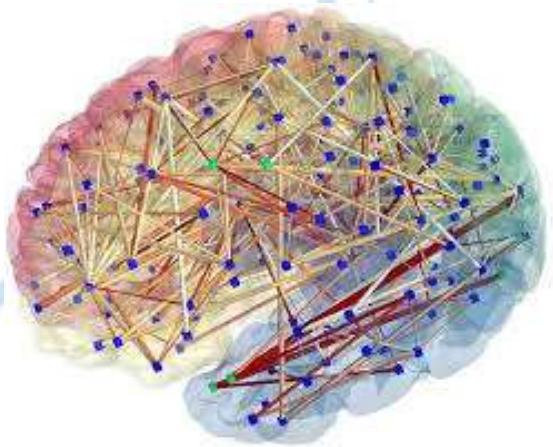
Algoritmi di terapia: il paziente non insulinotrattato la lezione dei grandi trial

Terapia per il diabete



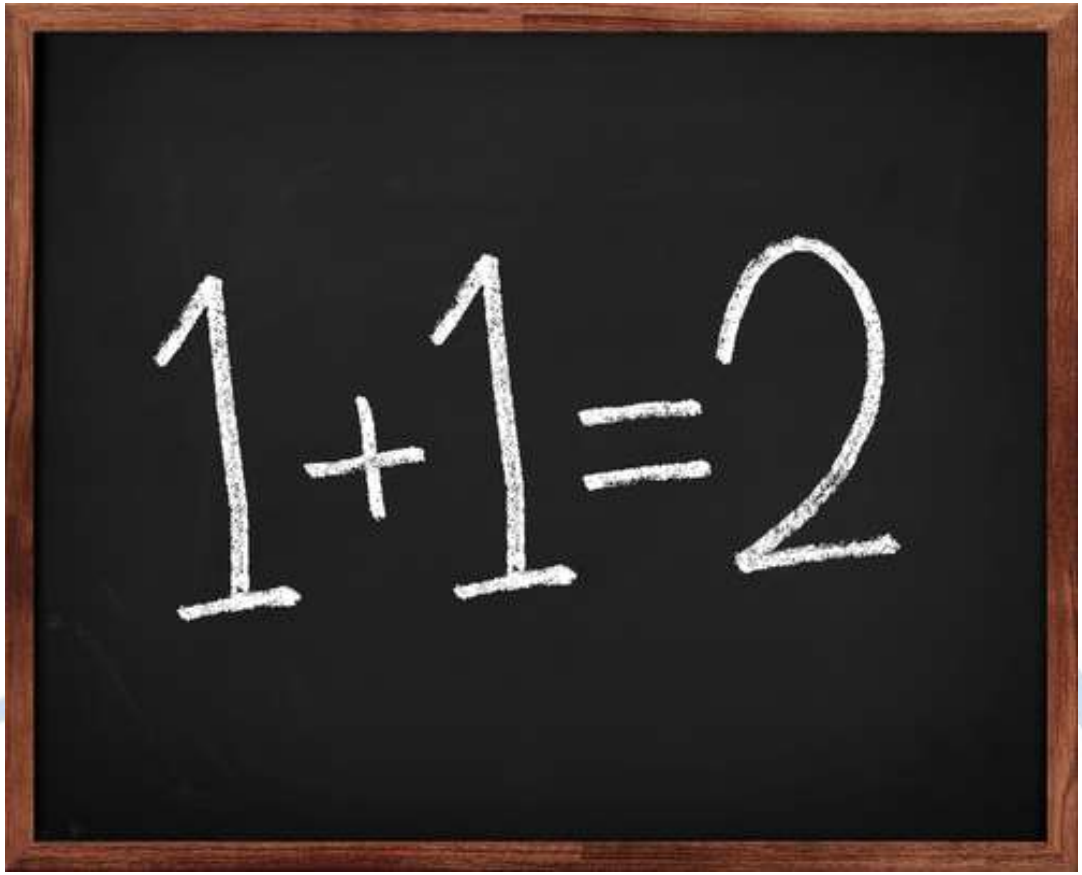
COMPLESSITA’



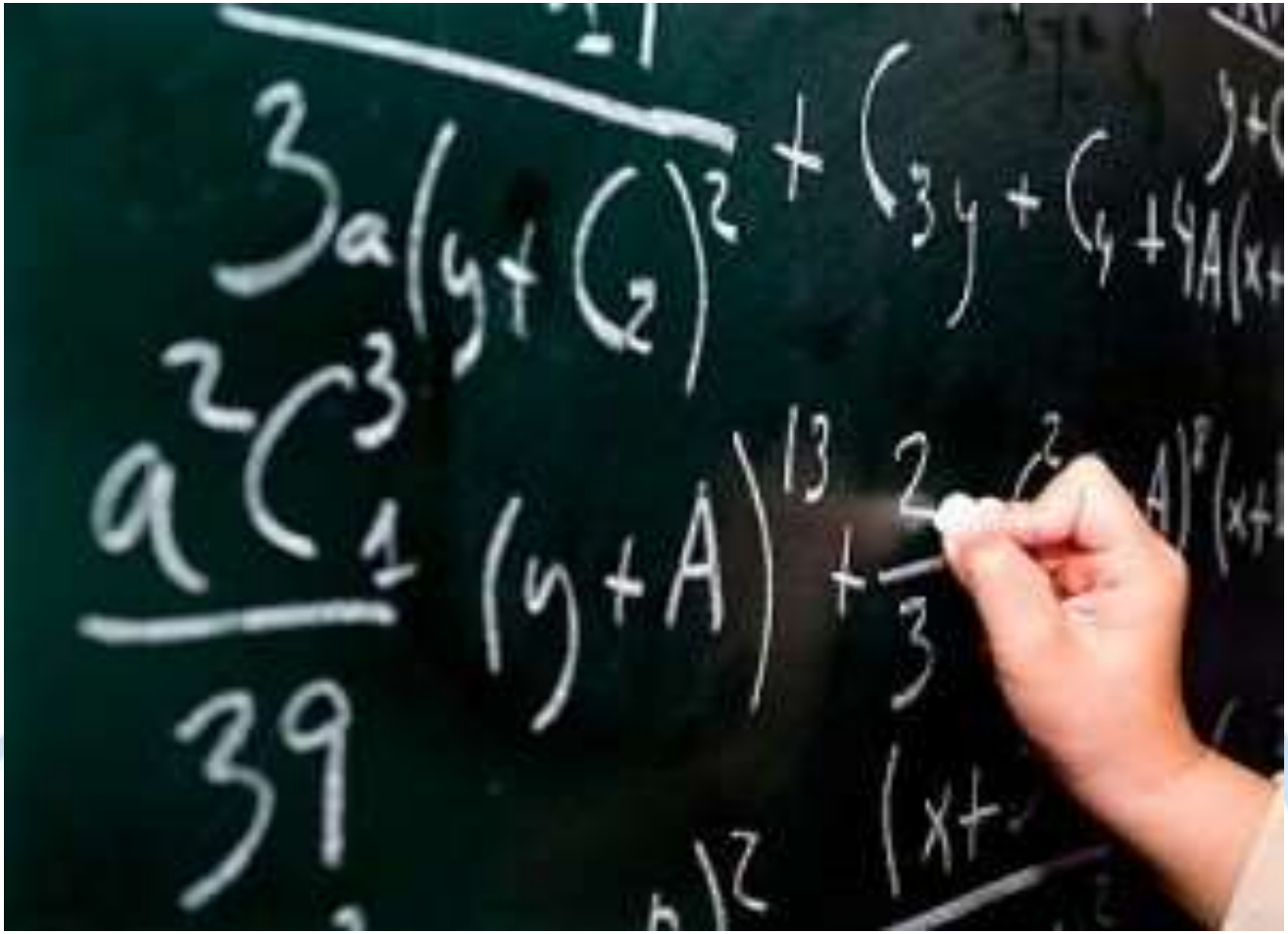
PERSONALIZZAZIONE



Nella cura della polmonite



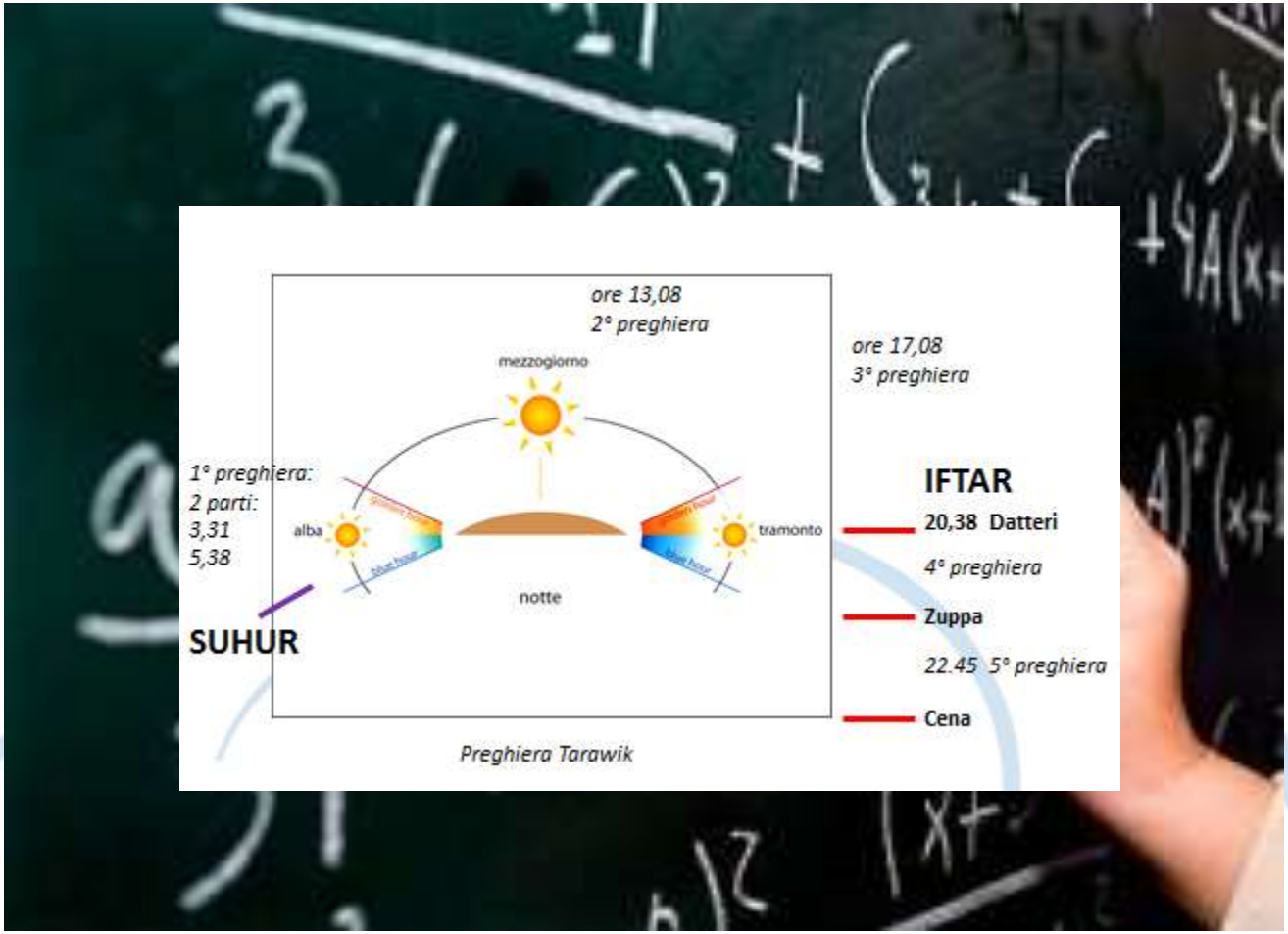
Nella cura del diabete



In collaborazione con

Scuola Permanente di Formazione Continua AMD

Nella cura del diabete durante il mese Ramadan



Obiettivi dell'Algoritmo AIFA

Presentare le diverse opzioni terapeutiche nell'ambito di quanto rimborsato dal SSN

Algoritmo come strumento di appropriatezza prescrittiva

Sebbene lasci la decisione finale al giudizio clinico secondo quanto indicato da:

- Principali Linee guida
- Società Scientifiche

Note:

- ✓I farmaci non rimborsati o in corso di negoziazione non sono inseriti nell'algoritmo.
- ✓Alcune classi di farmaci sebbene inserite nell'algoritmo prevedono limiti alla rimborsabilità in alcune circostanze.
- ✓La decisione terapeutica va condivisa con il paziente per migliorare l'aderenza alla terapia.

Criteri per la costruzione dell'Algoritmo AIFA AMD SID



- ✓ Linee guida internazionali
- ✓ (ADA, EASD, IDF)
- ✓ Linee guida nazionali (standard di cura SID-AMD)
- ✓ Solo pubblicazioni su riviste
- ✓ "peer review"
- ✓ RCTs su riviste "peer review" e con I.F. significativo
- ✓ Durata di almeno 24-26 settimane
- ✓ Metanalisi se citate nelle GLs

Standard italiani per la cura del diabete mellito 2014

Figura 2. Flow-chart per la terapia del diabete mellito di tipo 2.

Iniziare con solo intervento su stile di vita (se non grave scompenso metabolico [ref. 1])

↓

Aggiungere gradualmente metformina, fino alla dose di almeno 2 g/die

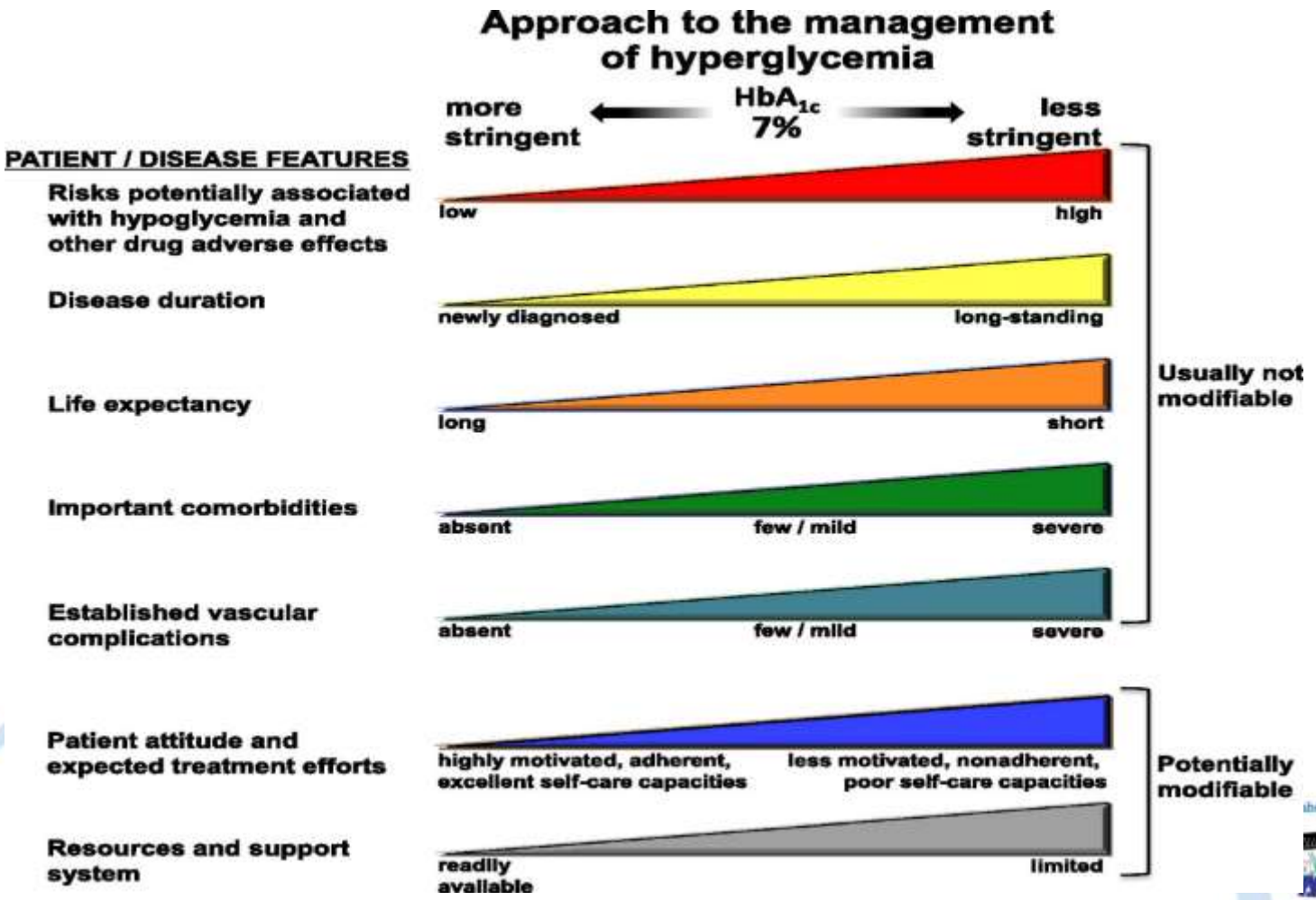
↓

Add on a metformina	Ipoglic.	Peso	Effetti indesid.	CVD	Fattori rischio CV	Scomp. cardiaco	Effetti GI	Costo
Gliptina	1A	1B	Rari	1A	1B	2B (2)	1A	Elevato
A.R. GLP-1	1A	1A	Non indicato in IRC	3B	1A	2B	1C	Elevato
Sulfonilurea o repaglinide	1D	1D	Non indicato in IRC (3)	3C (2)	1B	1B	1A	Basso
Pioglitazione	1A	1D	Fratture	1A	1A	1E	1A	Medio
Acarbosio	1A	1D	Rari	2B	2B	3C	1C	Basso
Gliflozina	1A	1A	Infezioni GU	3C	2B	2B	1A	???
Insulina basale	1D	1A	Rari	1B	1A	1B	1A	Medio

Colori:

- effetto o parametro negativo o sconsigliato
- effetto o parametro parzialmente negativo o sconsigliato
- effetto o parametro positivo o probabilmente positivo
- il farmaco non ha effetti significativi sul parametro o viene dato un giudizio neutro

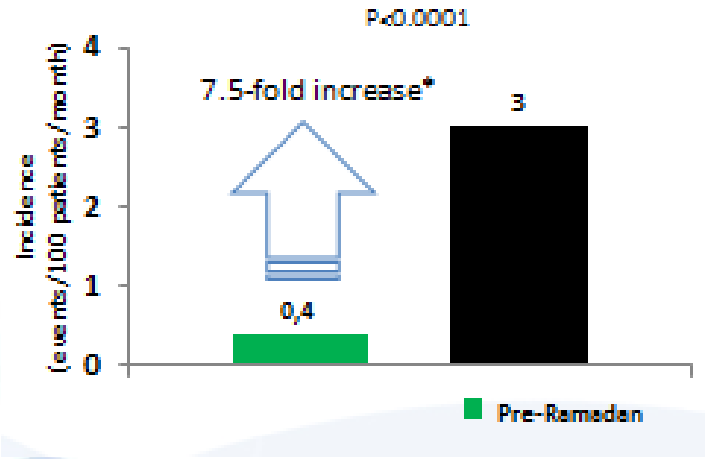
Management of Hyperglycemia in T2DM: A Patient-Centered Approach – ADA/EASD Position Statement 2015 Update



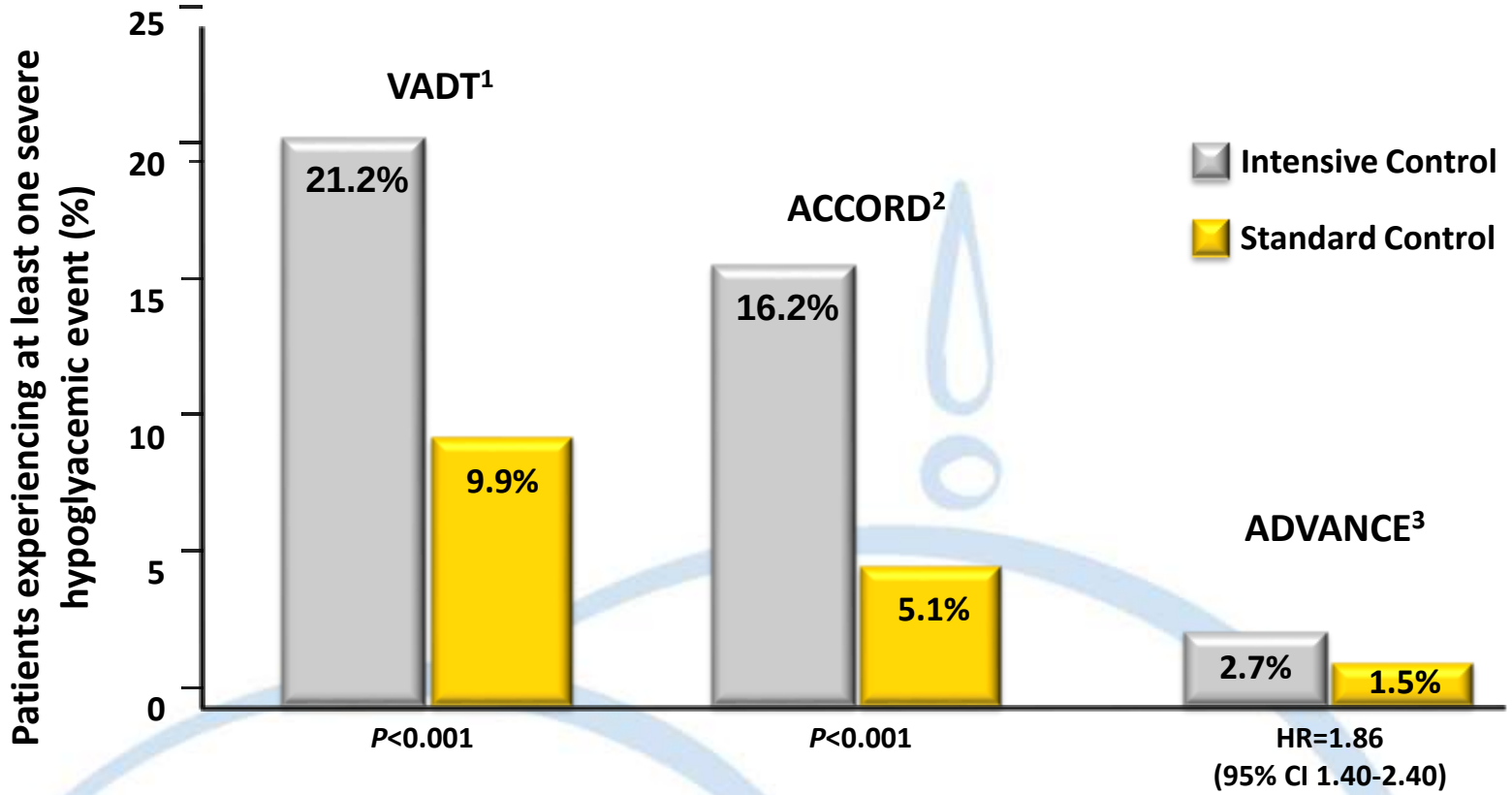
Inzucchi S E et al - Diabetes Care 2015; 38:140-149

Fattori di rischio per ipoglicemia

- Uso di insulina e SU
- Età avanzata
- Lunga durata di malattia
- Abitudini alimentari irregolari
- Attività fisica inappropriata
- Bassi valori di HbA1c
- **Periodi di digiuno rituale (es Ramadan)**
- Precedenti episodi ipoglicemici
- Scarsa consapevolezza dei sintomi
- Consumo eccessivo di alcool)



Gli eventi ipoglicemici severi negli studi ACCORD, ADVANCE and VADT (braccio a controllo glicemico stretto) sono associati a elevata mortalità



1. VADT Investigators. *N Engl J Med* 2009;360:129-139. 2. Bonds DE *et al. BMJ* 2010;340:b4909. 3. ADVANCE Study Group. *N Engl J Med* 2008;358(24):2560–72.

Impatto delle ipoglicemie sui costi indiretti ed intangibili nei soggetti con diabete di tipo 2

	Ipoglicemie lievi/moderate	Ipoglicemie severe
Riduzione produttività	Il 10% dei soggetti lascia il lavoro in anticipo e il 9% sta a casa il giorno successivo	Il 32% dei soggetti lascia il lavoro in anticipo e il 26% sta a casa il giorno successivo
Riduzione qualità della vita	Il 30% dei soggetti presenta maggiori paure di ipoglicemie dopo un evento	L'84% dei soggetti presenta maggiori paure di ipoglicemie dopo un evento

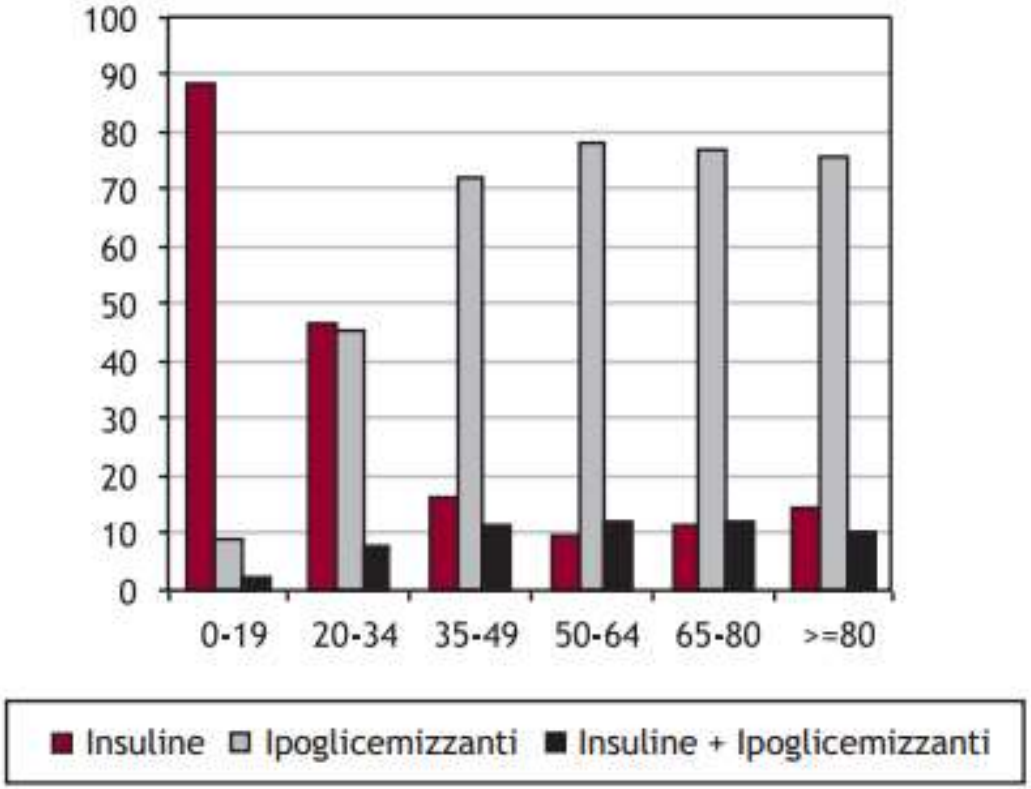
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Leiter LA et al. Canadian Journal of Diabetes 2005


Italia
~ 3,000,000 soggetti con diabete
~ 16,000 ricoveri l'anno per ipoglicemia severa
Spesa complessiva di ~ € 48,000,000 l'anno
Hypos Study



- Grafico 2.7 -
Trattamento con farmaci antidiabetici per classi di età negli stranieri



Osservatorio ARNO 2011
Diabete Il profilo assistenziale della popolazione con diabete

In collaborazione con
AMD
Permanente di
ne Continua AMD

Open DIAlogue
Diabete e relazioni transculturali

GISED

Gruppo di studio ADI-AMD-SID "Nutrizione e diabete"

COMMENTARY

Recommendations for Management of Diabetes During Ramadan

Update 2010

Monira Al-Arouj, MD[1]
Samir Assaad-Khalil, MD, PHD[2]
John Buse, MD, PHD[3]
Ibtihal Fahdil, MD, PHD[4]
Mohamed Fahmy, MD, PHD[5]
Sherif Hafez, MD, FACP[6]
Mohamed Hassanein, FRCP[7]
Mahmoud Ashraf Ibrahim,
David Kendall, MD[9]
Suhail Kishawi, MD[10]
Abdulrazzaq Al-Madani, M
Abdullah Ben Nakhi, MD[1]
Khaled Tayeb, MD[12]
Abraham Thomas, MD[13]

Table 3—*Recommended changes to treatment regimen in patients with type 2 diabetes who fast during Ramadan*

Before Ramadan	During Ramadan
Patients on diet and exercise control	Consider modifying the time and intensity of physical activity; ensure adequate fluid intake
Patients on oral hypoglycemic agents	Ensure adequate fluid intake
Biguanide, metformin 500 mg, three times daily	Metformin, 1,000 mg at the sunset meal, 500 mg at the predawn meal
TZDs, AGIs, or incretin-based therapies	No change needed
Sulfonylureas once a day	Dose should be given before the sunset meal; adjust the dose based on the glycemic control and the risk of hypoglycemia
Sulfonylureas twice a day	Use half the usual morning dose at the predawn meal and the usual dose at sunset meal
Patients on insulin	Ensure adequate fluid intake
Premixed or intermediate-acting insulin twice daily	Consider changing to long-acting or intermediate insulin in the evening and short or rapid-acting insulin with meals; take usual dose at sunset meal and half usual dose at predawn meal

Pazienti con diabete tipo 2 trattato con ipoglicemizzanti orali

RISCHIO BASSO

- Diabete Mellito in buon compenso con stile di vita, metformina, acarbosio, glitazonici e /o incretine senza complicanze

Insulinosensibilizzanti (metformina e pioglitazone)

Non inducono ipoglicemia. Il dosaggio non deve essere modificato.

Si suggerisce di distribuire il dosaggio della metformina per i 2/3 all' Iftar (sera) ed la dose rimanente più piccola al Sohor (mattino)

ramaḍān, رمضان

ORIGINAL ARTICLE

A double-blind, randomized, multicenter study evaluating the effects of pioglitazone in fasting Muslim subjects during Ramadan

Senthil Vasan[1], Nihal Thomas[1], Bharani[2], Mohammed Ameen[3], Sunil Abraham[4], Victoria Job[5], Beulah John[1], Rajani Karol[6], M. L. Kavitha[7], Kurian Thomas[8], M. S. Seshadri[1]

[1]Department of Endocrinology, [2]Mother's Care Centre, [3]Bhilal Hospital, [4]Low Cost Effective Care Unit, [5]Department of Clinical Biochemistry, [6]Department of Dietetics, [7]Department of Bio statistics, [8]Department of Clinical Epidemiology, Christian Medical College, Vellore, India

Il pioglitazone è sicuro ed efficace nel ridurre la glicemia nei pazienti diabetici durante il digiuno del mese Ramadan in associazione con altri ipoglicemizzanti orali.
Non influenza il numero delle ipoglicemie.
Il suo utilizzo è ha un significativo costo beneficio se associato ad altri ipoglicemizzanti orali

(OHAs) and the doses of other OHAs were titrated according to their glycemic status at each visit.

Pazienti con diabete tipo 2 trattato con ipoglicemizzanti orali

RISCHIO BASSO

- Diabete Mellito in buon compenso con stile di vita, metformina, acarbosio, glitazonici e /o incretine senza complicanze

- **La scelta del farmaco antidiabetico dovrebbe essere individualizzata alla luce del rischio di ipoglicemia**
- **Nuovi trattamenti farmacologici con ridotto potenziale ipoglicemico possono aver specifici vantaggi in questi pazienti**

Al-Arouj M et al. Diabetes Care 2010;33:1895–902

رمضان, *ramaḍān*

A meta-analysis of the hypoglycaemic risk in randomized controlled trials with sulphonylureas in patients with type 2 diabetes

The incidence of **severe hypoglycaemia** in patients treated with sulphonylureas was **1.2 [1.0–1.6]%.**

The overall risk of severe hypoglycaemia was increased more than threefold with sulphonylureas than with comparators.

The proportion of patients with at least one hypoglycaemia while on sulphonylureas was 17.4 [14.5–20.8]%.
The overall risk of any hypoglycaemia with sulphonylureas versus comparators was 3.69 [3.47–3.93] ($p < 0.001$).

Monami, Mannucci et al, Diabetes, Obesity and Metabolism
Volume 16, Issue 9, pages 833–840, September 2014

VECTOR

Vildagliptin **E**xperience **C**ompared **T**o GISED
gliclazide **O**bserved during **R**amadan

Confronto tra vildagliptin e gliclazide in associazione con metformina, in pazienti musulmani con diabete mellito di tipo 2 a digiuno durante il Ramadan

Obiettivo primario: determinare l'incidenza di **eventi ipoglicemici** nei pazienti musulmani che digiunano durante il Ramadan e trattati con

- **Vildagliptin + Metformina**

  o

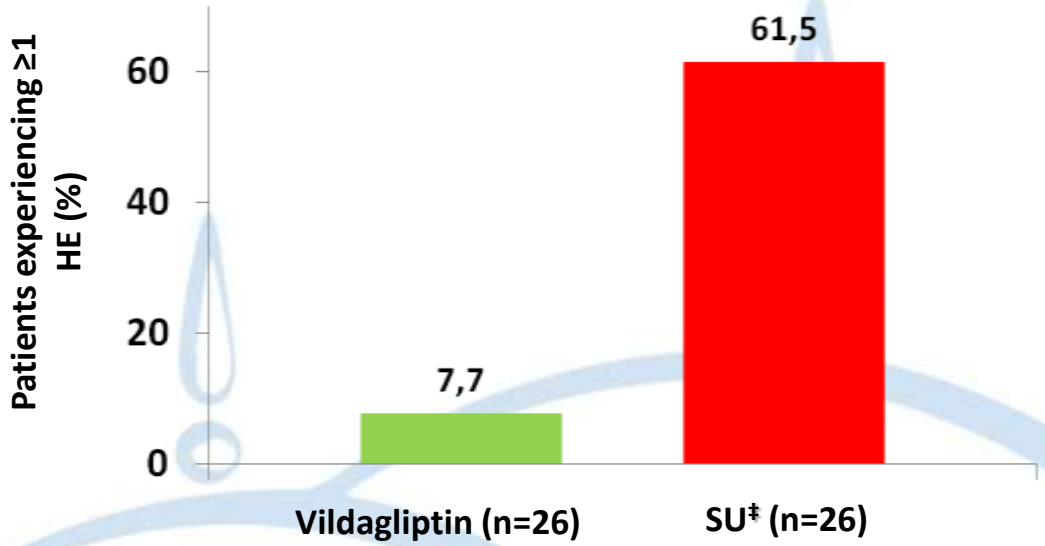
- **Glicazide + Metformina**

- **Obiettivi secondari:** impatto delle due terapie su
  - HbA_{1c}
  - Aderenza al trattamento

Hassanein M et al. Curr Med Res Opin 2011;27(7):1367-74

Episodi ipoglicemici in pazienti diabetici in Ramadan trattati con vildagliptin vs glicazide in add on a metformina

UK observational study in patients with T2DM fasting during Ramadan (baseline HbA1c >8.5%) treated with metformin in addition to the DPP4 inhibitor, vildagliptin or gliclazide



Between groups difference –53.8% (95% CI: –74.9 to –26.3); P<0.001

***Total number of HEs was 24 with gliclazide and 2 with vildagliptin, one severe HE with gliclazide & none with vildagliptin**

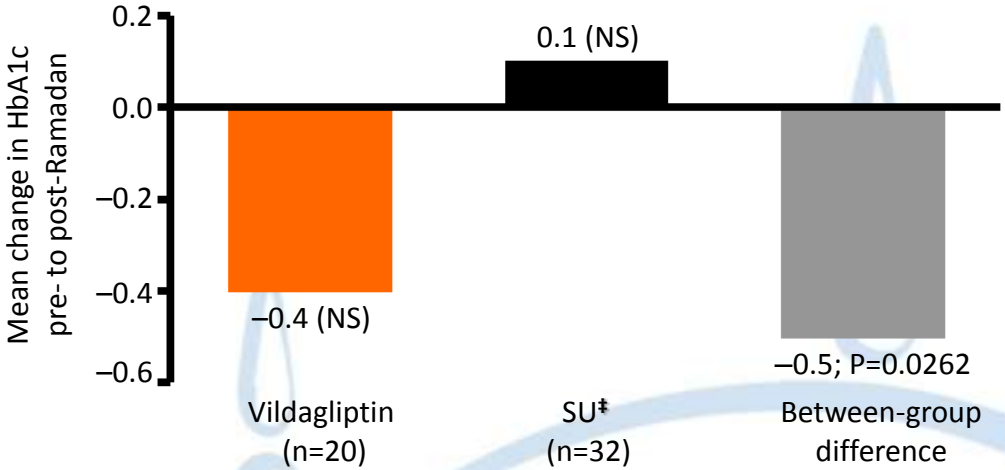
‡ SU = Sulfonylurea (gliclazide)

HE = hypoglycaemic event; T2DM = type 2 diabetes mellitus; CI = confidence interval; SU = sulphonylurea; DPP4 = dipeptidyl peptidase 4
Hypoglycaemic events defined as plasma glucose measurement <3.5 mmol/L with or without symptoms .*Hypoglycaemia was the only adverse event monitored

Devendra D et al. Int J Clin Pract 2009;63:1446–50

VECTOR study:
variazioni HbA1c in pazienti diabetici in Ramadan trattati con vildagliptin vs glicazide in add on a metformina

HbA1c reduction for vildagliptin vs. gliclazide pre- to post Ramadan; between-group difference –0.5% (P=0.0262)



- **Mean number of missed doses was lower with vildagliptin** (mean between-group difference –7.4; P=0.0204)
- Body weight remained unchanged in both groups

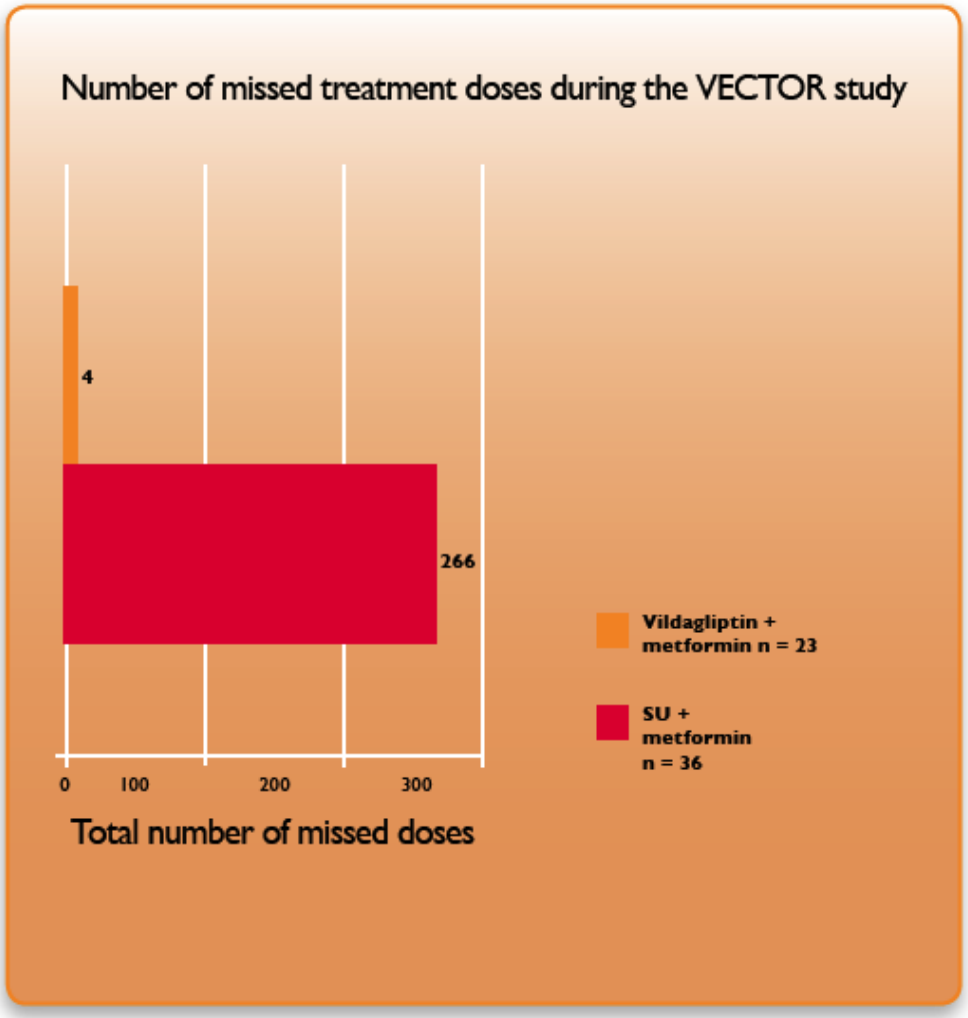
Prospective observational study of up to 16 weeks duration in 72 fasting Muslim patients with T2DM observed in UK clinical practice, receiving vildagliptin or SU as an add-on treatment to metformin; per protocol set with pre- and post Ramadan HbA1c assessments, HbA1c; safety set, AEs and SAEs.

‡ SU = Sulfonylurea (gliclazide); VECTOR= Vildagliptin Experience Compared To gliclazide Observed during Ramadan; AE = adverse event; SAE = severe adverse event; NS = non-significant difference pre- to post Ramadan

Hassanein M et al. Curr Med Res Opin 2011;27:1367–74

In collaborazione con AMD Scuola Permanente di Formazione Continua AMD

VECTOR Study:
Aderenza alla terapia nei due gruppi



- **The mean number of missed doses was markedly lower with Vildagliptin than with gliclazide** (0.2 vs 7.6; between-group difference −7.4 doses; p = 0.0204)

- On average, patients had 7 fold more missed doses with gliclazide than Vildagliptin

- Only 1 patient in the Vildagliptin group missed at least one dose, compared with 10 patients in the SU group

- There were a total of 4 missed doses in the Vildagliptin arm versus 266 in the SU arm

Hassanein M et al. Curr Med Res Opin 2011;27(7):1367-74

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The VIRTUE study

VildagliptIn expeRience compared wiTh sulfonylUreas obsErved during Ramadan

A multinational non-interventional study to assess the effects of vildagliptin relative to sulphonylurea as dual therapy with metformin (or as monotherapy*) in Muslim patients with type 2 diabetes fasting during Ramadan

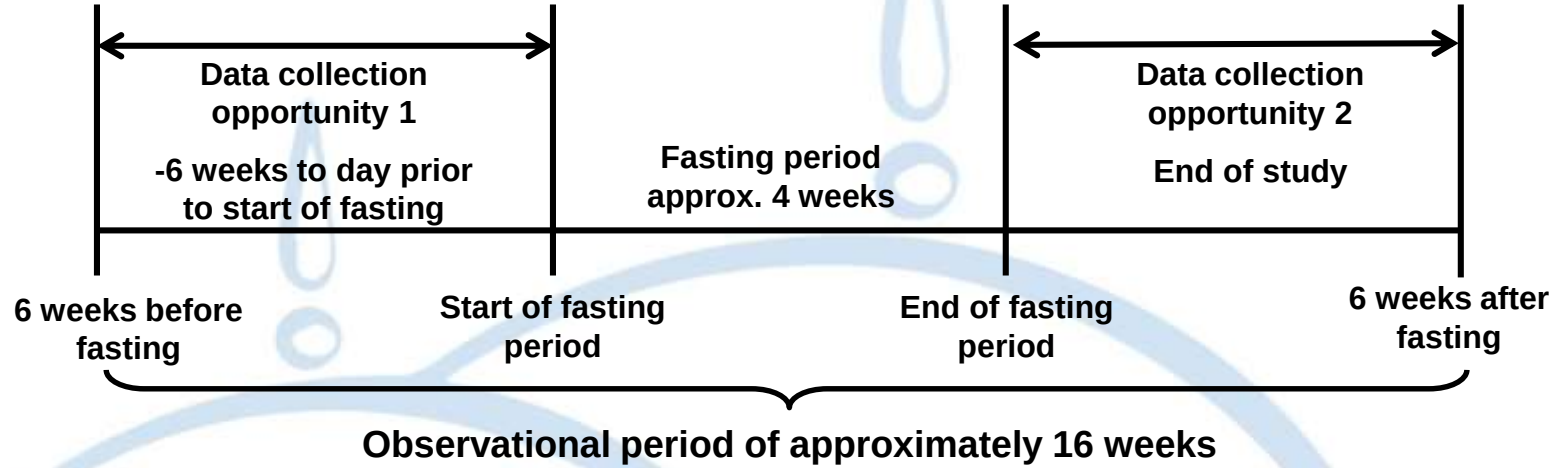
VIRTUE: study design

Two patient cohorts:

Patients on stable diabetes treatment (1:1)

vildagliptin plus metformin† or vildagliptin monotherapy*

SU plus metformin† or SU monotherapy*



†single pill combination allowed when available

*if applicable, as per local approved prescribing information

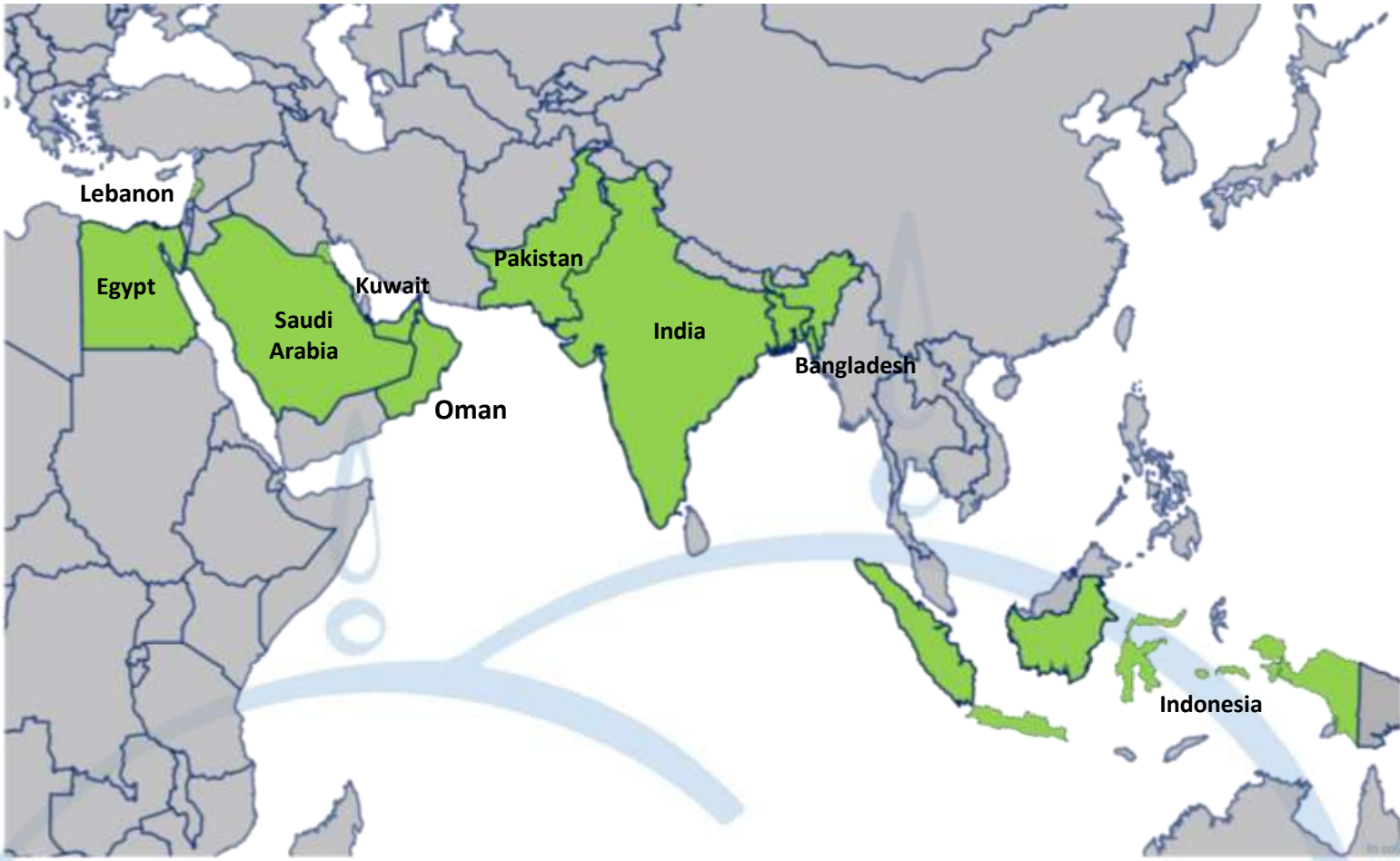
SU=sulphonylurea

Kadwa MY, et al. Diabetes Care Middle East Edition 2012;9(4)Suppl.:26 (Abstract 94-P);
Novartis, data on file 2013

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VIRTUE:

data from >1300 fasting T2DM patients pooled from 10 countries

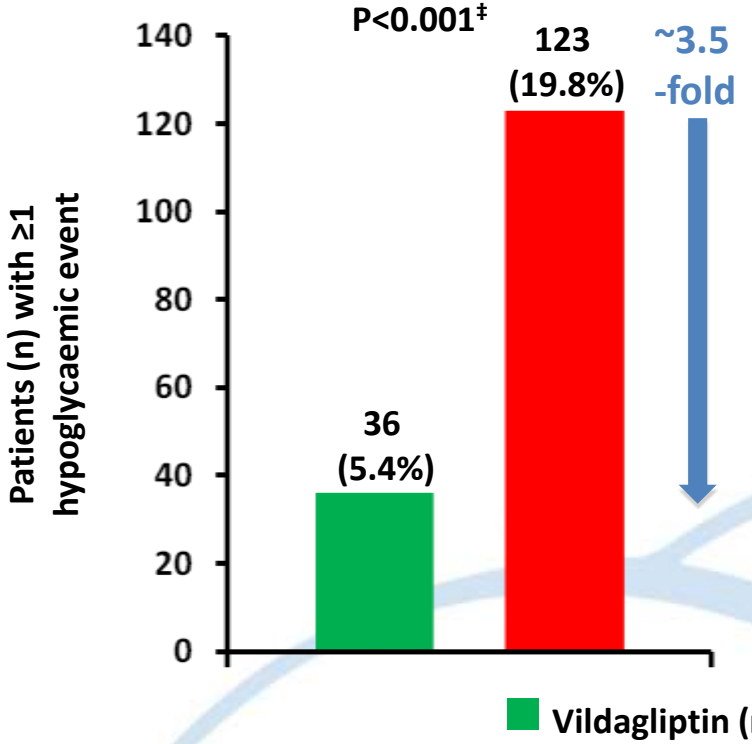


T2DM = Type 2 diabetes mellitus

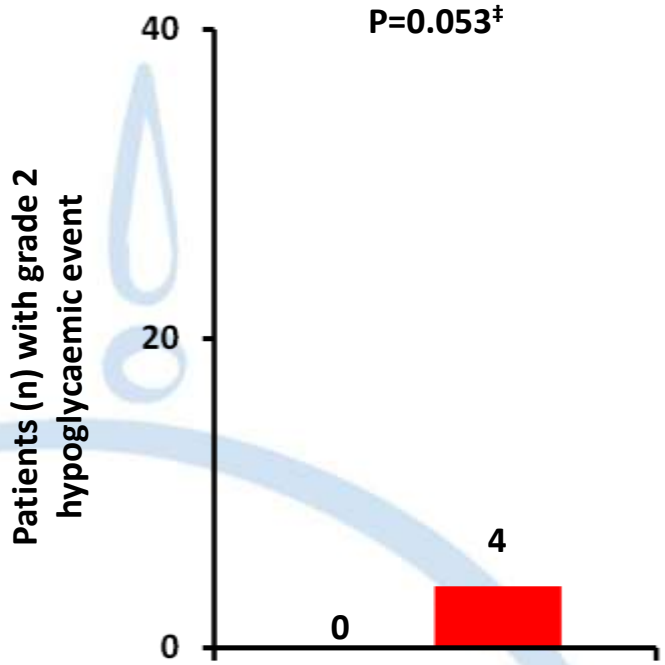
Kadwa MY, et al. Diabetes Care Middle East Edition 2012;9(4)Suppl.:26 (Abstract 94-P);
Novartis, data on file 2013

VIRTUE study: pazienti con ≥1 episodi ipoglicemici trattati con vildagliptin vs sulfoniluree in add a metformina

Patients with ≥1 hypoglycaemic event



Patients with grade 2 hypoglycaemic events



Vildagliptin (n=669†) SU (n=621†)

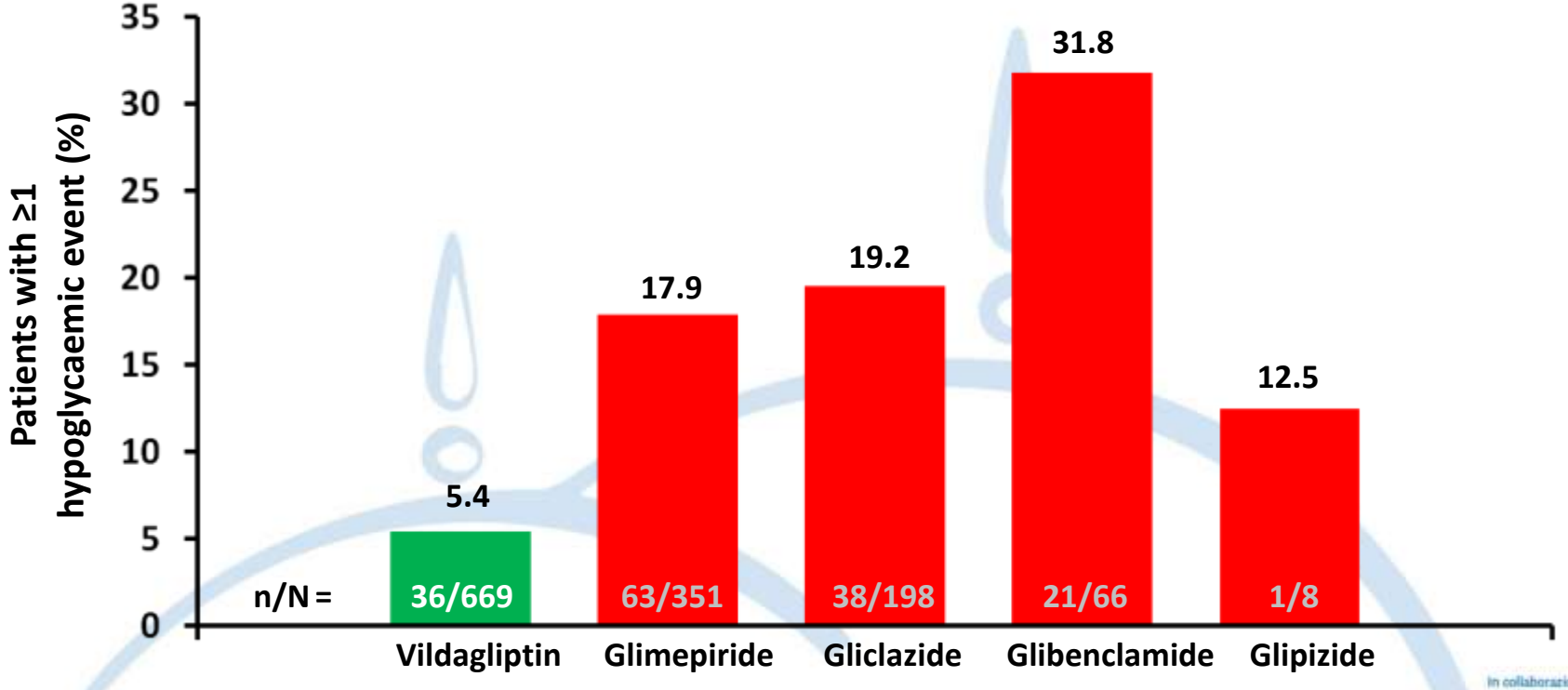
†Number of patients with a post baseline assessment of hypoglycaemic events. Hypoglycaemia defined as grade 1 (mild): reported symptoms by the patient and/or blood glucose measurement of <3.9 mmol/L (70 mg/dL) or grade 2 (severe): need for third party assistance ‡Fisher's exact test

SU = sulphonylurea

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Al-Arouj M. et al, International Journal of Clinical Practice 2013

VIRTUE:
i risultati migliori sulle ipoglicemie per vildagliptin sono indipendenti dalle sulfoniluree impiegate



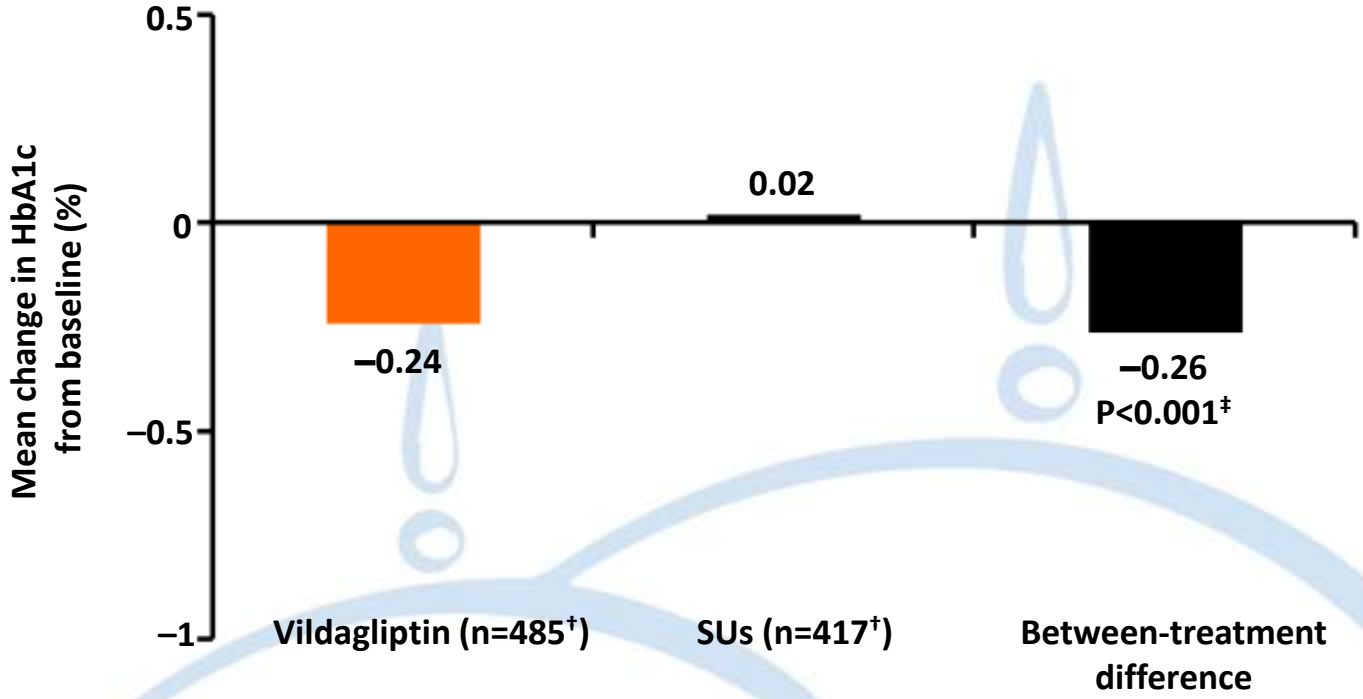
Post hoc descriptive analysis.
Safety set. SU = sulphonylurea

Al-Arouj M. et al, International Journal of Clinical Practice 2013

VIRTUE:

variazioni della HbA1c con vildagliptin vs Sus in add on a metformina

Mean change in HbA1c (%) pre- to post-Ramadan



†The within and between treatment differences were based only on patients with HbA1c levels assessed at both baseline and end of study. ‡Two-sample t test

SU = sulphonylurea; HbA1c = haemoglobin A1c

Al-Arouj M. et al, International Journal of Clinical Practice 2013

A double-blind, randomized trial, including frequent patient–physician contacts and Ramadan-focused advice, assessing vildagliptin and gliclazide in patients with type 2 diabetes fasting during Ramadan: the STEADFAST study

This article was published in the following Dove Press journal:
Vascular Health and Risk Management
28 May 2014

Conclusion: In line with the results from previous observational studies, vildagliptin was shown

In questo studio di intervento il vildagliptin ha confermato di essere sicuro, efficace e ben tollerato nei pazienti con T2DM durante il digiuno del mese Ramadan, con una consistente riduzione dell'incidenza di ipoglicemia, migliore controllo metabolico e ponderale.

In contrasto, la glicazide, in questo studio di intervento ,ha dimostrato una minore incidenza di ipoglicemia rispetto a precedenti studi. Si ipotizza che ciò sia il risultato di un continuo contatto telefonico con gli operatori sanitari in pazienti molto ben controllati. Situazione questa lontana da ciò che accade nella vita reale.

original article

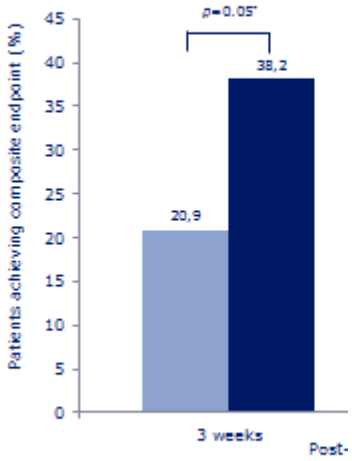
Diabetes, Obesity and Metabolism 2014.
© 2013 John Wiley & Sons Ltd

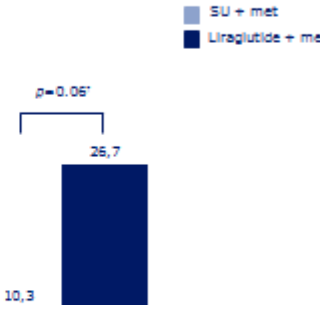
A randomized controlled trial comparing the GLP-1 receptor agonist liraglutide to a sulphonylurea as add on to metformin in patients with established type 2 diabetes during Ramadan: the Treat 4 Ramadan Trial

E. M. Brady[1,†], M. J. Davies[1,2,3,†], L. J. Gray[1,3,4], M. A. Saeed[5], D. Smith[5], W. Hanif[5] & K. Khunti[1,2,3]

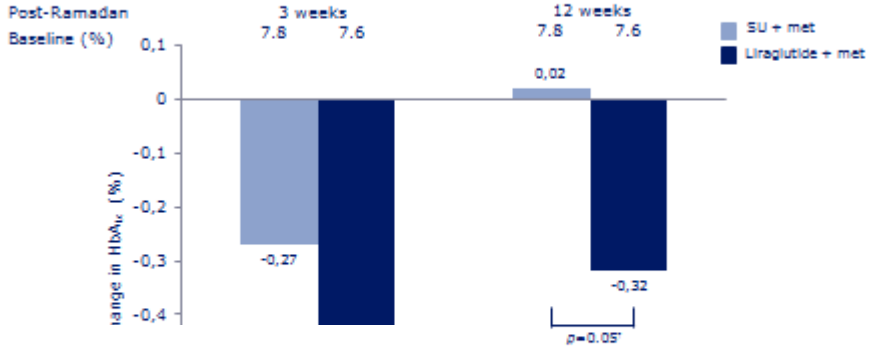
Aims: To compare a sulphonylurea with the glucagon like peptide-1 (GLP-1) receptor agonist liraglutide in combination with metformin in patients on mono/dual oral therapy with established type 2 diabetes fasting during Ramadan.

Primary endpoint: HbA_{1c} <7.0%, no weight gain and no severe hypoglycaemic events

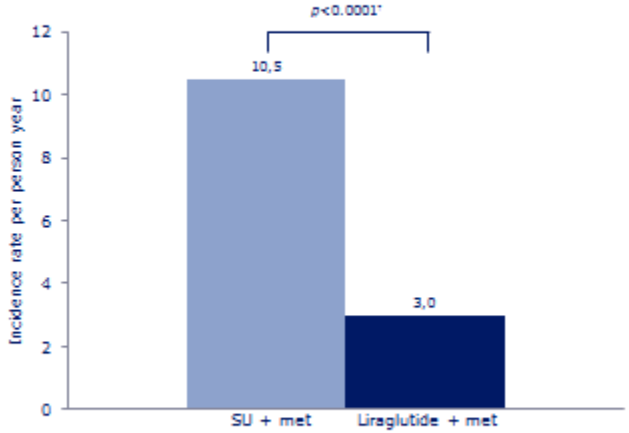




Additional secondary endpoint: Change in HbA_{1c}



Incidence of hypoglycaemia*



*Adjusted OR (95% CI) = 2.99 (1.00, 8.97); †Adjusted OR (95% CI) = 4.08
CI, confidence interval; HbA_{1c}, glycosylated haemoglobin; met, metformin; OI
Adapted from Brady EM et al. *Diabetes Obes Metab* 2014; doi: 10.1111/dom.1

*Defined as patients experiencing one or more blood glucose readings ≤3.9 mmol/l, recorded by blood-glucose self-monitoring diaries
†IRR (95% CI) = 0.29 (0.19, 0.41)
CI, confidence ratio; IRR, incidence rate ratio; met, metformin; SU, sulphonylurea
Adapted from Brady EM et al. *Diabetes Obes Metab* 2014; doi: 10.1111/dom.13249

Sulfaniluree

Da utilizzare con cautela per possibili ipoglicemie.

Tra le più sicure la glimepiride e glicazide, il cui dosaggio deve comunque essere ridotto.

Non si sono registrate ipoglicemie severe con l'utilizzo di repaglinide

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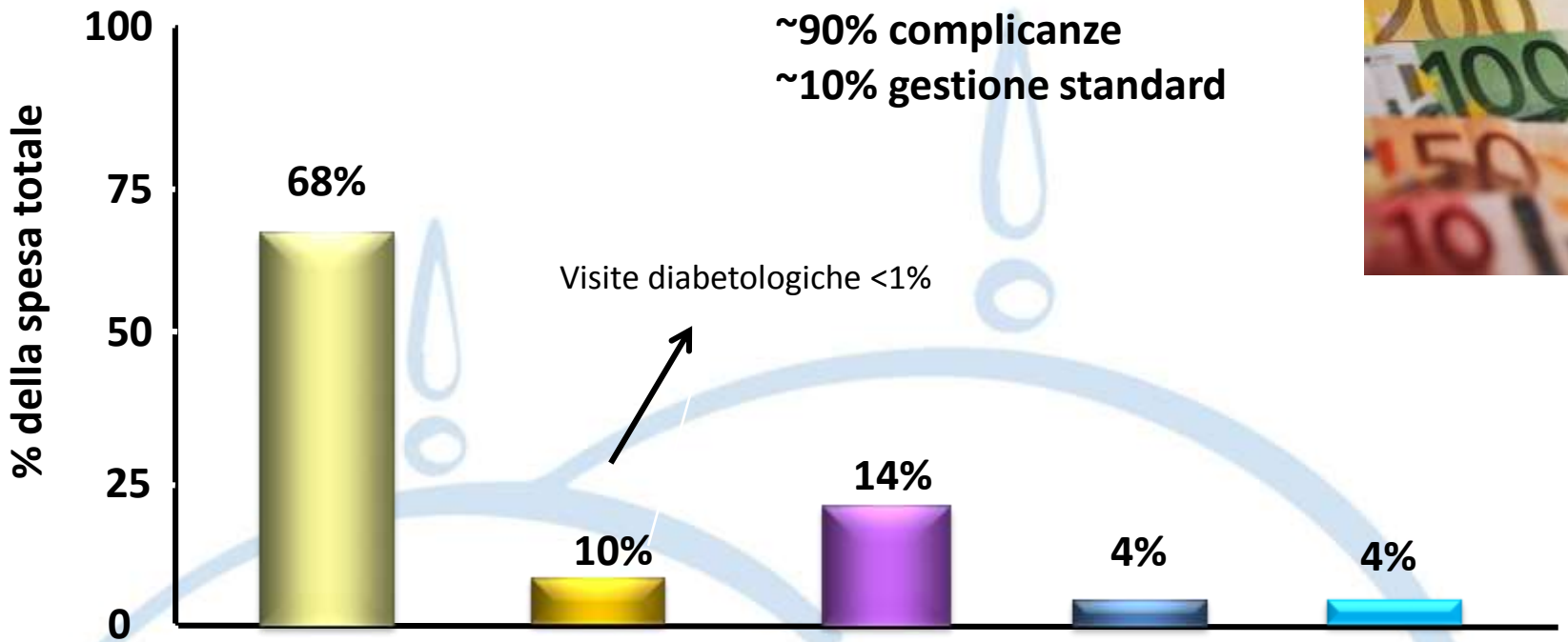
Indian J Endocrinol Metab. 2012 Jul-Aug; 16(4): 503–507.
doi: 10.4103/2230-8210.97994
PMCID: PMC3401744

Role of oral hypoglycemic agents in the management of type 2 diabetes mellitus during Ramadan

Mir Iftikhar Bashir, Md Farugue Pathan,[1] Syed Abbas Raza,[2] Jamal Ahmad,[3] A. K. Azad Khan,[4] Osama Ishtiaq,[5] Rakesh K. Sahay,[6] Aisha Sheikh,[7] and Abdul Hamid Zargar[8]

In molte parti del mondo **le sulfaniluree** sono farmaci di prima linea , **perché i meno costosi,** ma sicuramente, come dimostrato per glibenclamide e clorpromamide, associati significativamente ad ipoglicemie severe durante il digiuno del Ramadan.
Le sulfaniluree di seconda generazione, glicazide, glipizide e glimepiride si sono dimostrate più sicure.
Rispetto alla glibenclamide, **la repaglinide ha dimostrato un minor numero di ipoglicemie**

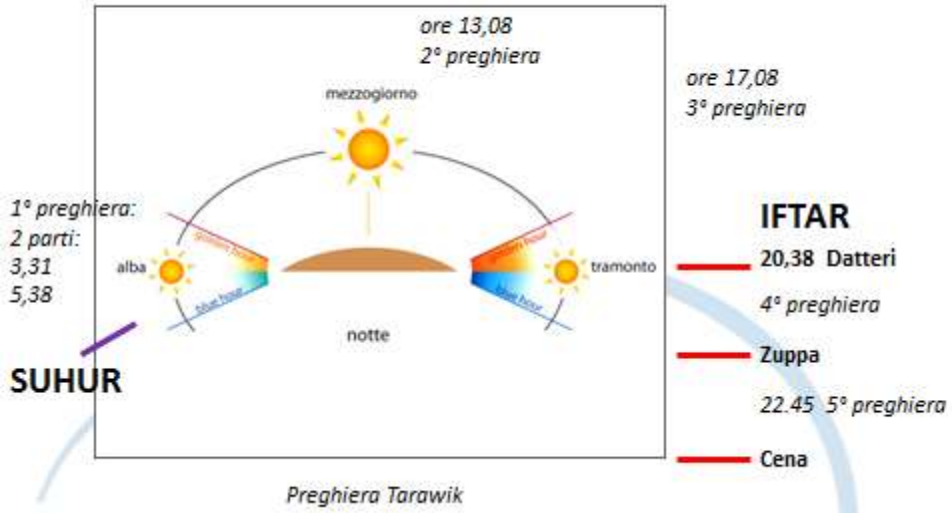
La spesa per i farmaci antidiabetici rappresenta solo il 4% del totale Italia 2012 (ARNO)



Int J Clin Pract. 2010 Jul;64(8):1090-4. doi: 10.1111/j.1742-1241.2009.02262.x. Epub 2010 Apr 30.

Maintenance of glycaemic control with the evening administration of a long acting sulphonylurea in male type 2 diabetic patients undertaking the Ramadan fast.

Zargar AH[1], Siraj M, Jawa AA, Hasan M, Mahtab H.



atients from Bangladesh, Pakistan and India,
ase (MR) 60 mg monotherapy, switched to
madan, and reverted to the morning schedule
in fasting plasma glucose (FPG) before and

creased by 0.01 mmol/l (0-0.2, p = 0.3) with
ased by 0.2 mmol/l (0.1-0.3, p = 0.01) after
reverting to morning medication 20 days later. There were 5 (3.7%) hypoglycaemic episodes before, 3 (2.2%) during and 2 (1.5%) after Ramadan.

CONCLUSION: Male type 2 diabetic patients undertaking the Ramadan fast can safely maintain

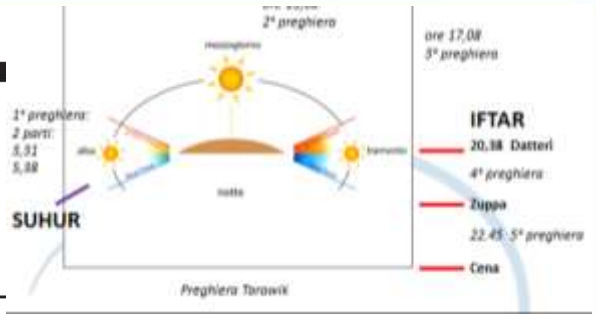
Lo spostamento della somministrazione della glicazide 60 mg a rilascio prolungato la sera prima dell'Iftar si è dimostrato sicuro rispetto alla comparsa di ipoglicemie

Reviews/Commentaries/ADA Statements
COMMENTARY

Recommendations for Management of Diabetes During Ramadan

Update 2010

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Le sulfaniluree che vengono somministrate 2 volte al giorno devono essere somministrate: Con dose piena la sera all'Iftar, e dose dimezzata al Sohor

Table 3—*Recommended changes to treatment regimen in patients with type 2 diabetes who fast during Ramadan*

Before Ramadan	During Ramadan
Patients on diet and exercise control	Consider modifying the time and intensity of physical activity; ensure adequate fluid intake
Patients on oral hypoglycemic agents	Ensure adequate fluid intake
Biguanide, metformin 500 mg, three times daily	Metformin, 1,000 mg at the sunset meal, 500 mg at the predawn meal
TZDs, AGIs, or incretin-based therapies	No change needed
Sulfonylureas once a day	Dose should be given before the sunset meal; adjust the dose based on the glycemic control and the risk of hypoglycemia
Sulfonylureas twice a day	Use half the usual morning dose at the predawn meal and the usual dose at sunset meal
Patients on insulin	Ensure adequate fluid intake
Premixed or intermediate-acting insulin twice daily	Consider changing to long-acting or intermediate insulin in the evening and short or rapid-acting insulin with meals; take usual dose at sunset meal and half usual dose at predawn meal

L'appropriatezza di intervento significa :

Un rigoroso e tempestivo utilizzo della terapia farmacologica

Una terapia personalizzata

Una fenotipizzazione delle persone in base ai reali bisogni

Una personalizzazione degli interventi di cura tenendo conto del pattern metabolico, ma anche dello stile di vita

La coscienza che la spesa diretta per la cura al diabete comprende farmaci, presidi e "prestazioni" per l'assistenza, (ambulatoriali e /o di ricovero) che comportano l'impiego di risorse professionali e tecnologiche, che complessivamente assorbono una consistente quota del finanziamento sanitario in ogni paese;

Percorsi di prescrizione strutturata.