) (mean glycemia value/24 h of experiment 1). *B* and *C*: FMD and nitrotyrosine measured during the experiments and 24 h after the end. Bars indicate SEM.

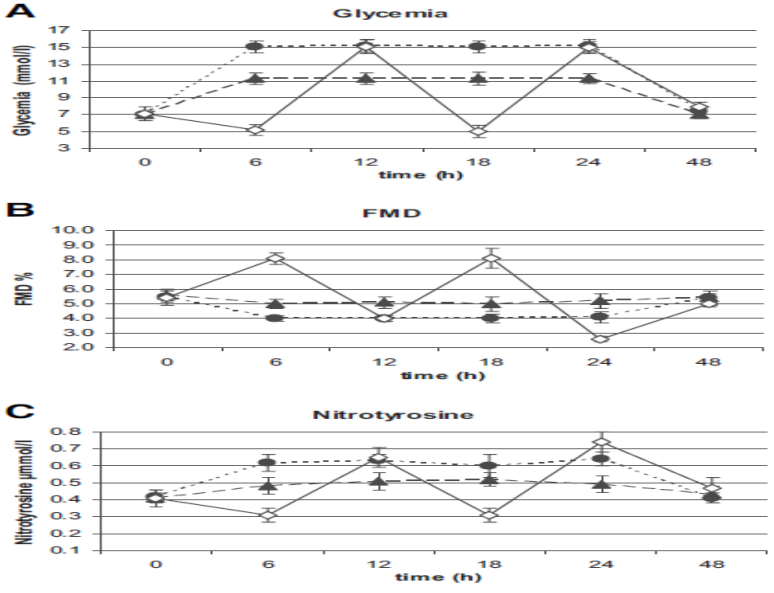


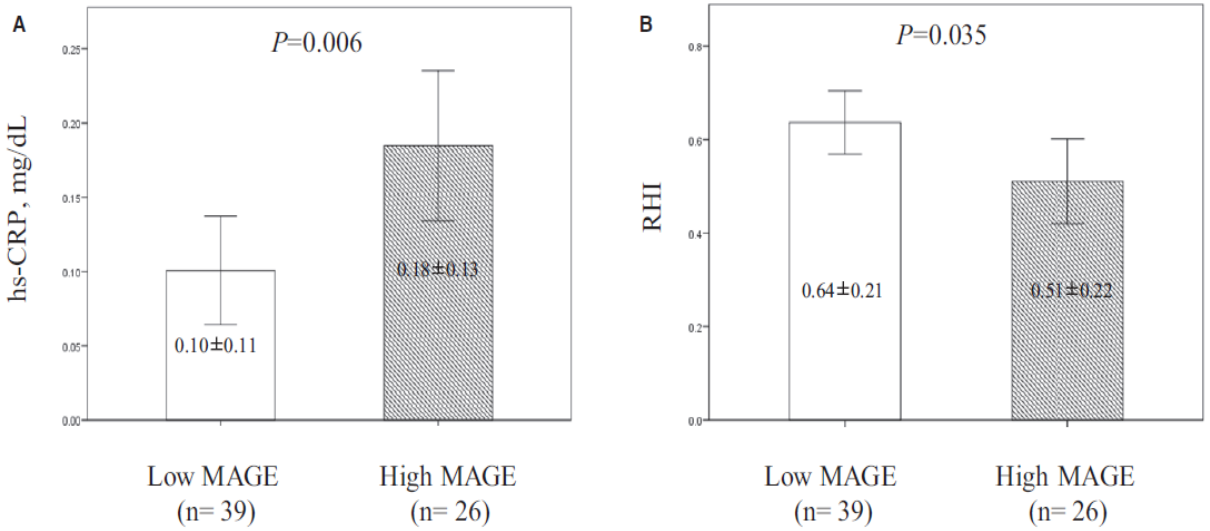
FIG. 2. Hyperglycemic clamps in diabetic patients. For 24 h, glycemia *1*) was increased at 15 mmol/l every 6 h and normalized for the next 6 h (◇), *2*) maintained at 15 mmol/l (●) (peak value), and *3*) maintained at 10 mmol/l (▲) (mean glycemia value/24 h of experiment 1). *B* and *C*: FMD and nitrotyrosine measured during the experiments and 24 h after the end. Bars indicate SEM.

CONCLUSIONS—These data suggest that oscillating glucose can have more deleterious effects than constant high glucose on endothelial function and oxidative stress, two key players in favoring cardiovascular complications in diabetes.

Antonio Cerielloand all, DIABETES, VOL. 57, MAY 2008

Effects of the Mean Amplitude of Glycemic Excursions and Vascular Endothelial Dysfunction on Cardiovascular Events in Nondiabetic Patients With Coronary Artery Disease

Tomonori Akasaka, MD; Daisuke Sueta, MD, PhD; Noriaki Tabata, MD; Seiji Takashio, MD, PhD; Eiichiro Yamamoto, MD, PhD; Yasuhiro Izumiya, MD, PhD; Kenichi Tsujita, MD, PhD; Sunao Kojima, MD, PhD; Koichi Kaikita, MD, PhD; Kunihiko Matsui, MD, PhD; Seiji Hokimoto, MD, PhD



65 patients non diabétiques coronariens
12 mois de suivi
Relation Mage reactivia hyperemia index (FHI) CV evens(CV death,MI, unstable angina and revascularisation)

J Am Heart Assoc.2017;6:e004841. DOI:10.1161/JAHA.116.004841.

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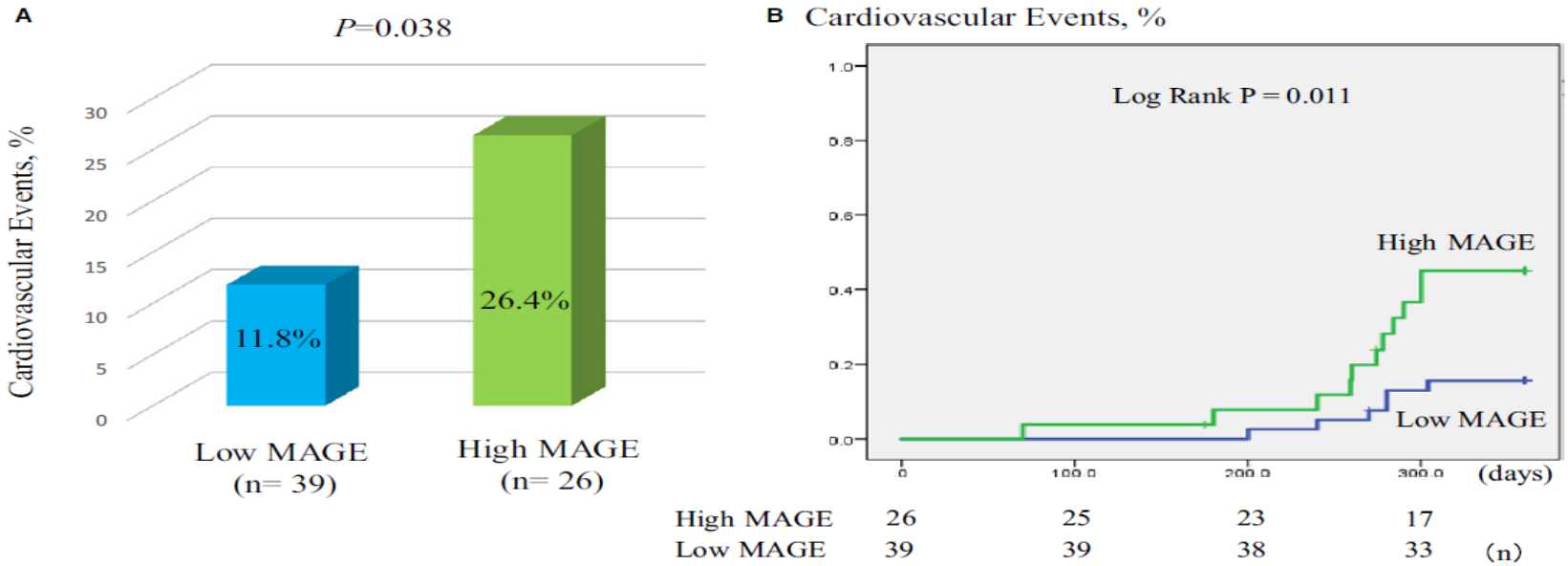
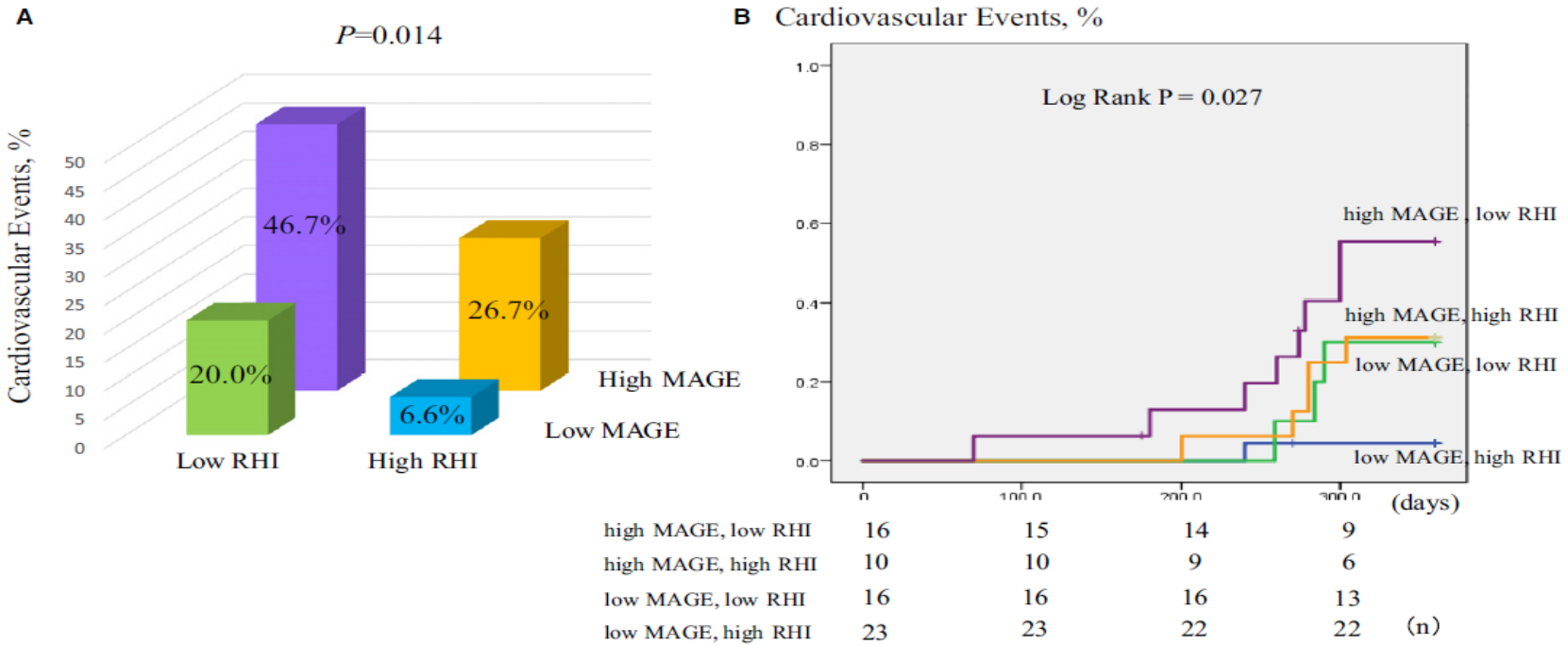


J Am Heart Assoc.2017;6:e004841. DOI:10.1161/JAHA.116.004841.

Effects of the Mean Amplitude of Glycemic Excursions and Vascular Endothelial Dysfunction on Cardiovascular Events in Nondiabetic Patients With Coronary Artery Disease

Tomonori Akasaka, MD; Daisuke Sueta, MD, PhD; Noriaki Tabata, MD; Seiji Takashio, MD, PhD; Eiichiro Yamamoto, MD, PhD; Yasuhiro Izumiya, MD, PhD; Kenichi Tsujita, MD, PhD; Sunao Kojima, MD, PhD; Koichi Kaikita, MD, PhD; Kunihiko Matsui, MD, PhD; Seiji Hokimoto, MD, PhD



J Am Heart Assoc.2017;6:e004841. DOI:10.1161/JAHA.116.004841.

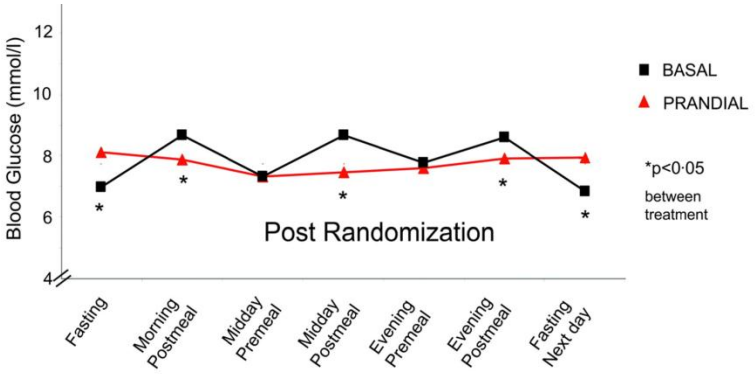
A Decrease in Glucose Variability Does Not Reduce Cardiovascular Event Rates in Type 2 Diabetic Patients After Acute Myocardial Infarction

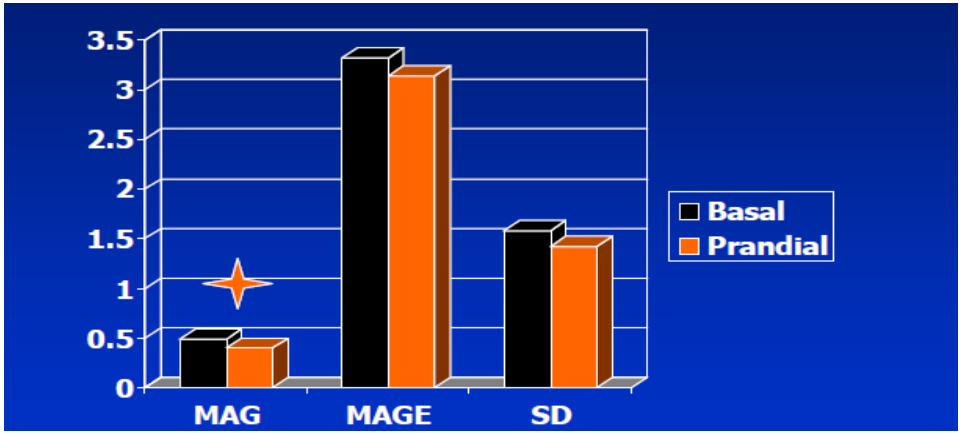
A reanalysis of the HEART2D study

SARAH E. SIEGELAAR, MD[1]
LISA KERR, MSPH[2]
SCOTT J. JACOBER, DO[2]
J. HANS DEVRIES, MD, PHD[1]

Diabetes Care 34:855–857, 2011

Type 2 diabetic patients after acute myocardial infarction were randomized to an insulin treatment strategy targeting postprandial (PRANDIAL; n = 557) or fasting/interprandial (BASAL; n = 558)





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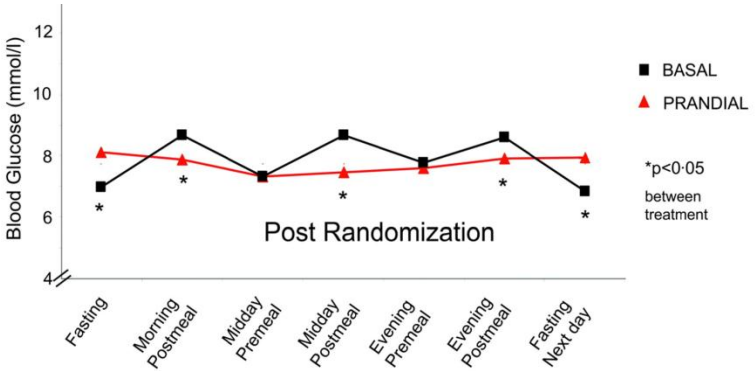

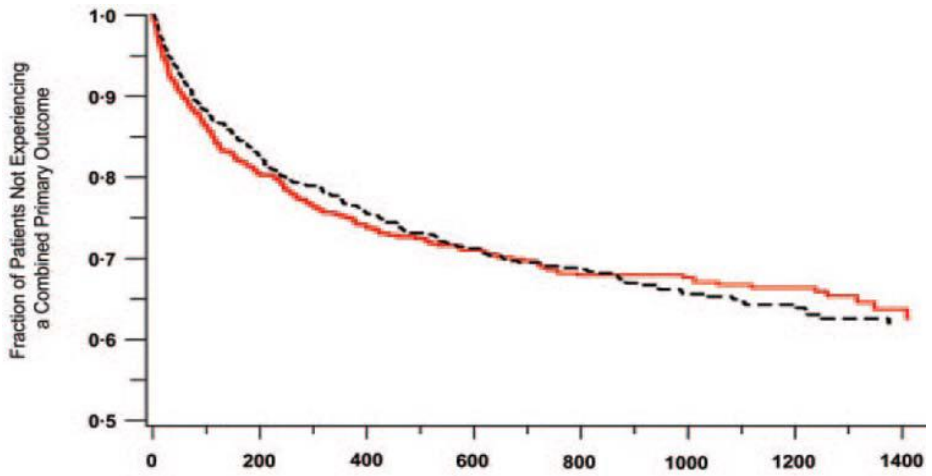

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Diabetes Care 34:855–857, 2011

CONCLUSIONS—A PRANDIAL strategy demonstrated lower intraday GV vs. a BASAL strategy with similar overall glycemic control but did not result in a reduction in cardiovascular outcomes. This does not support the hypothesis that targeting GV would be beneficial in reducing subsequent secondary cardiovascular events.

Plan

- Limites de l’HbA1c
- Définition de la variabilité glycémique et moyens de mesure
- Variabilité glycémique et complications du diabète
- Variabilité glycémique et hypoglycémie
- Conclusion

The relationship between glycaemic variability and hypoglycaemia is established

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 14, Number 11, 2012

DOI: 10.1089/dia.2012.0099

DTT
Diabetes Technology & Therapeutics

ORIGINAL ARTICLE

Rate of Hypoglycemia in Insulin-Treated Patients with Type 2 Diabetes Can Be Predicted from Glycemic Variability Data

Yongming Qu, Ph.D.,[1] Scott J. Jacober, D.O.,[1] Qianyi Zhang, Ph.D.,[1] Linda L. Wolka, B.S.,[1]* and J. Hans DeVries, M.D., Ph.D.[2]

PRIMARY CARE DIABETES 9 (2015) 290–296

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primary care diabetes

Original research

Relationships among different glycemic variability indices obtained by continuous glucose monitoring

Yoshifumi Saisho[a,*], *Chihiro Tanaka*[a], *Kumiko Tanaka*[a], *Rachel Roberts*[b], *Takayuki Abe*[b], *Masami Tanaka*[a], *Shu Meguro*[a], *Junichiro Irie*[a], *Toshihide Kawai*[a], *Hiroshi Itoh*[a]

[a] *Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan*
[b] *Center for Clinical Research, Keio University School of Medicine, Tokyo, Japan*

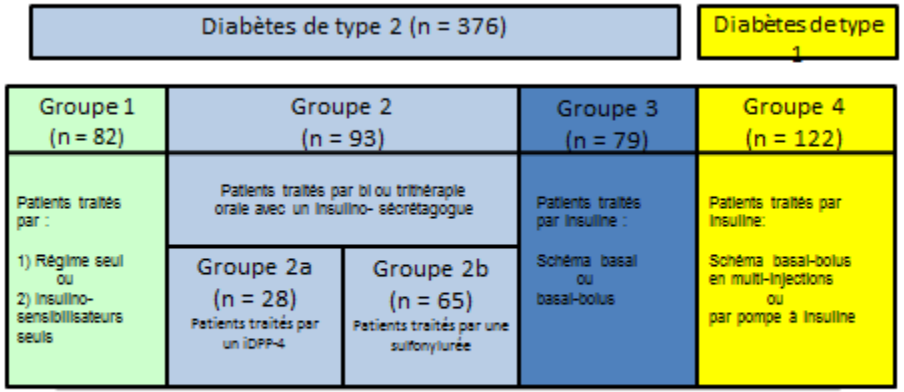
Higher rates of confirmed hypoglycaemia are associated with greater within-subject variability in fasting plasma glucose in type 1 and type 2 diabetes: A meta-analysis

Bode *et al. Diabetologia* 2013;56(Suppl. 1):S423

Toward Defining the Threshold Between Low and High Glucose Variability in Diabetes

Louis Monnier,[1] Claude Colette,[1] Anne Wojtusciszyn,[2] Sylvie Dejager,[3] Eric Renard,[2] Nicolas Molinari,[4] and David R. Owens[5]

Diabetes Care 2017;40:832–838 | https://doi.org/10.2337/dc16-1769



Description des groupes de patients individualisés pour déterminer la limite entre les diabètes stables et « labiles »
Monnier L.,et al. Diabetes Care. Published online December 30, 2016

Incidence of hypoglycemia (top panel) and results of 24-h mean interstitial glucose values given as medians, with IQRs and 10th and 90th percentiles (bottom panel) when patients of each group were divided into two subgroups according to whether %CVs were.36 or#36%.

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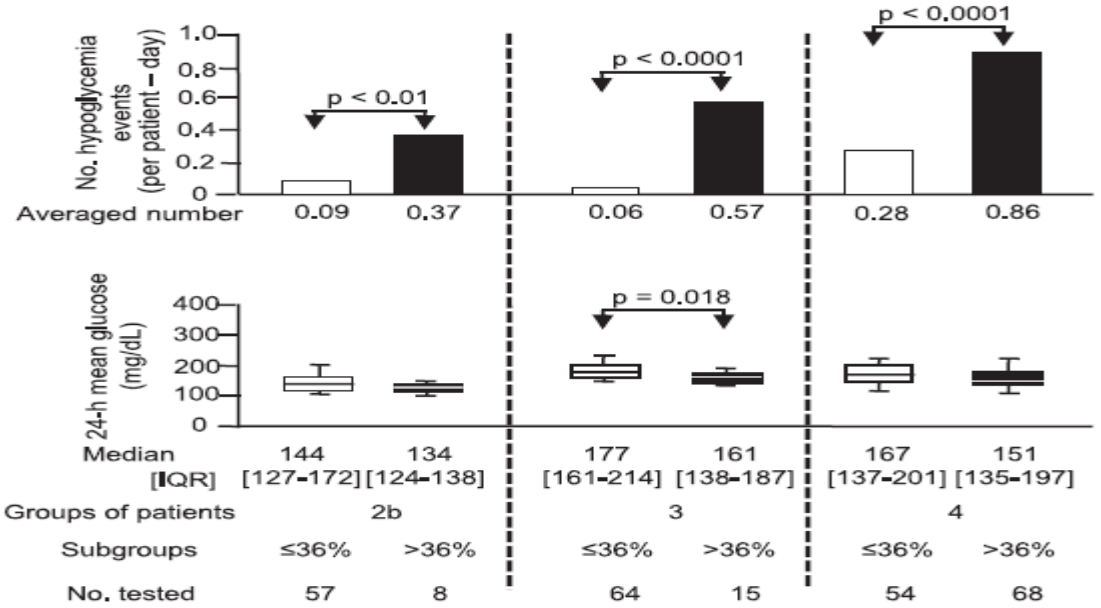


Incidence of hypoglycemia (top panel) and results of 24-h mean interstitial glucose values given as medians, with IQRs and 10th and 90th percentiles (bottom panel) when patients of each group were divided into two subgroups according to whether %CVs were.36 or#36%.

The effect of glucose variabilité on QTc duration and dispersion in patients with type 2 Diabetes mellitus

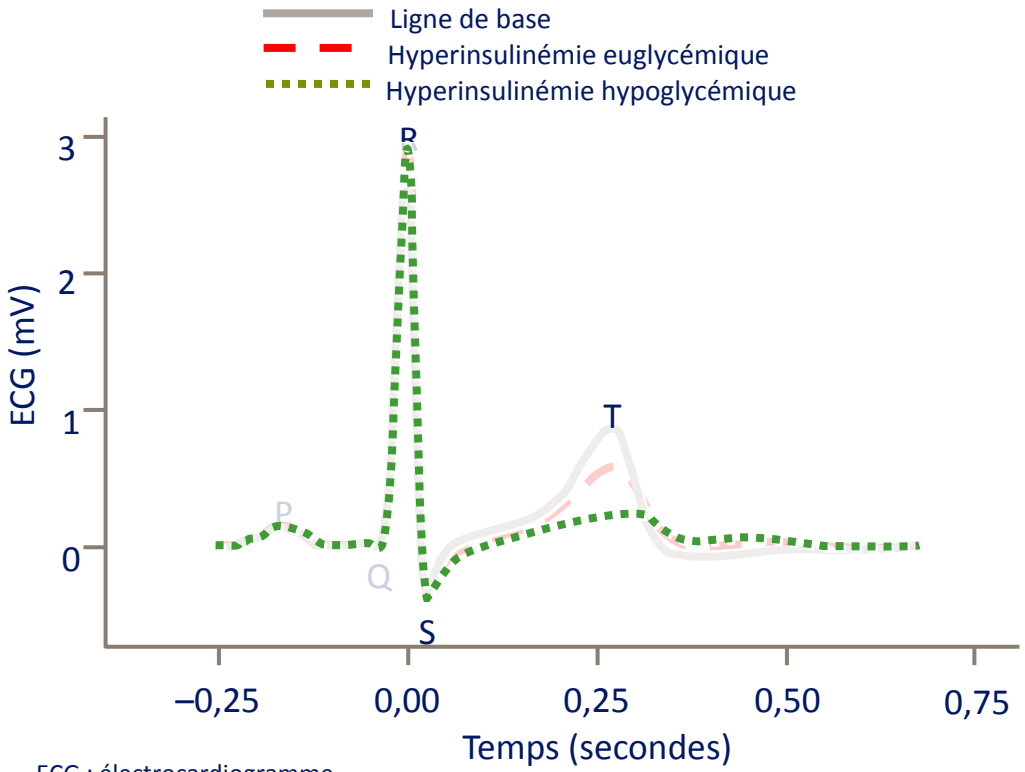
Table-III: The effect of QTc prolongation on the glycemic parameters and complications.

	QTc ≤ 440 ms	*QTc> 440 ms*	*P*
SD	37.78 ± 16.63	45.14 ±24.45	0.008
CV	23.48 ± 9.03	26.09 ±10.39	0.6
Fasting glucose (mg/dl)	165.22 ±7.49	164.79 ±49.31	0.958
HbA1c (%)	7.97 ±1.71	8.23 ±1.63	0.366
Diabetes duration	9.67 ±7.01	10.09 ±9.73	0.714
Neuropathy	22.5%	6.2%	0.507
Retinopathy	9%	2.6%	0.602
Nephropathy	11.2%	2.5%	0.306

275 consecutive patients with type 2 diabetes.
GV.deviation (SD) and coefficient of variation (CV) from 7 point glucose measures.
We investigated the relationship of GV parameters with QT parameters.

Yasar Sertbas and all,The effect of glucose variability on QTc duration and dispersion in patients with Type 2 Diabetes Mellitus. Pak J Med Sci. 2017;33(1):22-26.

L’hypoglycémie est associée à des anomalies de l'ECG



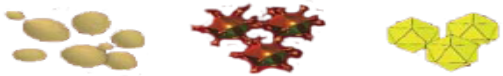
ECG : électrocardiogramme

- Anomalies dans :
  - Conduction atrio-ventriculaire
  - Repolarisation ventriculaire
- Libération de catécholamines, entraînant :
- ↓ K^+
- Amplification de l’onde R
- Aplatissement de l’onde T
- Dépression du segment ST
- Prolongation de l’espace QT
- Risque d’arythmie cardiaque

Laitinen *et al*. *Ann Noninvasive Electrocardiol* 2008;13:97–105

Physiopathologie des conséquences cardiovasculaires de l'hypoglycémie

↑ CRP ↑ VEGF ↑ IL-6



Inflammation

↑Activation des ↑neutrophiles

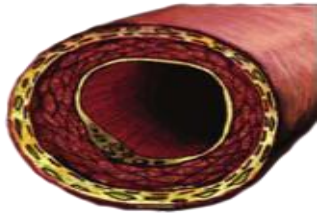
↑ Activation ↑plaquettaire

↑ Facteur VIII

Anomalies de la coagulation sanguine

Hypoglycémie

Dysfonction endothéliale



↓Vasodilatation

Réponse sympatho-surrénale

↑ Adrénaline

Anomalies du rythme

Variabilité de la fréquence cardiaque

Changements hémodynamiques

↑ Charge de travail cardiaque
↑ Contractilité
↑ Débit

CRP : protéine C-réactive ; IL-6 : interleukine 6 ; VEGF : facteur de croissance endothélial vasculaire.

Adaptation de Desouza *et al. Diabetes Care*. 2010;33:1389-94; Frier *et al. Diabetes Care*. 2011;34(Suppl 2):S132-S137

Diabetologia (2018) 61:48–57
DOI 10.1007/s00125-017-4423-z

ARTICLE

Day-to-day fasting glycaemic variability in DEVOTE: associations with severe hypoglycaemia and cardiovascular outcomes (DEVOTE 2)

Bernard Zinman[1] · Steven P. Marso[2] · Neil R. Poulter[3] · Scott S. Emerson[4] · Thomas R. Pieber[5] · Richard E. Pratley[6,7] · Martin Lange[8] · Kirstine Brown-Frandsen[8] · Alan Moses[8] · Ann Marie Ocampo Francisco[8] · Jesper Barner Lekdorf[8] · Kajsa Kvist[8] · John B. Buse[9] · on behalf of the DEVOTE Study Group

Table 2 Variability and HbA_{1c} levels by variability group

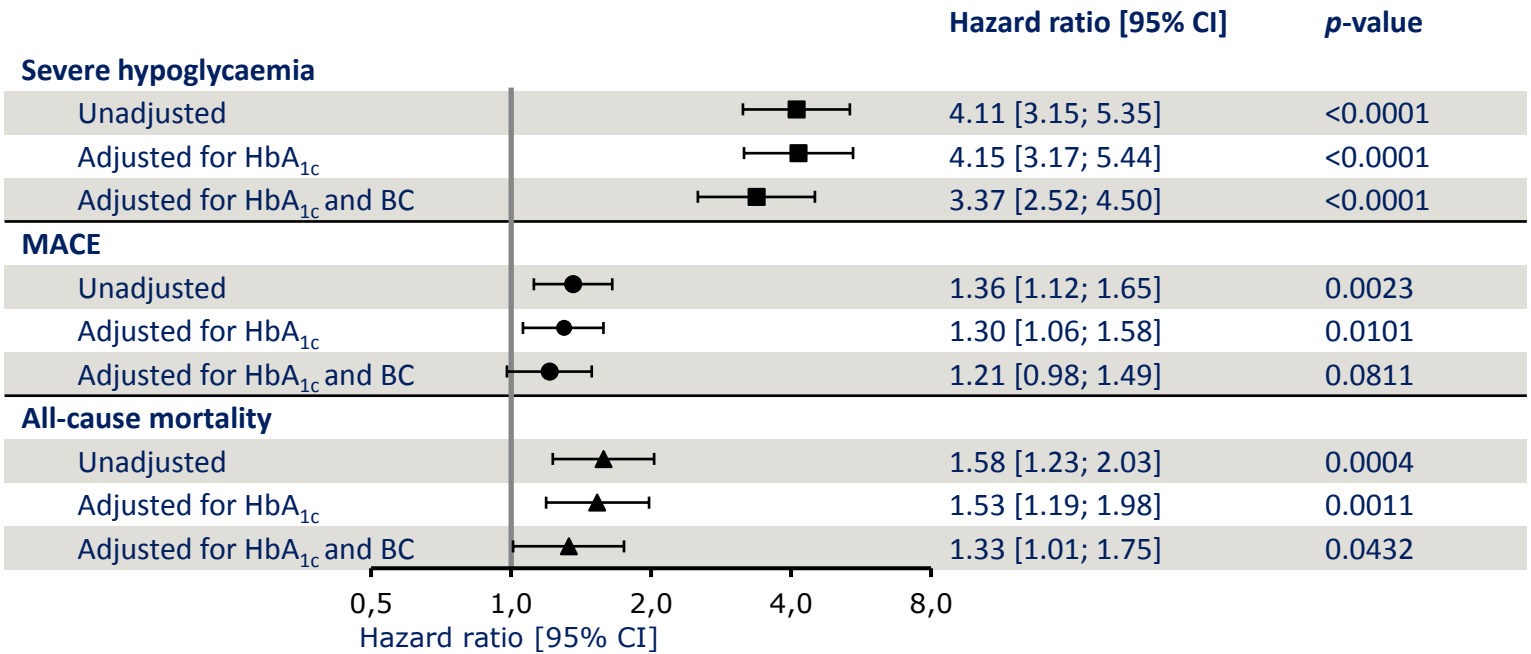
Variability/HbA_{1c}	Low variability $n = 2528$	Medium variability $n = 2530$	High variability $n = 2528$
Variability[a]			
Mean ± SD	14 ± 3%	23 ± 2%	36 ± 9%
Min, Max	1%, 19%	19%, 27%	27%, 138%

DEVOTE :Outcomes by variability group

Outcome	Low variability $n = 2528$		Medium variability $n = 2530$		High variability $n = 2528$	
	Events	Rate	Events	Rate	Events	Rate
Severe hypoglycaemia	83	1.69	116	2.38	237	5.00
MACE	187	3.84	219	4.49	267	5.48
Cardiovascular death	75	1.50	83	1.65	116	2.30
Non-fatal MI	90	1.83	104	2.11	117	2.37
Non-fatal stroke	37	0.75	50	1.00	61	1.23
All-cause mortality	115	2.30	131	2.61	171	3.40

MI, myocardial infarction; rate, events per 100 patient-years of observation

Association between day-to-day fasting glycaemic variability and outcomes



Variability is reported on a continuous scale

Adjusted for HbA_{1c}: most recent HbA_{1c} on a continuous scale. Adjusted for HbA_{1c} and BC: most recent HbA_{1c} on a continuous scale and BC (investigational product, sex, region, age at baseline, smoking status at baseline, diabetes duration at baseline, cardiovascular risk-group inclusion criteria, insulin-naïve at baseline and renal function [eGFR] at baseline). BC, baseline characteristics; CI, confidence interval

Plan

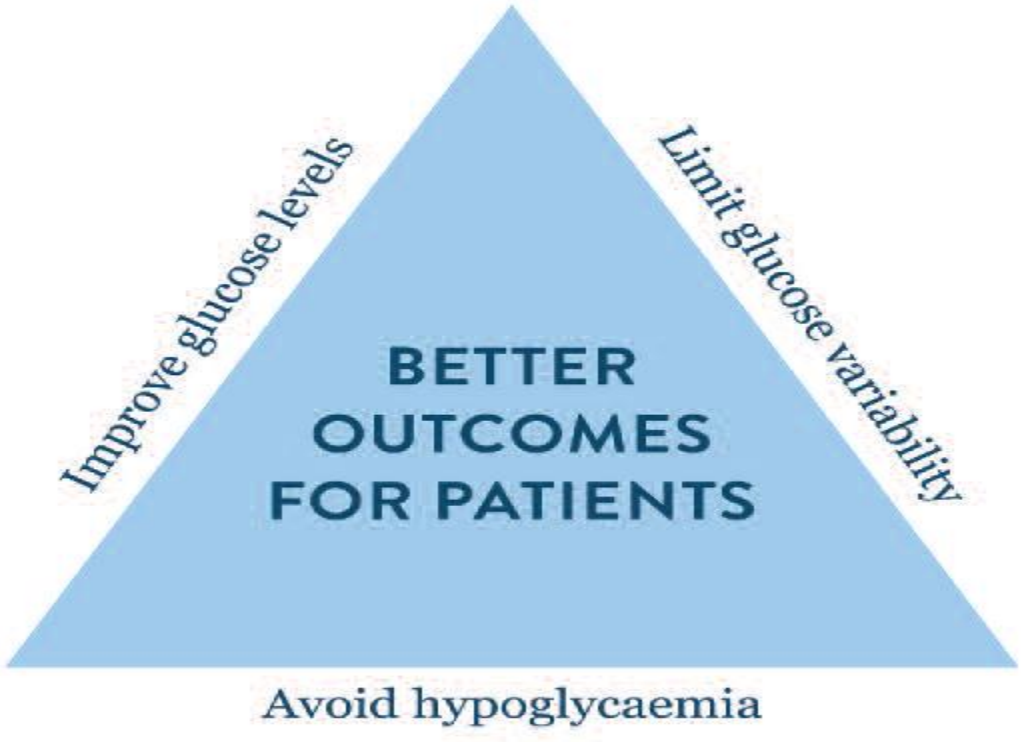
- Limites de l’HbA1c
- Définition de la variabilité glycémique et moyens de mesure
- Variabilité glycémique et complications du diabète
- Variabilité glycémique et hypoglycémie
- Conclusion

- La prise en charge de la glycémie est généralement basée sur la mesure de l'HbA1c, ce qui nous dit peu de choses sur la variabilité de la glycémie.

- La variabilité du glucose peut être un important déterminant du risque d'hypoglycémie et de complications du diabète à long terme.

- Le triangle du soin du diabète rassemble le besoin d'optimisation du niveau de glucose dans le sang, évitant l'hypoglycémie et la réduction de la variabilité glycémique est un concept utile dans la gestion du diabète.

The Triangle of Diabetes Care



GERRY RAYMAN Glycaemic control, glucose variability and the Triangle of Diabetes Care *Br J Diabetes* 2016;16(Suppl1):S3-S6

Seuils et cibles Thérapeutiques