2014 ICDM Breakfast Symposium. Oct 18, 2014 Grand Hilton, Seoul

HALLYM UNIVERSITY MEDICAL CENTER

Metabolic Karma

- Essential Solution in Type2 DM -

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Contents

KARMA ?

What goes around, comes around

"the intent and actions of an individual (with respect to metabolic control) influence the future health of that individual"

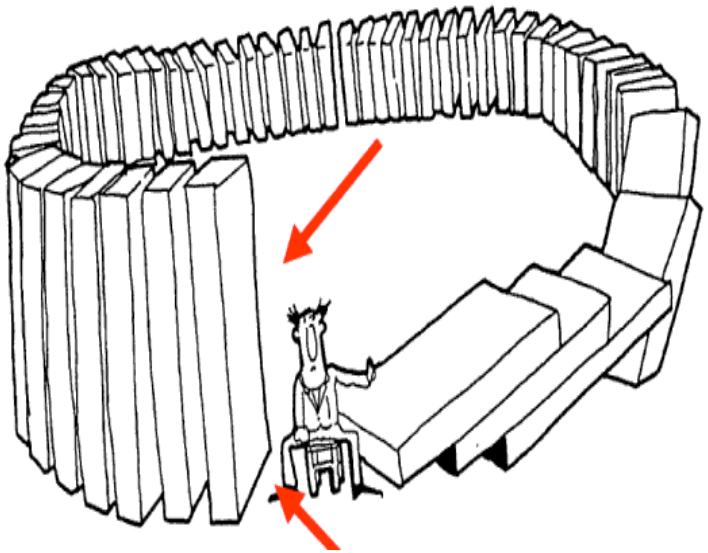
Karma , the Legacy Effect

Metabolic Karma = Legacy effect

Early glycemic control to minimize exposure to hyperglycemia will return as better quality of life in later in life.

In other words..

The longer diabetes patients are exposed to hyperglycemia, the chance of suffering from diabetic complication increases.

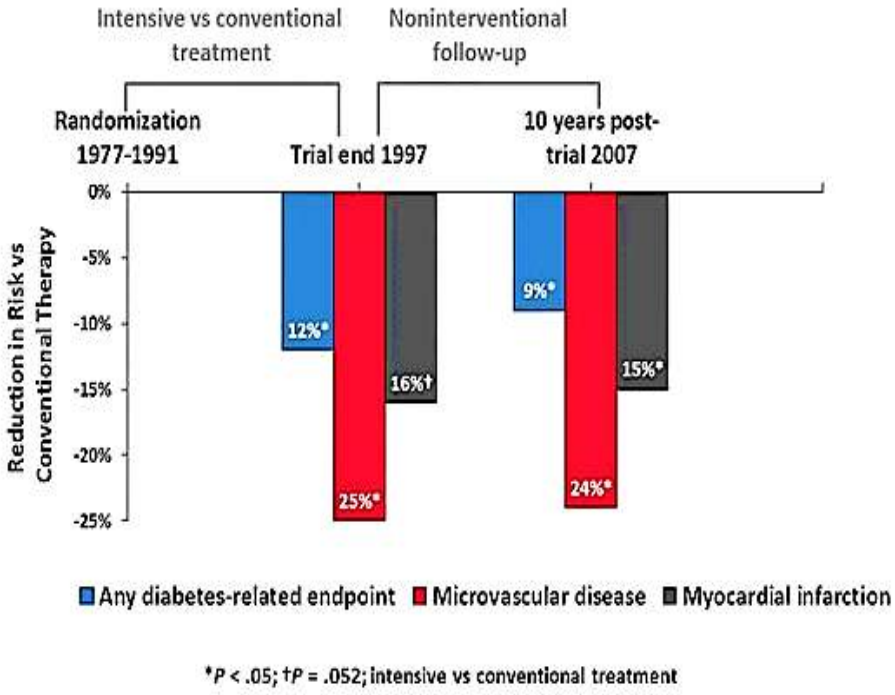


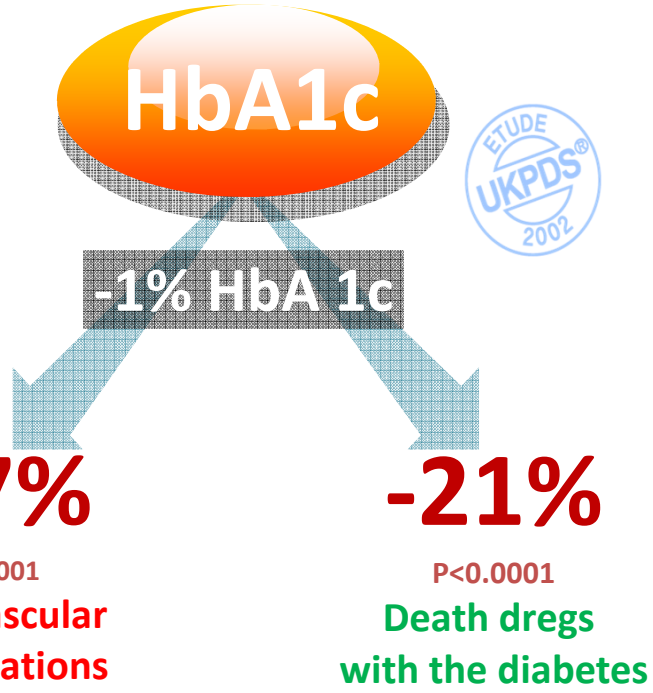
Merlin C. Thomas, Advances in Chronic Kidney Disease, Vol 21, No 3 (May), 2014: pp 311-317
Glycemic Exposure, Glycemic Control, and Metabolic Karma in Diabetic Complications

Metabolic Karma in diabetic complications

UKPDS

Intensive glycemic control returns as long lasting benefit



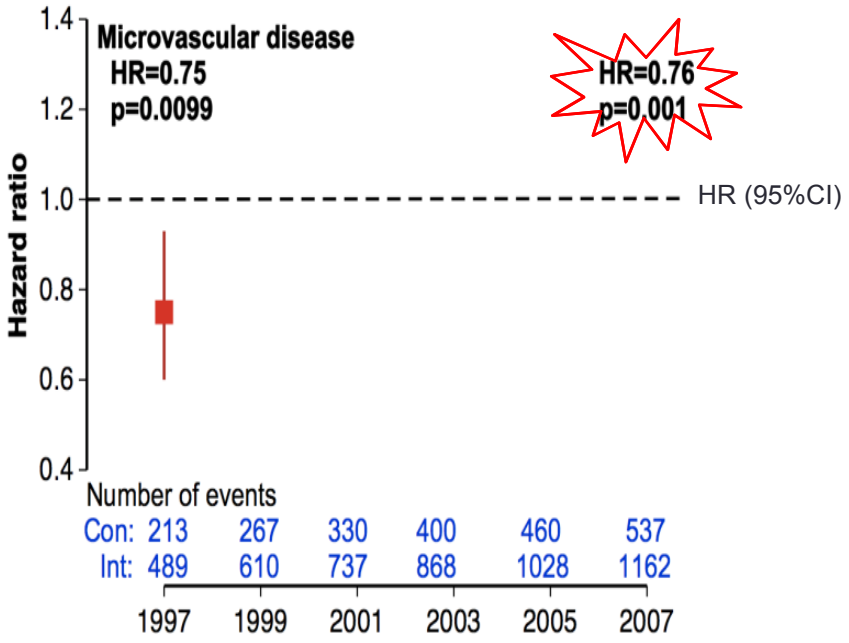


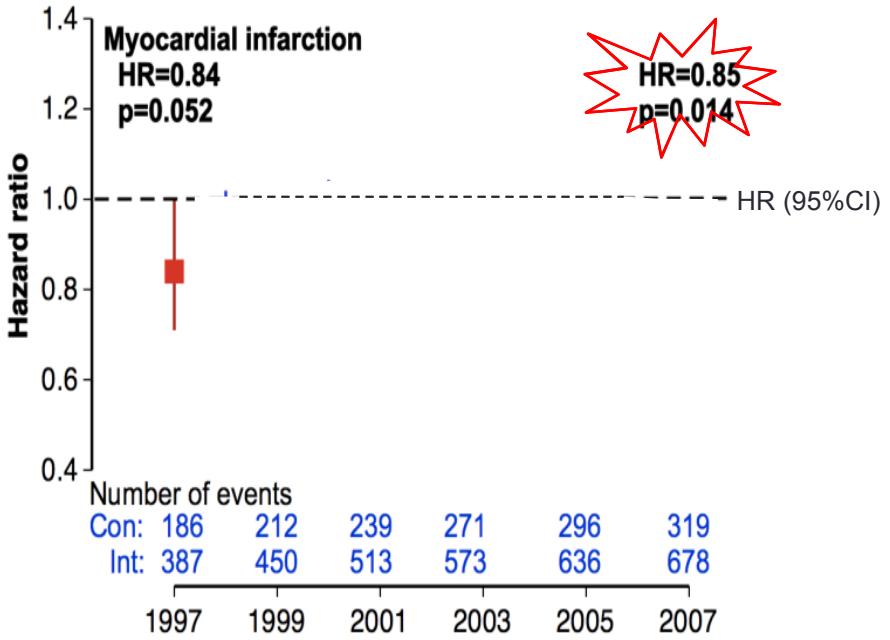
Holman RR, et al. N Engl J Med. 2008;359(15):1577–1589.
UKPDS Group. Lancet. 1998;352(9131):837–853.

Stratton IM et al. UKPDS 35. BMJ 2000; 321: 405 – 12.

Legacy effect of glycemic control never disappears?

Intensive (SU/Ins) vs. Conventional glucose control





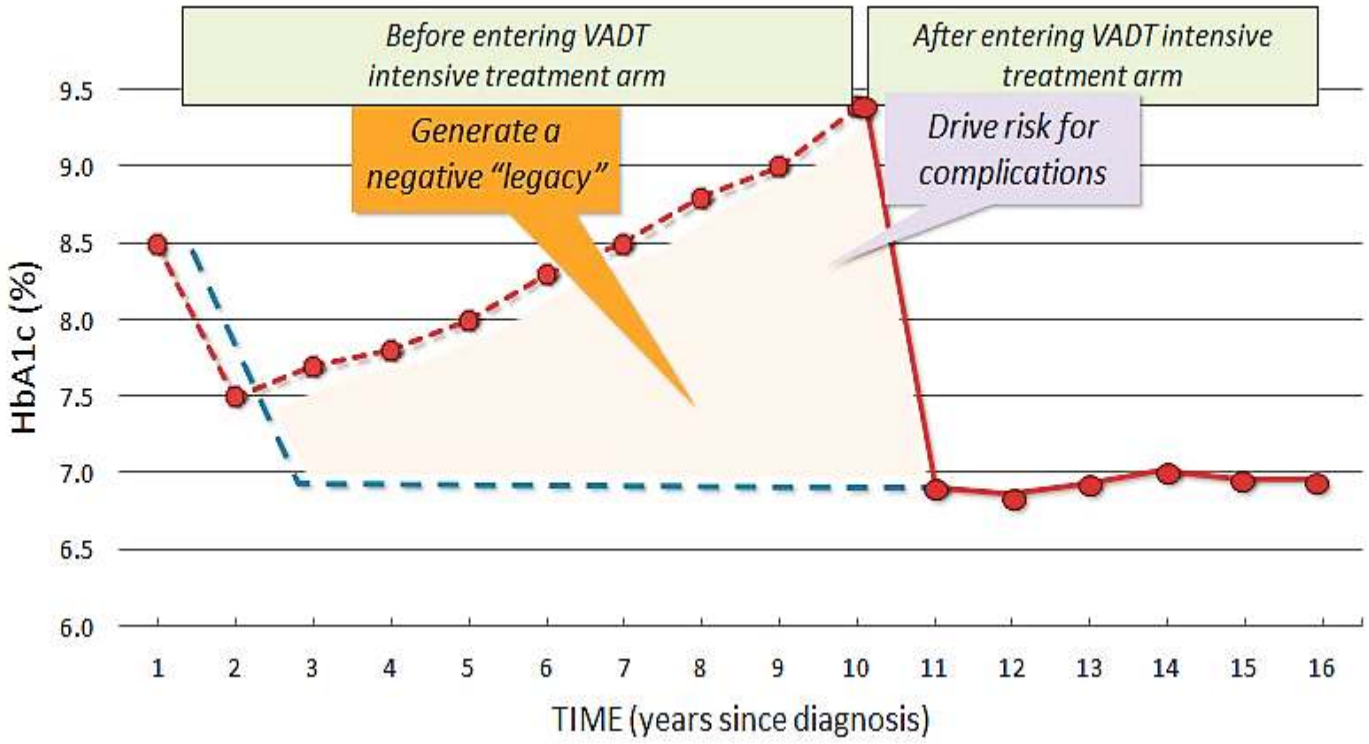
The more interesting findings were observed after UKPDS. 10 years of non-interventional F/U of post trial was conducted. During that period, the risk of all microvascular complications and MI was continuously low in the previous intensive treatment patient group.

Holman RR et al. **N Engl J Med**. 2008;359:1577–1589

*De Vries JH **Diabetologia**. 2011;54:705–706

Legacy effect of bad glycemic control never disappears?

Exposure to hyperglycemia returns as negative legacy effect (VADT).
Mean duration of diabetes in this study population was over 10 years and the prevalence of CVD was also high.



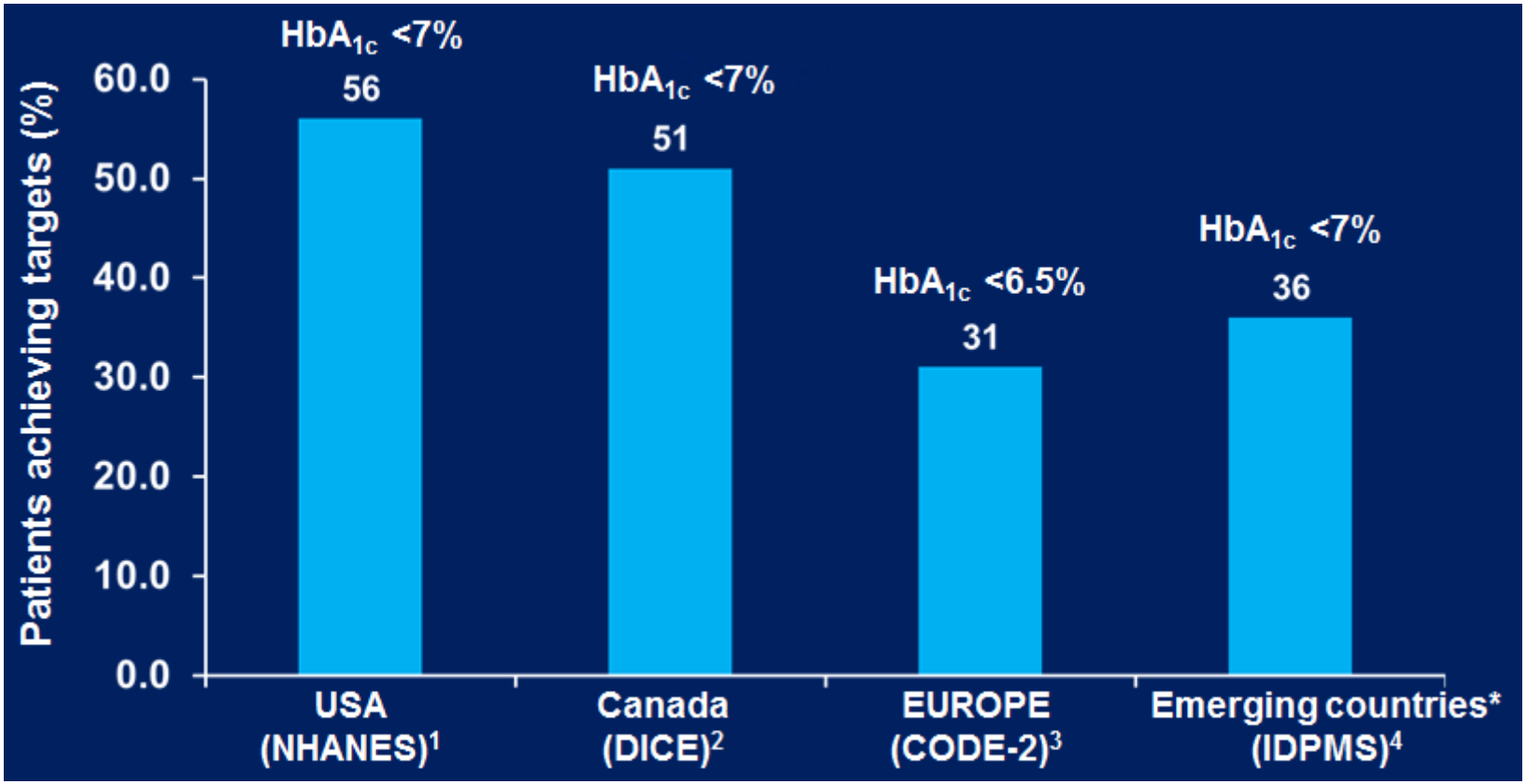
Therefore, the intensive glycemic control in the patients with high risk of CVD can not reduce the potential risk of complications

Del Prato S. *Diabetologia.* 2009; 52: 1219–1226.

Essential Solution in Type 2 DM

Amaryl® | Amaryl®-M | Amaryl®-MeX

Uncontrolled Hyperglycemia is a Global problem in clinical practice



***Asia, Eastern Europe, Latin America and the Middle East and Africa**
It is well known that the early intensive glycemic control is very important for the good legacy effect. However, the percentage of patient achieving target is very low.

1. Hoerger TJ et al., Diabetes Care 2008;31:81–86. 2. Harris SB et al., Diabetes Res Clin Pract 2005;70:90–97.
3. Liebl A et al., Diabetologia 2002;45:S23–8. 4. Chan JC et al., Diabetes Care 2009;32:227–233.

Reaching Target Goal is not EASY

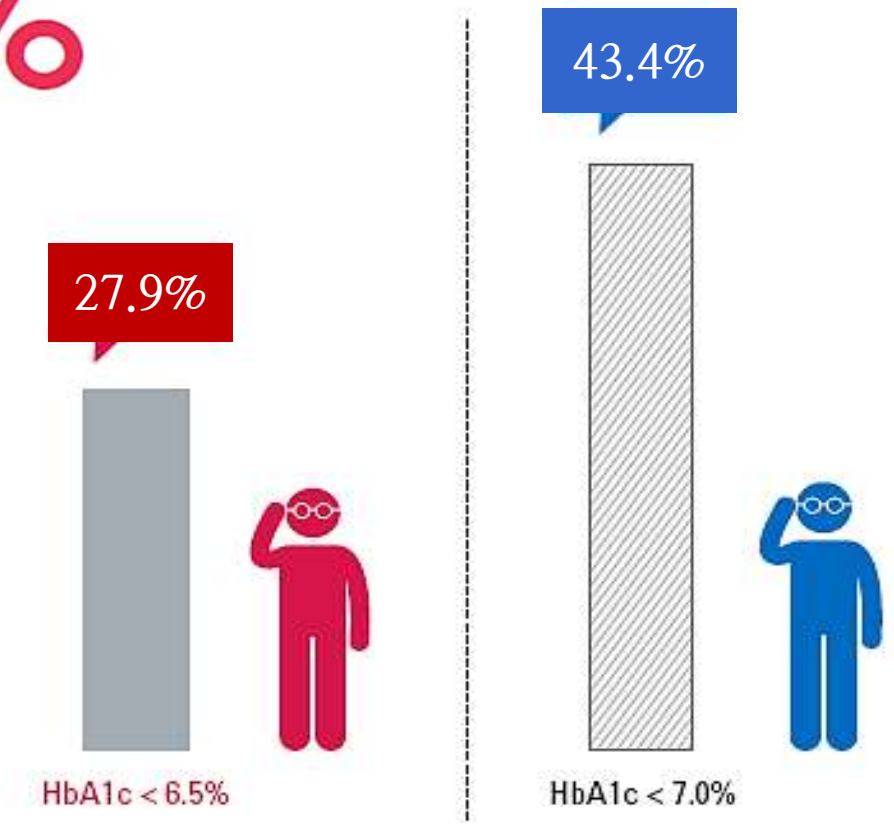
- Target Goal achievement rate in Korean Diabetes patients

<30%

Glycemic Control

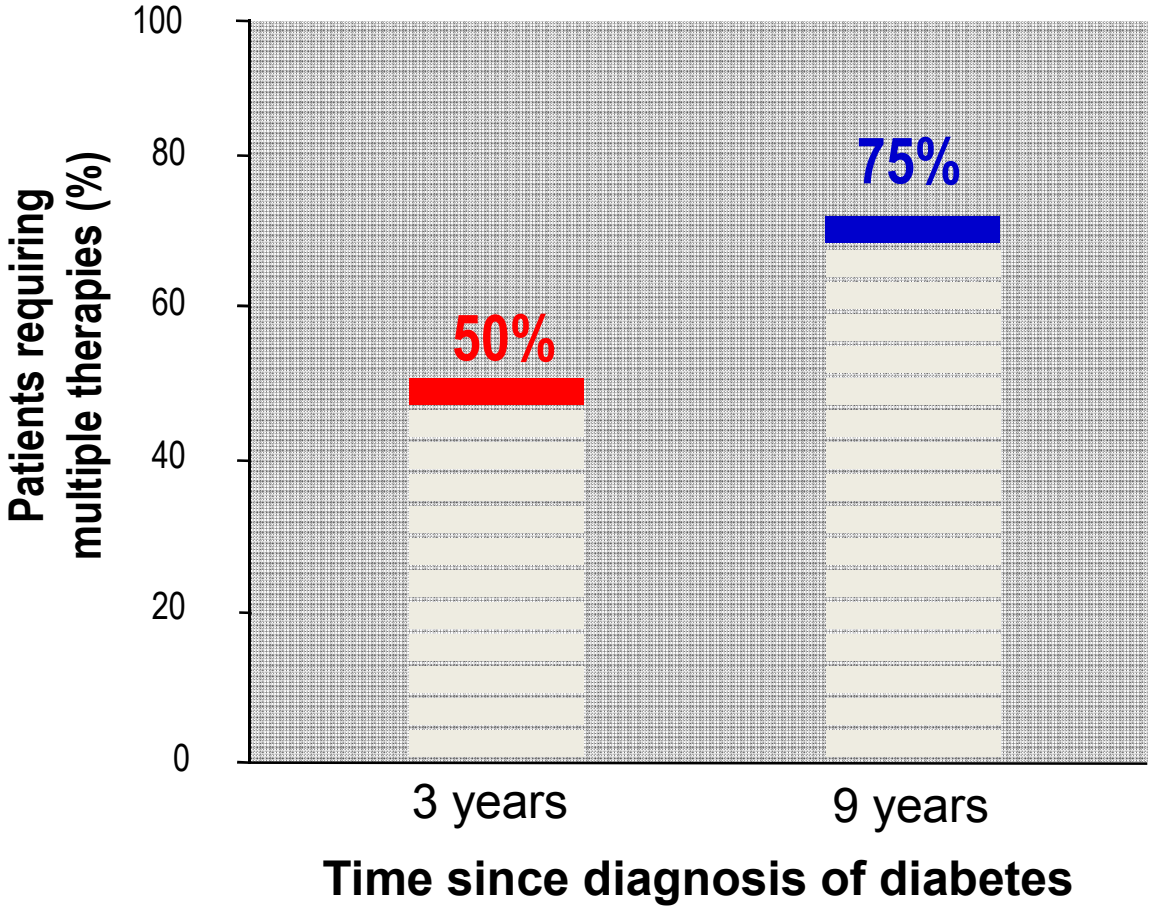
KDA HbA1c < 6.5%

ADA HbA1C < 7.0%



2012 Diabetes fact from KDA & National Health Insurance corporation

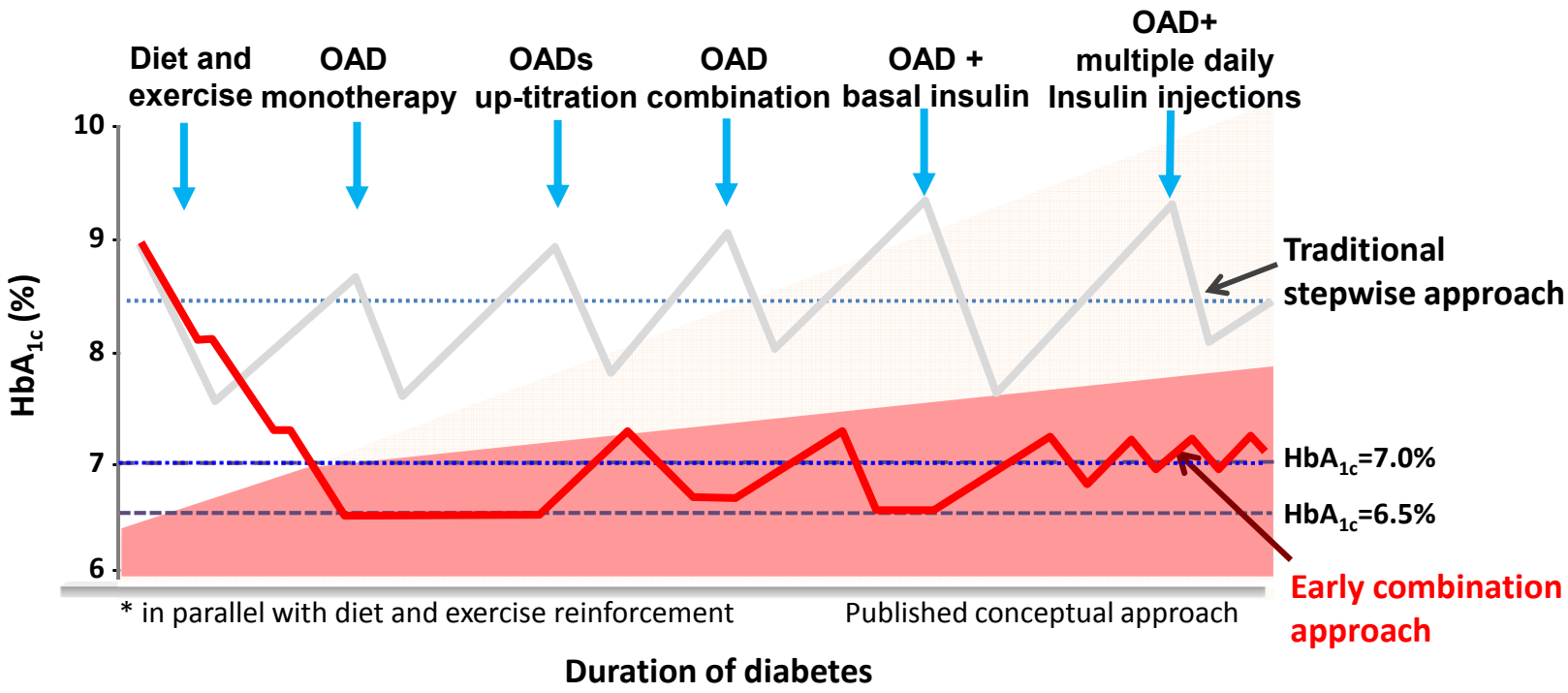
UKPDS:
Loss of glycemic control leads to the need for combination therapy



Turner RC, et al. UKPDS 49. JAMA 1999; 281:2005–2012.

Early combination therapy may achieve target goal

Move from REACTIVE Stepwise Treatment to a More PROACTIVE Approach



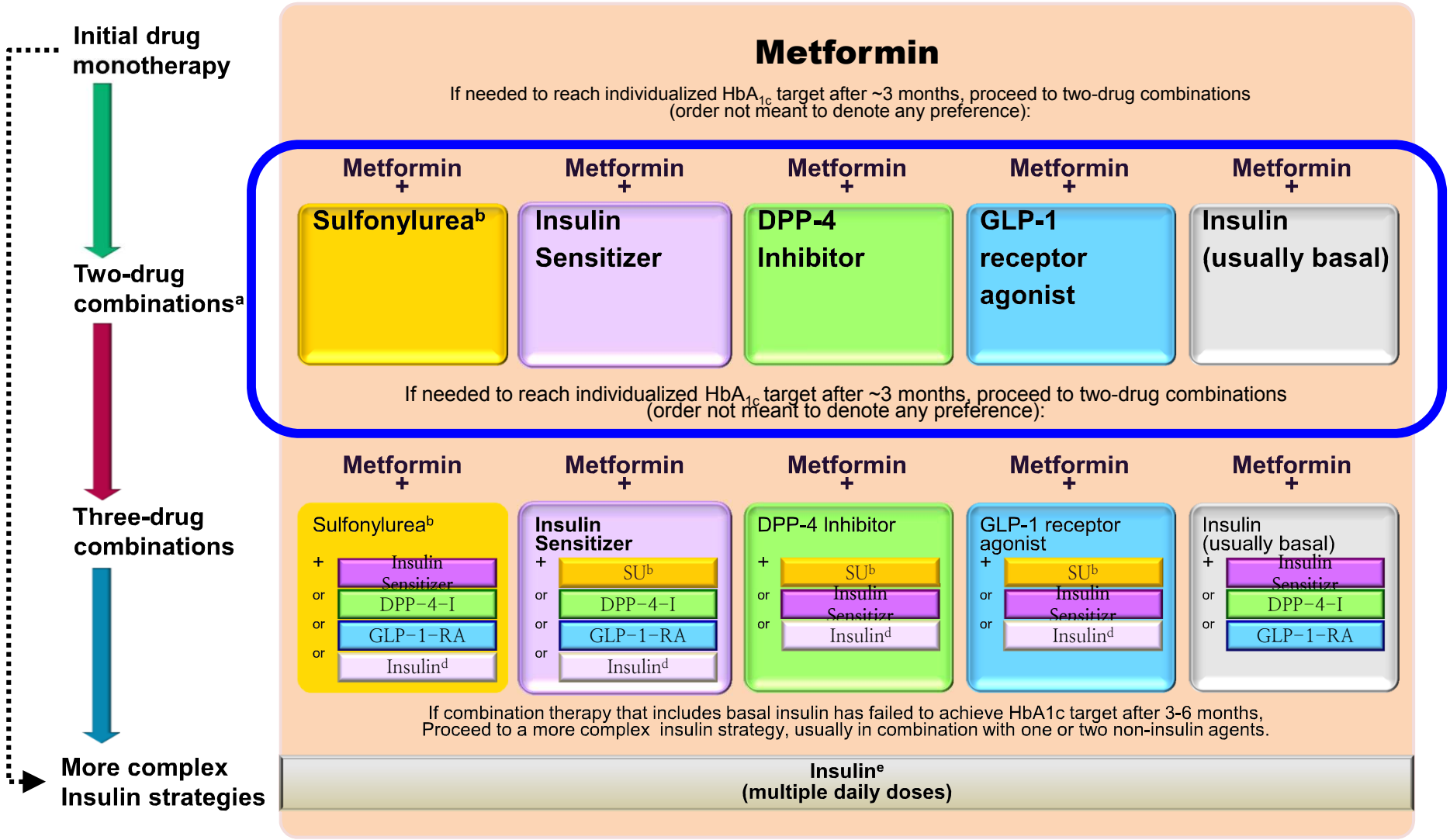
* The Stepwise approach(grey line) often leads to unacceptable delays in both achieving and maintaining glycaemic goals. The Early combination approach(red line) represents the same sequence of events of treatment for the individual, but with each stage brought forward, to provide better and more rapid glycaemic control and therefore improve the patient's glycaemic profile.

OAD=oral antihyperglycemic agent

1. Del Prato S et al. *Int J Clin Pract* 2005;59:1345–1355.

ADA Standards of Medical Care in Diabetes 2014

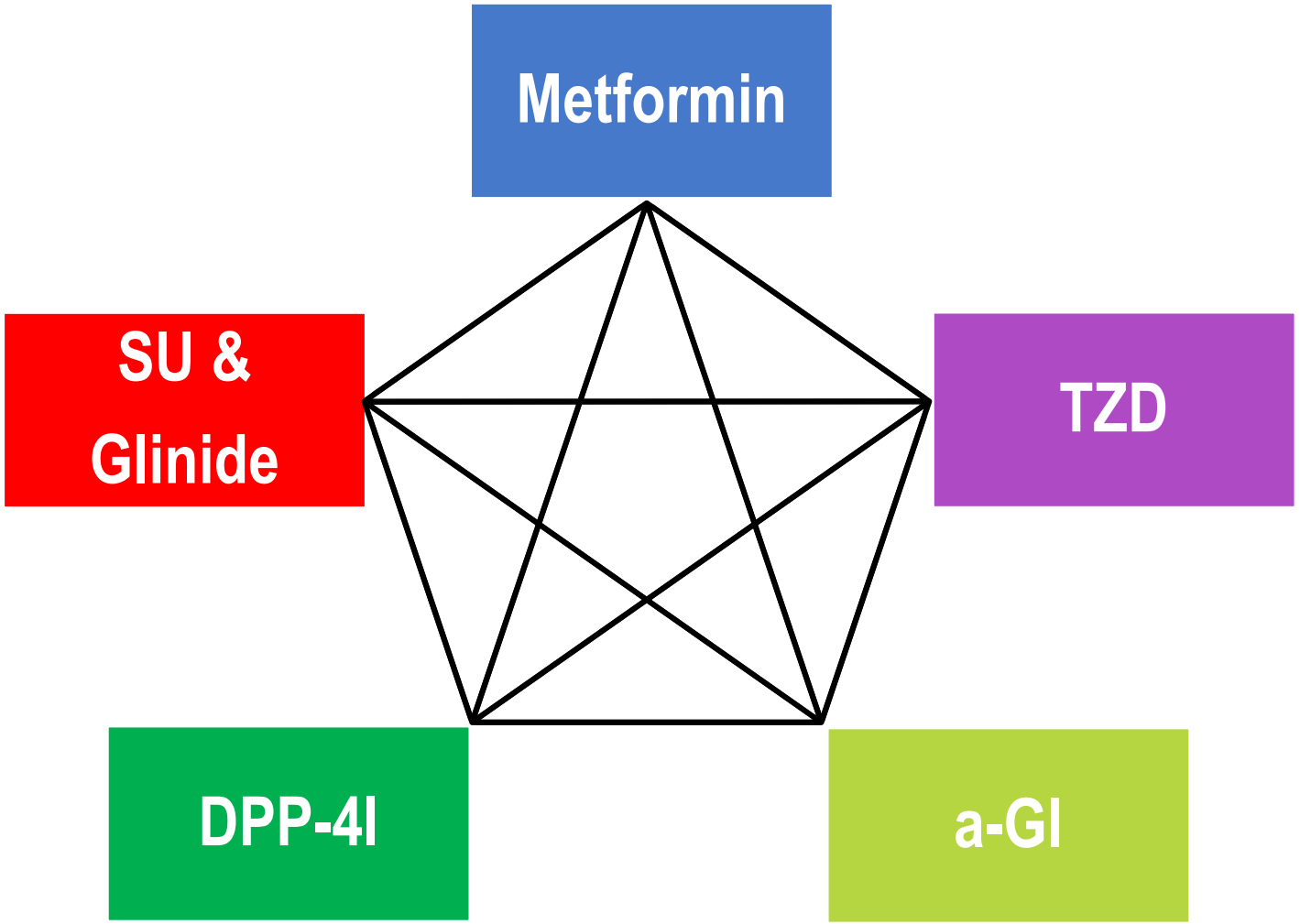
ADA also recommended early combination therapy with second line regimen after metformin



T2DM Antihyperglycemic Therapy: General Recommendations

Diabetes Care 2012;35:1364-79. Diabetologia 2012;55:1577-96.

What is your choice for the early intensive treatment strategy?



What next after metformin?

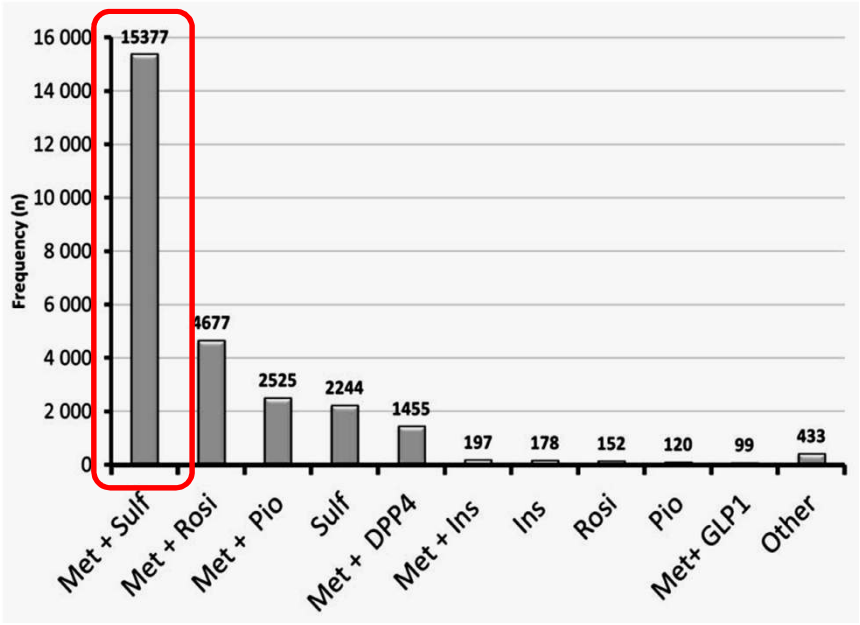
ORIGINAL ARTICLE

Endocrine Research

What Next after Metformin? A Retrospective Evaluation of the Outcome of Second-Line, Glucose-Lowering Therapies in People with Type 2 Diabetes

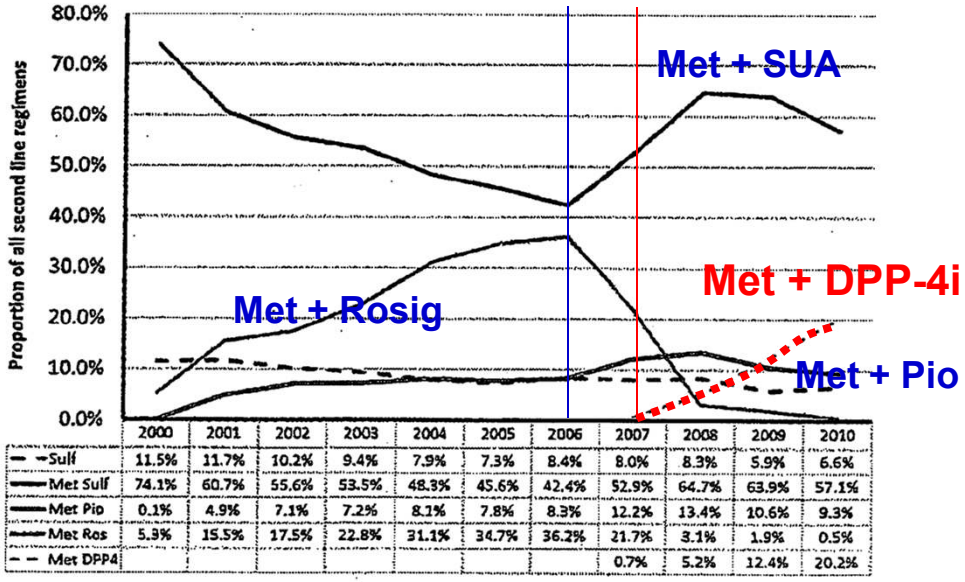
- **Retrospective data from the UK General Practice Research Database was used.**

Try to find out which drug was used of 2nd-line regimens following 1st-line metformin therapy (2000–2011). For all that, SUA was the most commonly used during the whole research periods.



A total of 27,457 patients were identified as switching to an eligible 2nd-line therapy during the selected time period.

Trend for selected 2nd-line regimens
as a proportion of all 2nd-line regimens, by year



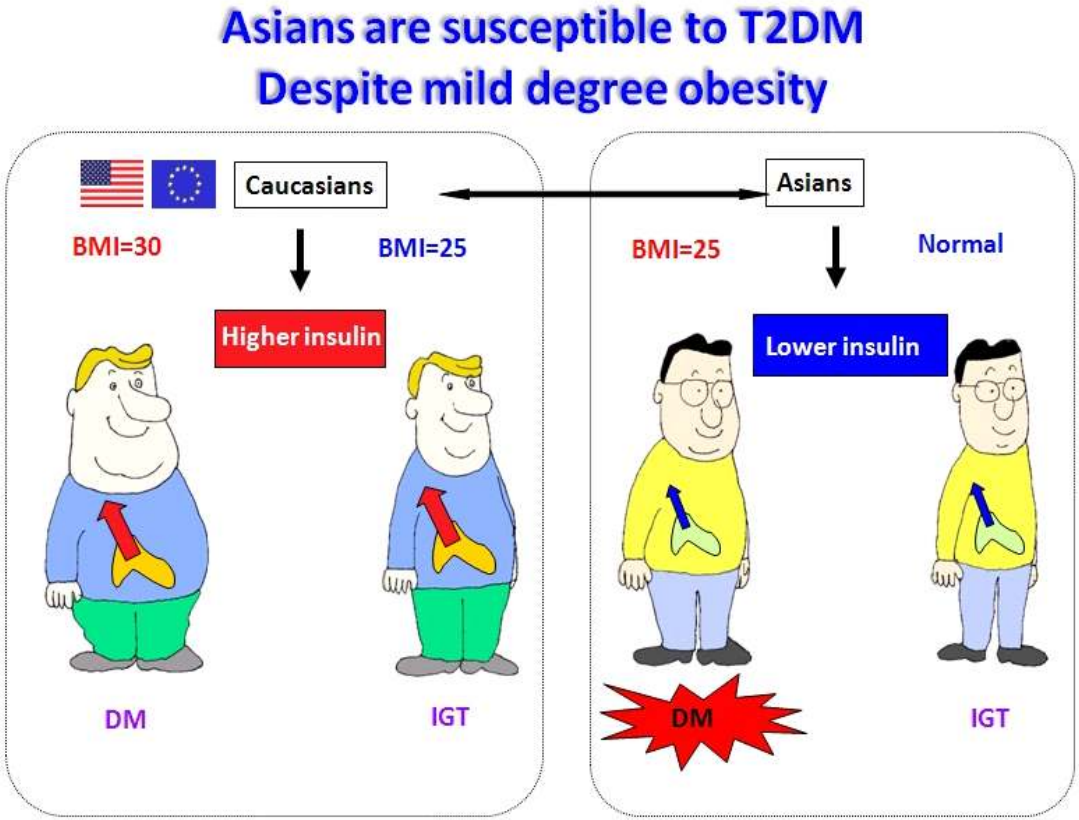
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Sulf	11.5%	11.7%	10.2%	9.4%	7.9%	7.3%	8.4%	8.0%	8.3%	5.9%	6.6%
Met Sulf	74.1%	60.7%	55.6%	53.5%	48.3%	45.6%	42.4%	52.9%	64.7%	63.9%	57.1%
Met Pio	0.1%	4.9%	7.1%	7.2%	8.1%	7.8%	8.3%	12.2%	13.4%	10.6%	9.3%
Met Ros	5.3%	15.5%	17.5%	22.8%	31.1%	34.7%	36.2%	21.7%	3.1%	1.9%	0.5%
Met DPP4								0.7%	5.2%	12.4%	20.2%

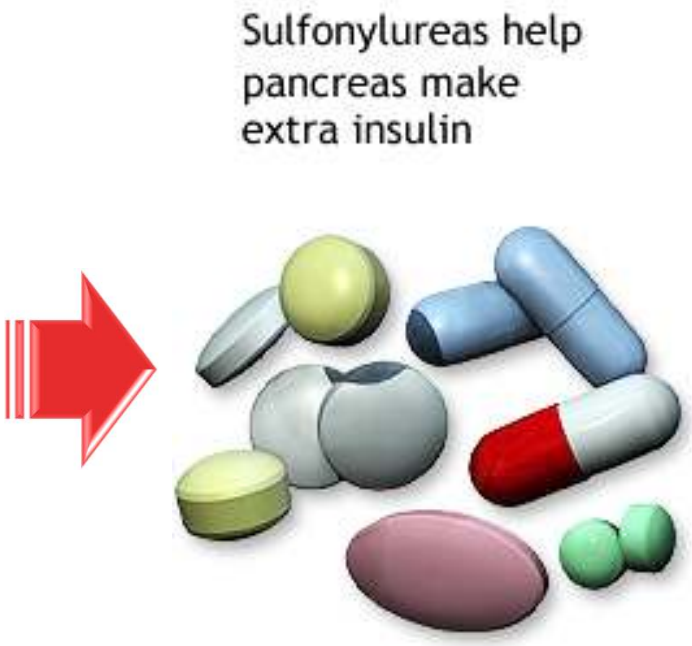
Sulf, sulfonylurea; Met Sulf, metformin+sulfonylurea; Met Pio, metformin+pioglitazone; Met Ros, metformin+ rosiglitazone; Met DPP4, metformin+ DPP4 inhibitor

J Clin Endocrinol Metab 2012;97:4605-4612. U.K based General Practice Research Database

What is your intensive strategy?

There are many reasons why SUA is still the most commonly used. One of the most important reason is the direct stimulatory effect of pancreatic beta-cells.

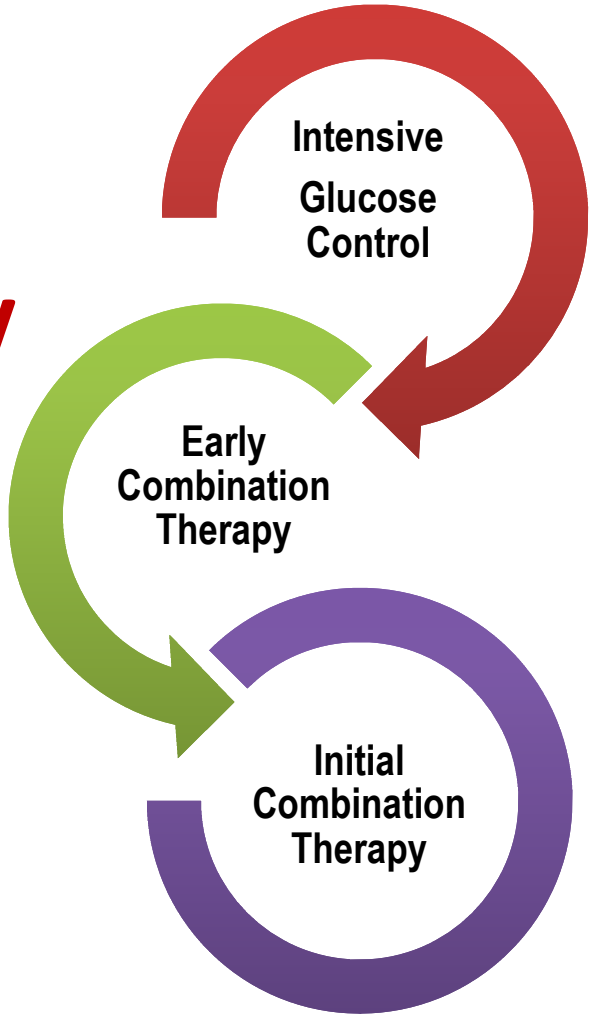




Beta cell failure is the more dominant pathophysiology in Asian. So, we usually start with SUA for the rapid and intensive glycemic control..

Author: Kohjiro Ueki Session: Diabetes: similarities and differences between East and West Event: Lisbon 2011 Date: September 15, 2011 16:55 Room: Jorge Hall

Clinical Evidences of Early Intensive Combination Therapy with Sulfonylurea



Glimepiride + Met FDC vs. Met Up-titration
- A study design to compare

Efficacy of glimepiride/metformin fixed-dose combination vs metformin uptitration in type 2 diabetic patients inadequately controlled on low-dose metformin monotherapy: A randomized, open label, parallel group, multicenter study in Korea

Hye-soon Kim[1], Doo-man Kim[2], Bong-soo Cha[3], Tae Sun Park[4], Kyoung-ah Kim[5], Dong-lim Kim[6], Chioon Hee Chung[7], Jeong-hyun Park[8], Hak Chul Jang[9], Dong-seop Choi[10]*

[1]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, [2]Department of Internal Medicine, Hallym University College of Medicine, [3]Department of Internal Medicine, Yonsei University College of Medicine, [4]Department of Internal Medicine, Konkuk University School of Medicine, [5]Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, Seoul, [6]Department of Endocrinology and Metabolism, Chonbuk National University Hospital, Jeonju, [7]Department of Internal Medicine, Dongguk University College of Medicine, Goyang, [8]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, [9]Paik Institute for Clinical Research, Department of Internal Medicine, College of Medicine, Inje University, Busan, and [10]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

- **Design:** Randomized, open label, parallel group, multicenter study in KOREA
- **Subject:** Patients have been on metformin 500~1000mg/day for at least 4weeks (HbA1c level 7.0~10.0%)

- **Primary end point:** Change in HbA1c
- **Secondary end point:** Change in FPG/PPG, Rate reaching HbA1c <7% & FPG <140mg/dL

J Diabetes Invest 2014; doi: 10.1111/jdi.12201

Glimepiride + Met FDC vs. Met Up-titration
- Efficacy

- **HbA1c <7%**
  G/M FDC: 74.7%
  MET UP: 46.6%
- **FPG <140mg/dL**
  G/M FDC: 84.7%
  MET UP: 65.1%

A1c and FPG were more decreased in FDC than Met up titration

Table 2 | Adjusted mean changes in glycated hemoglobin, fasting plasma glucose and 2-h postprandial plasma glucose

Group	*n*	Baseline Mean ± SD	End of study Mean ± SD	Adjusted mean change from baseline (95% CI)	Change G/M FDC vs Met UP (95% CI)	*P*-value
HbA1c (%)						
G/M FDC	99	7.9 ± 0.8	6.6 ± 0.7	−1.2 (−1.3 to −1.1)	−0.4 (−0.6 to −0.3)	<0.0001
Met UP	103	7.8 ± 0.7	7.0 ± 0.7	−0.8 (−0.9 to −0.6)		
FPG (mg/dL)						
G/M FDC	98	156.7 ± 33.2	117.3 ± 21.0	−35.7 (−39.7 to −31.7)	−17.1 (−22.8 to −11.5)	<0.0001
Met UP	103	148.1 ± 26.9	133.0 ± 20.3	−18.6 (−22.5 to −14.6)		
PPG (mg/dL)						
G/M FDC	97	233.6 ± 66.7	180.9 ± 57.3	−50.6 (−60.8 to −40.3)	−8.1 (−22.4 to 6.3)	0.2681
Met UP	102	228.0 ± 69.0	187.4 ± 52.1	−42.5 (−52.5 to −32.5)		

CI, confidence interval; G/M FDC, glimepiride/metformin fixed-dose combination; Met Up, metformin uptitration treatment; SD, standard deviation.

J Diabetes Invest 2014; doi: 10.1111/jdi.12201

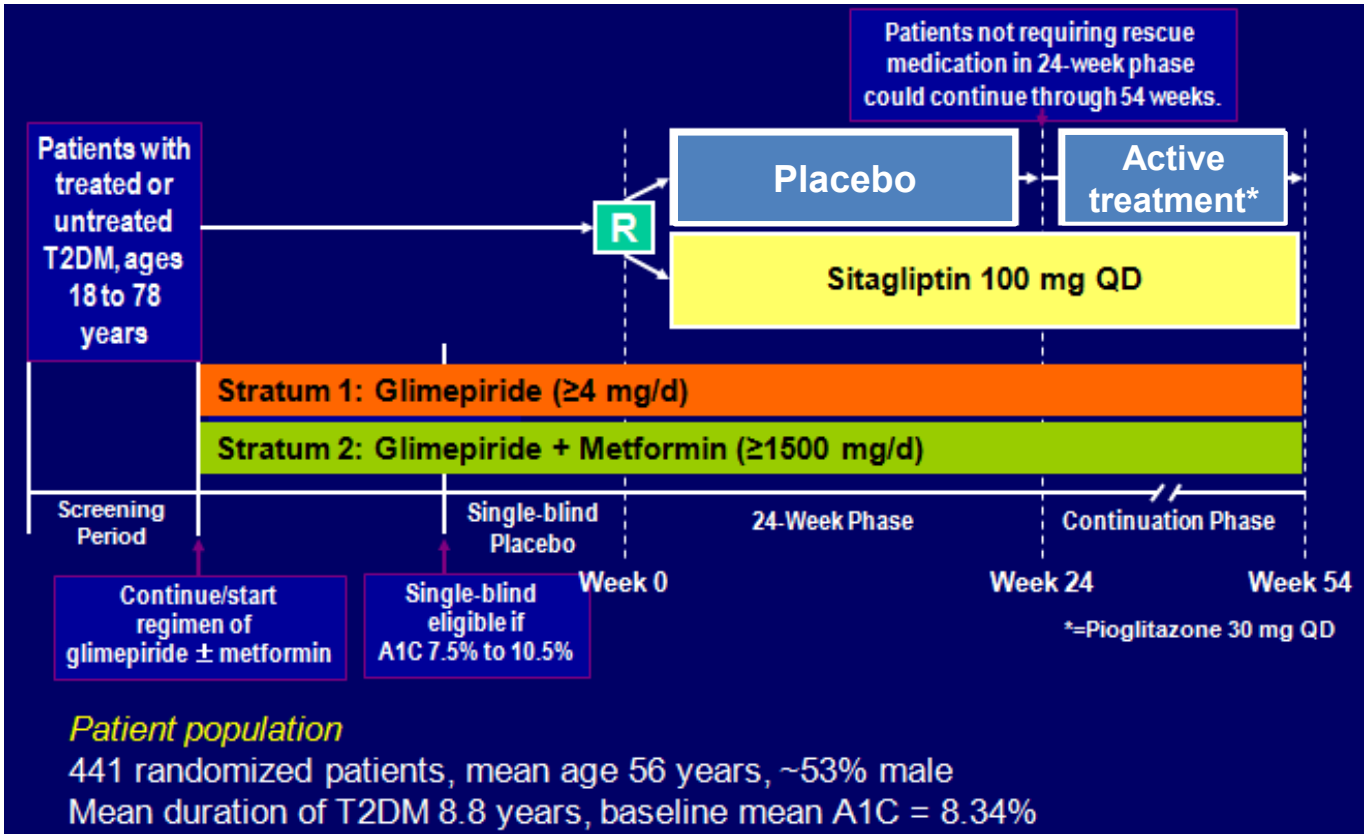
Glimepiride + Met FDC vs. Met Up-titration
- Safety rate

	G/M FDC (n = 100)	Met UP (n = 108)
AEs*, n (%)		
≥1 AE	34 (34.0)	34 (31.5)
≥1 possibly drug-related AEs	5 (5.0)	8 (7.4)
≥1 Serious AEs	1 (1.0)	3 (2.8)
Discontinuations due to AEs	0	3 (2.8)
AEs ≥ 2% in either treatment groups, n (%)		
Abdominal pain upper	4 (4.0)	1 (0.9)
Diarrhea	1 (1.0)	5 (4.6)
Chest pain	2 (2.0)	2 (1.9)
Nasopharyngitis	7 (7.0)	5 (4.6)
Upper respiratory tract infection	0	5 (4.6)
Headache	3 (3.0)	0
Hypoglycemia, n (%)/event		
Any hypoglycemia	41 (41.0)/100	6 (5.6)/6
Titration period	19 (19.0)/31	3 (2.8)/3
Maintenance period	29 (29.0)/68	2 (1.9)/2
Symptomatic hypoglycemia	39 (39.0)/96	4 (3.7)/4
Nocturnal hypoglycemia	2 (2.0)/2	0/0
Severe hypoglycemia	0/0	0/0
Hypoglycemia checked with SMBG, no. events (%)		
Hypoglycemia checked with SMBG	81 (100)	4 (100)
<50 mg/dL	1 (1.2)	0 (0.0)
50–60 mg/dL	9 (11.1)	1 (25.0)
60–70 mg/dL	24 (29.6)	1 (25.0)
≥70 mg/dL	47 (58.0)	2 (50.0)

*Adverse events (AEs) excluding hypoglycemia. G/M FDC, glimepiride/metformin fixed-dose combination; Met Up, metformin uptitration treatment, SMBG, self-monitored blood glucose.

J Diabetes Invest 2014; doi: 10.1111/jdi.12201

SU±Met+DPP-4I vs. SU±Met+Placebo
- A study design to compare



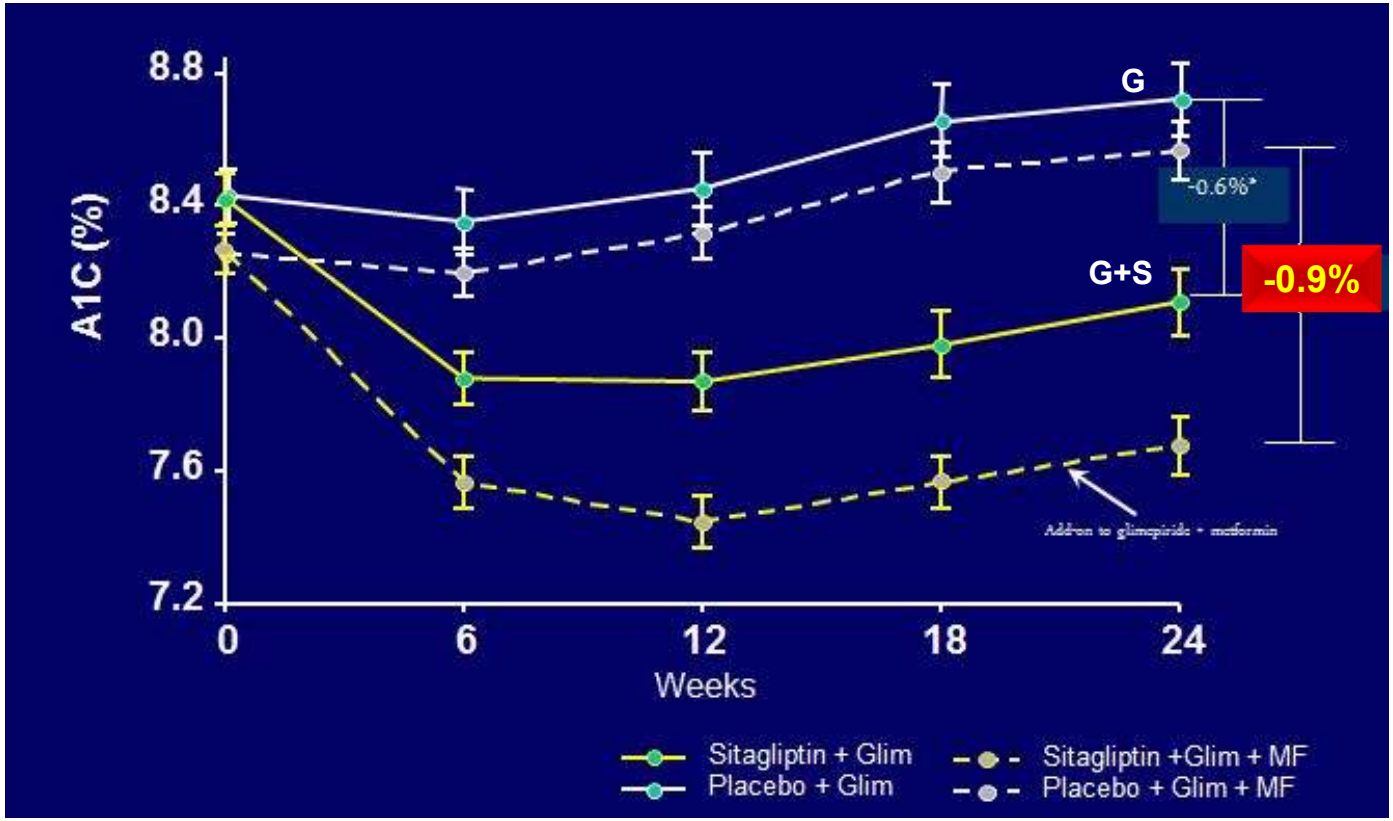
Another study was tried to compare the efficacy between intensive triple combination and dual combination therapy

- **Primary Endpoint:** Change in HbA_{1c} from baseline to Week 24
- **Secondary endpoint:** FPG, 2-h post-meal glucose and lipid measurements

Diabetes Obes Metab 2007;9:733-745

SU±Met+DPP-4I vs. SU±Met+Placebo
- Efficacy

A1C change from Baseline – By Stratum
Placebo-controlled Add-on to Glimepiride (+/- metformin) Study



A1c difference between G/G+S was 0.6%. By the way, initial intensive triple combination showed more decreased A1c compare to dual combination.

Adapted from Hermansen et al. *Diabetes Obes Metab* 2007;9:733-745

SU±Met+DPP-4I vs. SU±Met+Placebo
- Safety rate

n (%)	Sitagliptin 100 mg q.d.			Placebo		
	Entire cohort (n = 222)	Glimepiride (n = 106)	Glimepiride + metformin (n = 116)	Entire cohort (n = 219)	Glimepiride (n = 106)	Glimepiride + metformin (n = 113)
One or more AEs	132 (59.5)	59 (55.7)	73 (62.9)	103 (47.0)	43 (40.6)	60 (53.1)
Drug-related AEs†	33 (14.9)	12 (11.3)	21 (18.1)	15 (6.8)	7 (6.6)	8 (7.1)
Serious AEs (SAEs)	12 (5.4)	5 (4.7)	7 (6.0)	8 (3.7)	6 (5.7)	2 (1.8)
Drug-related SAEs†	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	1 (0.5)‡	0 (0.0)	1 (0.9)‡	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations because of AEs	5 (2.3)	3 (2.8)	2 (1.7)	3 (1.4)	1 (0.9)	2 (1.8)
Discontinuations because of drug-related AEs†	1 (0.5)	1 (0.9)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.9)
Discontinuations because of SAEs	3 (1.4)	2 (1.9)	1 (0.9)	1 (0.5)	1 (0.9)	0 (0.0)
Discontinuations because of drug-related SAEs†	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clinical AEs of special interest						
Hypoglycaemia	27 (12.2)	8 (7.5)	19 (16.4)	4 (1.8)	3 (2.8)	1 (0.9)
Overall gastrointestinal AEs	11 (5.0)	6 (5.7)	5 (4.3)	10 (4.6)	2 (1.9)	8 (7.1)
Selected gastrointestinal AEs						
Abdominal pain	5 (2.3)	3 (2.8)	2 (1.7)	2 (0.9)	0 (0.0)	2 (1.8)
Diarrhoea	3 (1.4)	2 (1.9)	1 (0.9)	6 (2.7)	2 (1.9)	4 (3.5)
Nausea	1 (0.5)	0 (0.0)	1 (0.9)	1 (0.5)	0 (0.0)	1 (0.9)
Vomiting	3 (1.4)	1 (0.9)	2 (1.7)	1 (0.5)	0 (0.0)	1 (0.9)

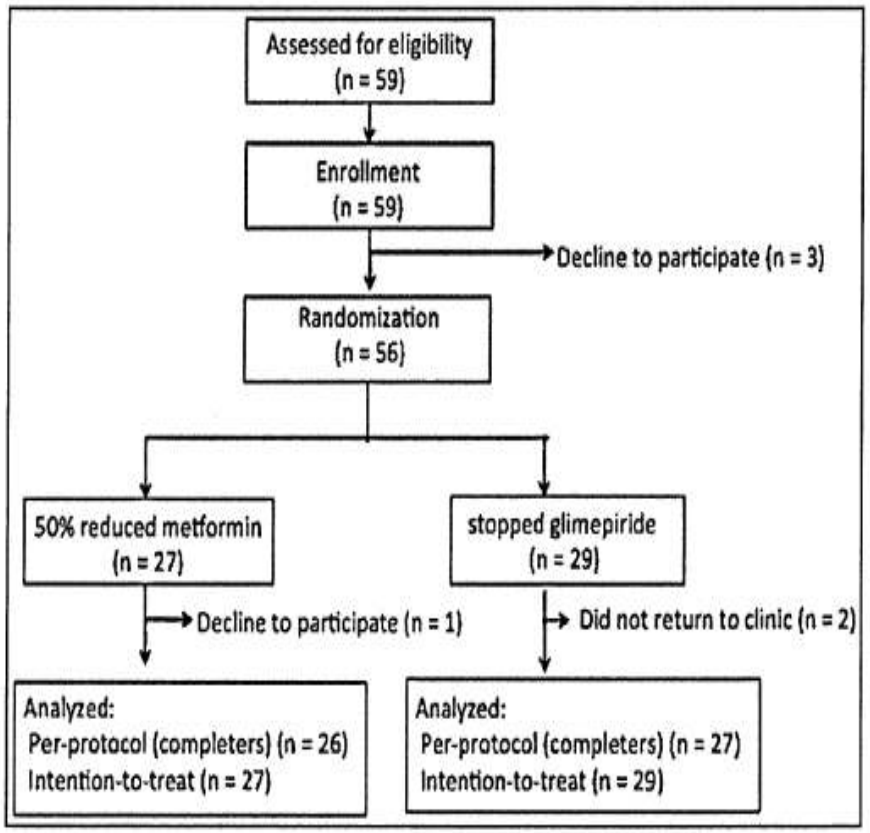
AE, adverse experience.

And the rate of all drug-related SAE was not different in all study patient just except hypoglycemia, that is more prevalent in triple combination therapy

Adapted from Hermansen et al. *Diabetes Obes Metab* 2007;9:733-745

Glimepiride + Met + DPP-4 inhibitor
- Study Design

Study design : 3 month, single-center, open-label, randomized study
Subjects : T2DM patients who had been treated with **50mg of sitagliptin, ≥1,000mg of metformin, and ≤1mg of glimepiride** with an **HbA1c level of <7.4% during at least 3 months**



This study also aimed

To see if

1) the dose of metformin can be decreased

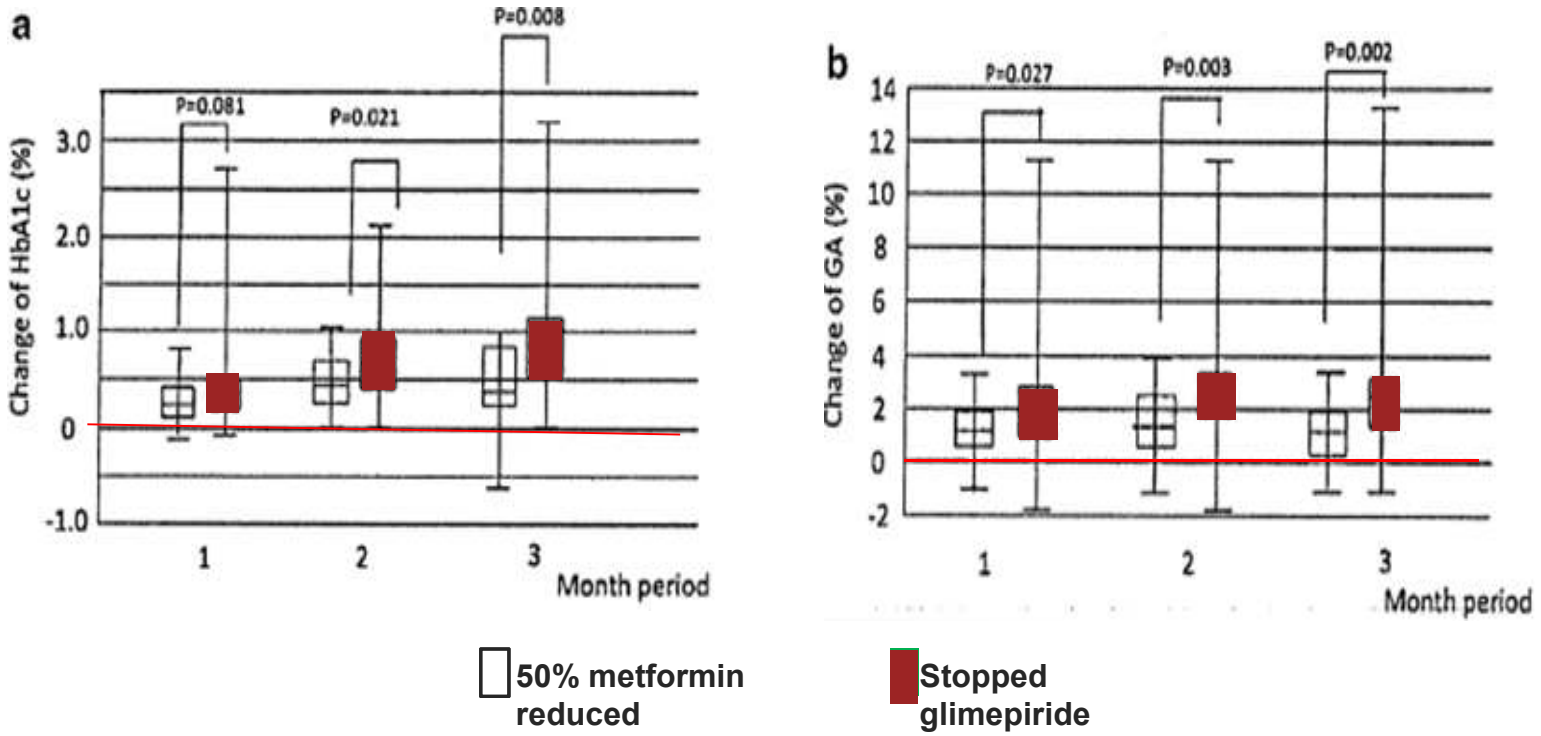
or

2) sulfonylurea treatment can be stopped

after achieving satisfactory glycemic control with triple OAD therapy

Diabetes Technol Ther. 2013 Apr;15(4):335-41.

Glimepiride + Met + DPP-4 inhibitor
- Conclusion



Significantly greater changes were observed in HbA1c and glycated albumin levels in patents who discontinued glimepiride than in patients with a 50% reduced metformin dose.

Diabetes Technol Ther. 2013 Apr;15(4):335-41.

In spite of the powerful efficacy data,

Unsolved issue, Safety & Durability

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Glimepiride: the 3rd generation Sulfonylurea

Many SUAs are available now.

We continue to generalize about SUs, but the safety profiles are different

The incidence of severe hypoglycemia with various SUs

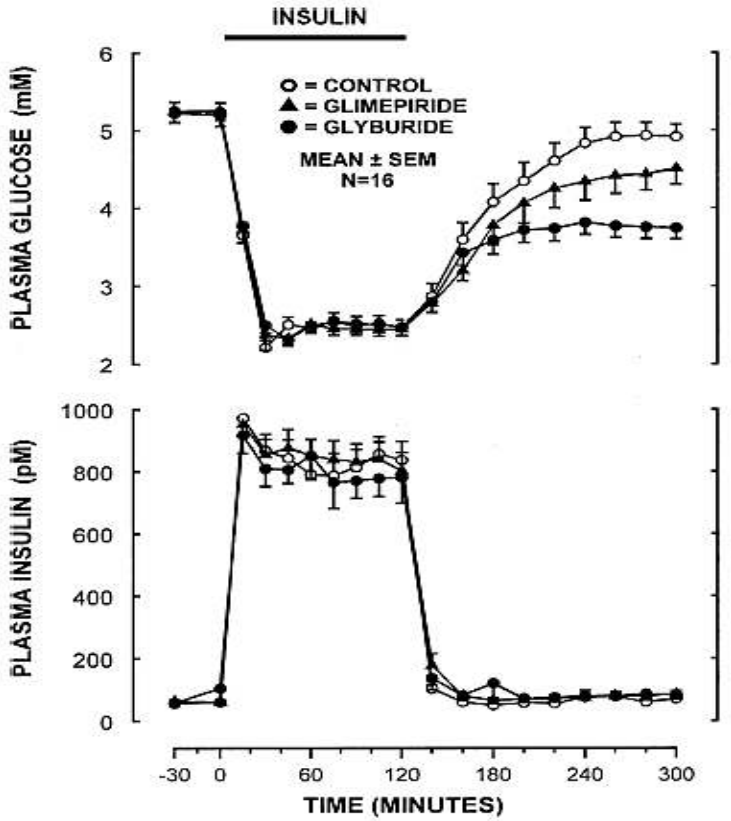
Duration	Population	Number of diabetic patients requiring a hypoglycaemia-associated hospital admission/ emergency call out per drug	Incidence of severe hypoglycaemia/ 1000 person-years	Mortality(%) of patients experiencing hypoglycaemic episodes
5 Years	190,000	49 / chlorpropamide 14 / glibenclamide	5.8 chlorpropamide 16.0 glibenclamide	1.4
7 Years	76,000	79 / glibenclamide	6.8 glibenclamide	10
2 Years	76,000	26 / glibenclamide	Not stated	5.9
12 Years	200,000	15 / glibenclamide 1 / chlorpropamide 10 / glibornuride 2 / gliclazide	2.24 long-acting SU 0.75 short-acting SU	0
4 Years	200,000	38 / glibenclamide 1 / glibenclamide + 6 / **glimepiride**	5.6 glibenclamide **0.86 glimepiride**	**0**

Exp Clin Endocrinol Diabetes. 2003 Oct;111(7):405-14.

Glimepiride: the 3rd generation Sulfonylurea

We continue to generalize about SUs, but the safety profiles are different

In the comparison study between Glimepiride and Glyburide on recovery from hypoglycemia was more rapid in glimepiride



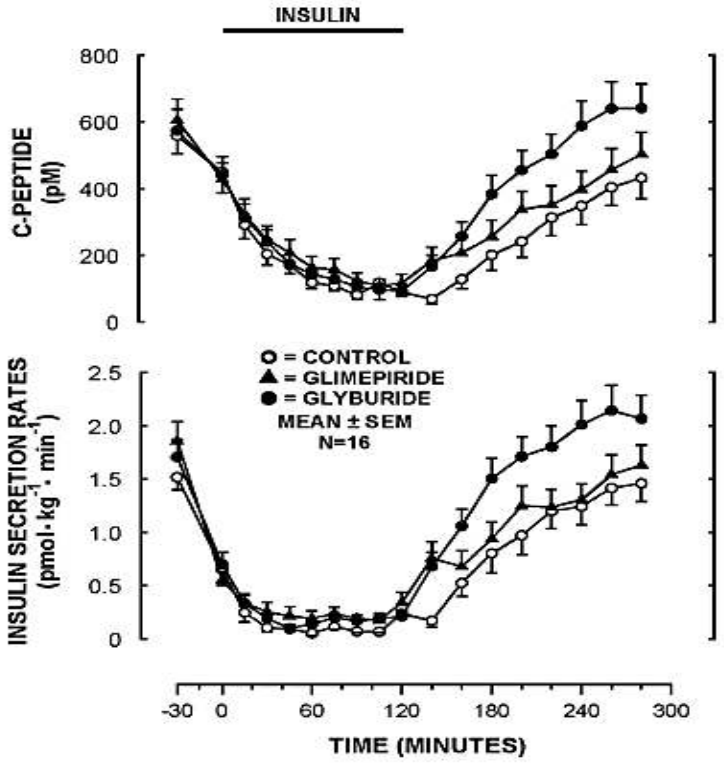


Fig. 2. Plasma C-peptide and insulin secretory rates.

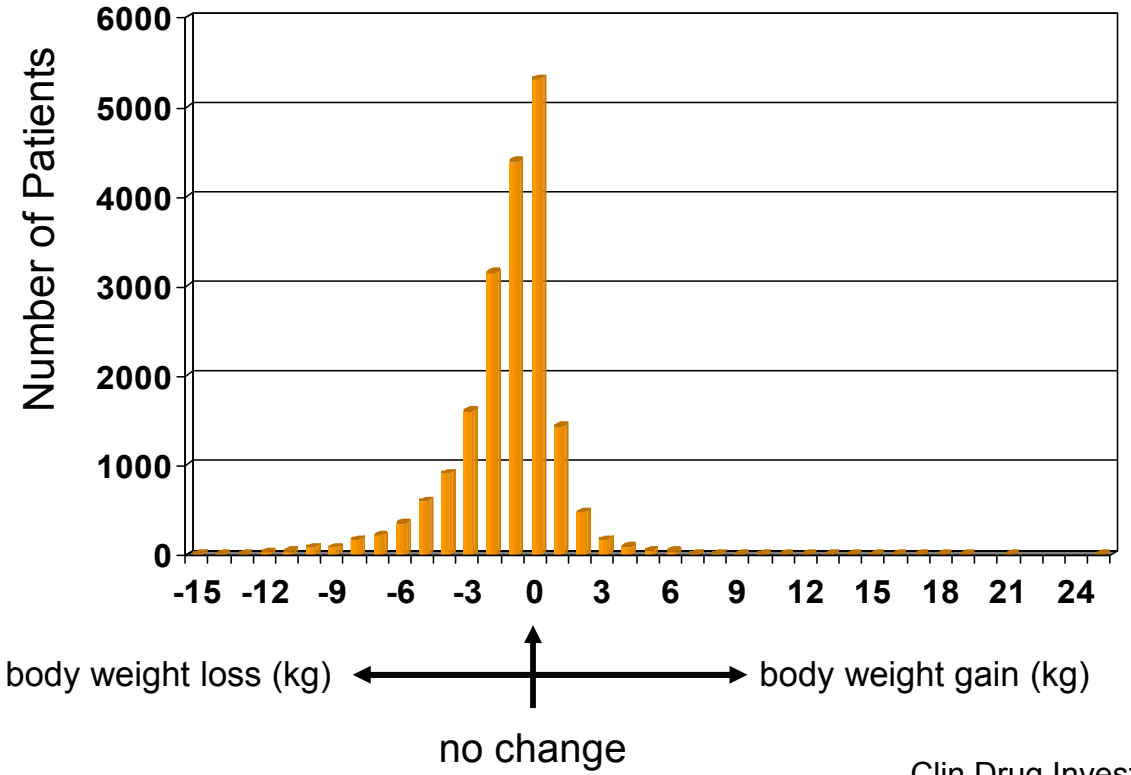
Metabolism Clinical and Experimental 55 (2006) 78–83

Glimepiride: the 3rd generation Sulfonylurea

We continue to generalize about SUs, but the safety profiles are different

Glimepiride showed weight neutrality different from most of the other SUAS

In Large-scale Surveillance Study (Germany): Change of body weight - individual data

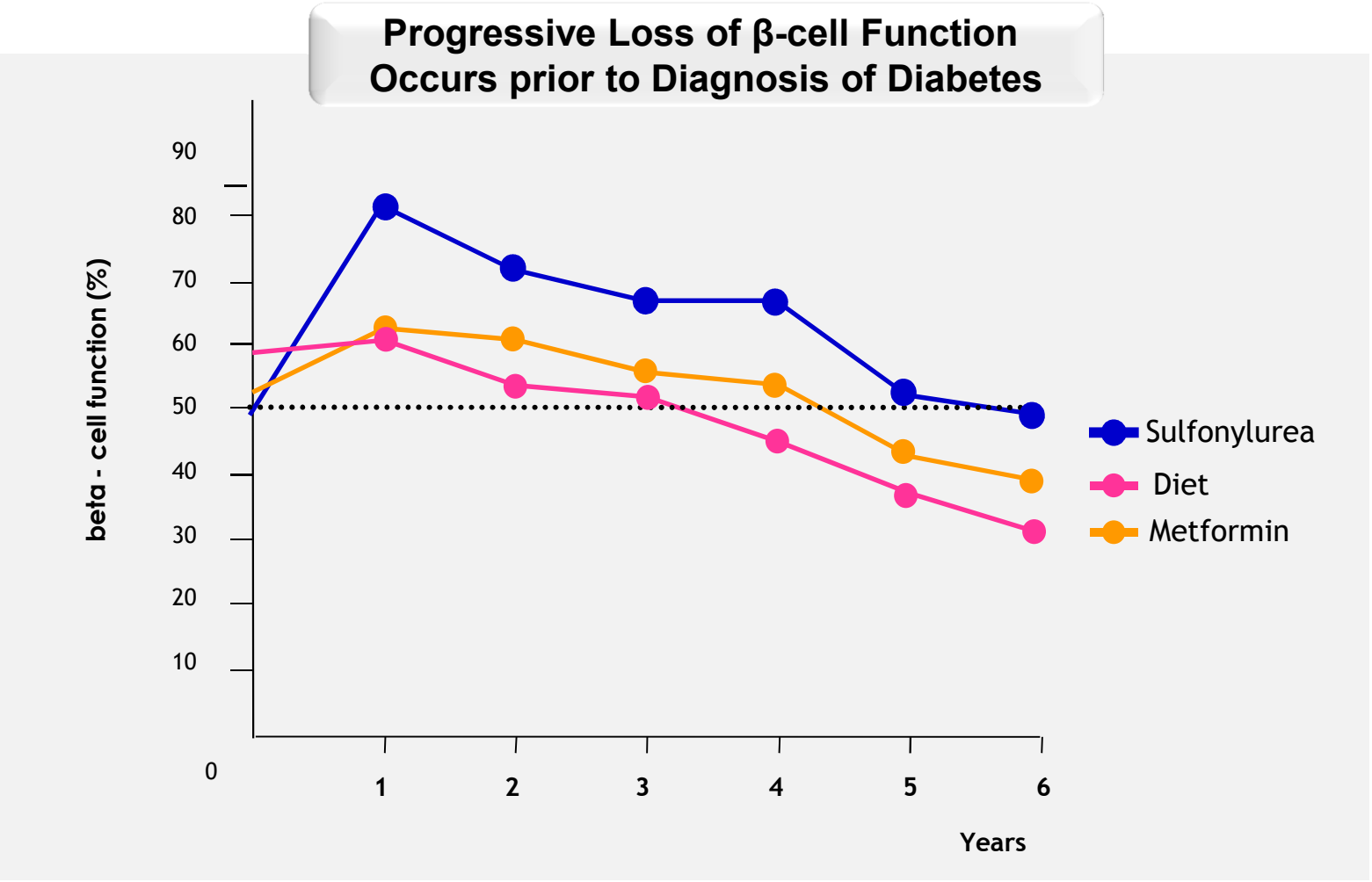


Clin Drug Invest, 2001, 21, 597-604

Sulfonylurea is really facing a CRISIS?

There has been debate about Sulfonylureas and possibly associated β-cell function decline

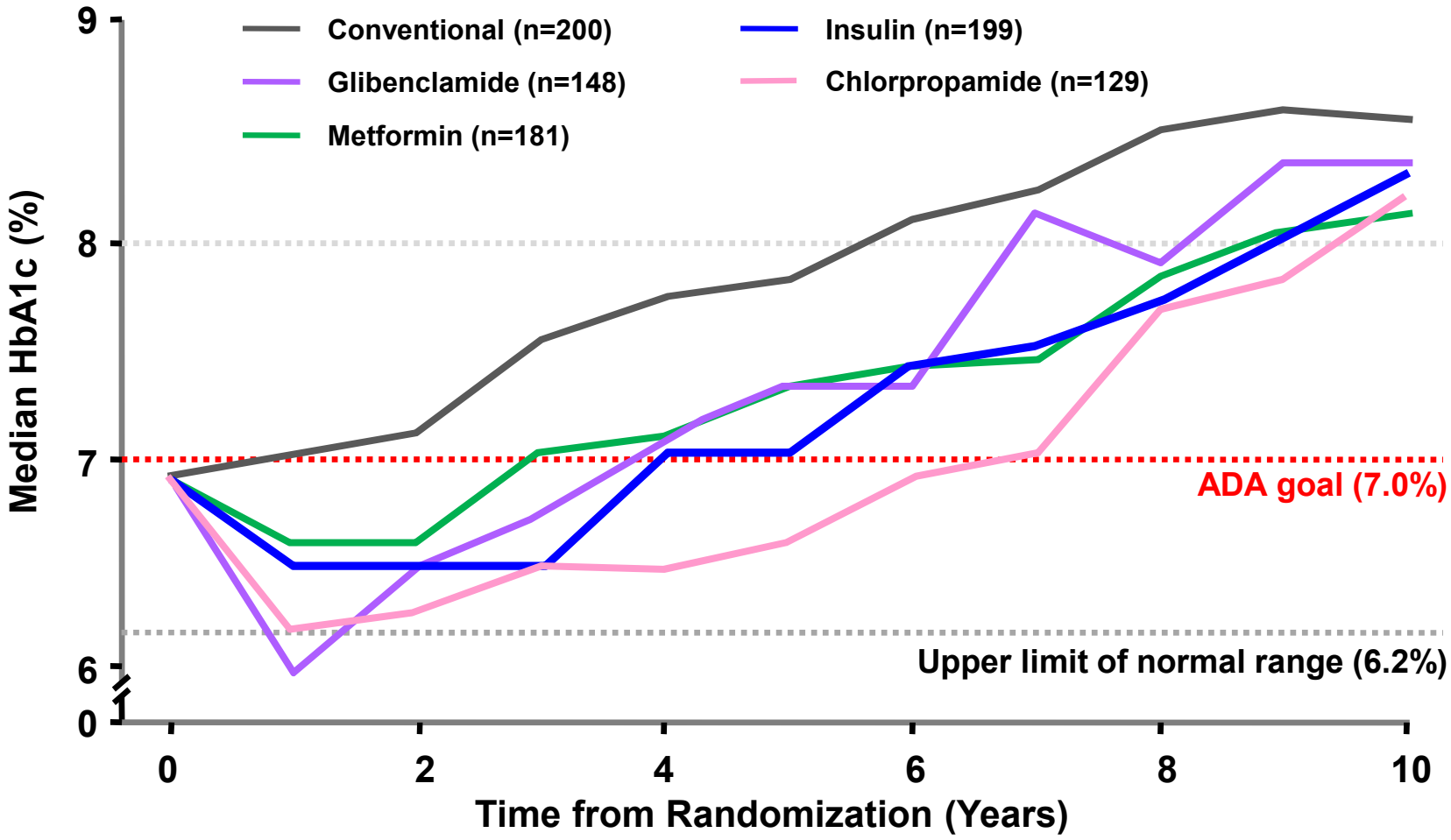
β-cell function was progressively declines as a natural course of diabetes progression (UKPDS)



UKPDS Group (UKPDS 16), Diabetes, 1995 44 (1249-1258)

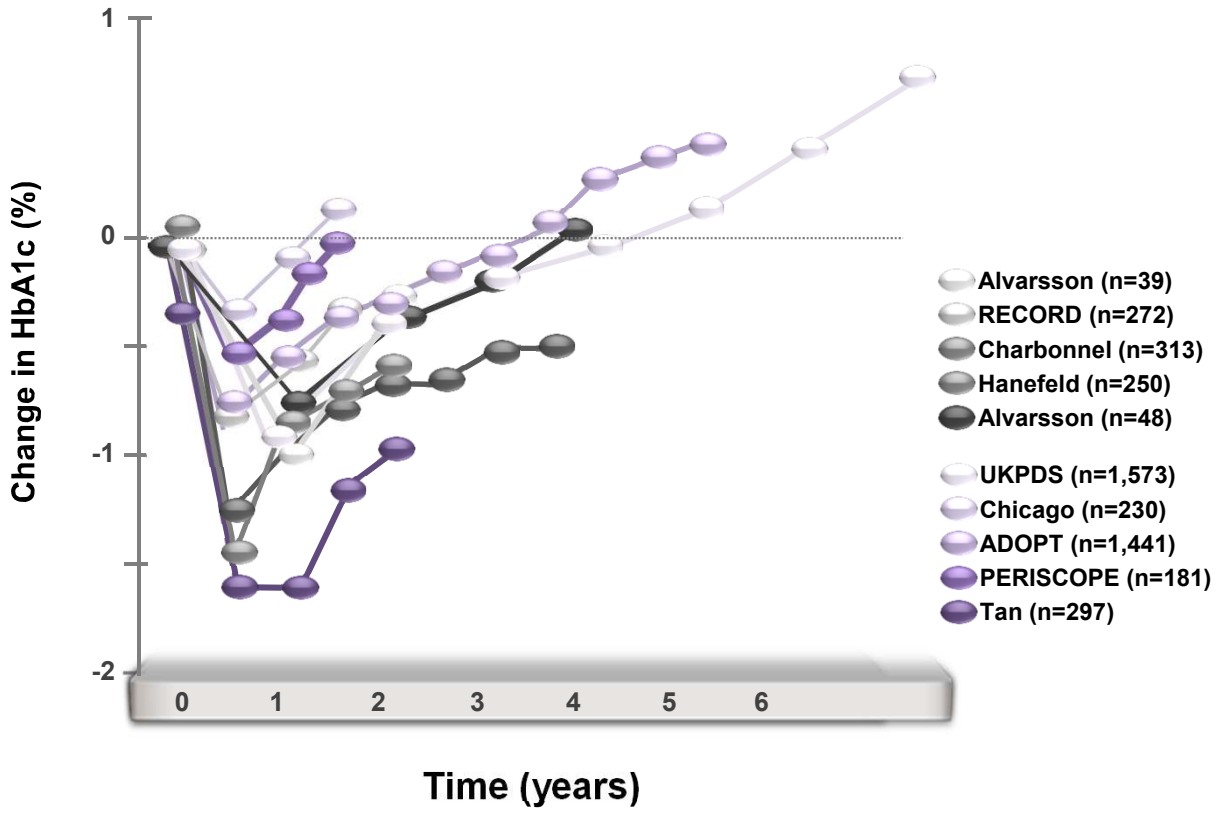
consequently,

UKPDS: Glycemic Control Worsens over Time



ADA=American Diabetes Association; HbA1c=hemoglobin A1c.
Adapted from UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998; 352: 854–865.

Do all sulfonylurea show failure to glycemic control over time?

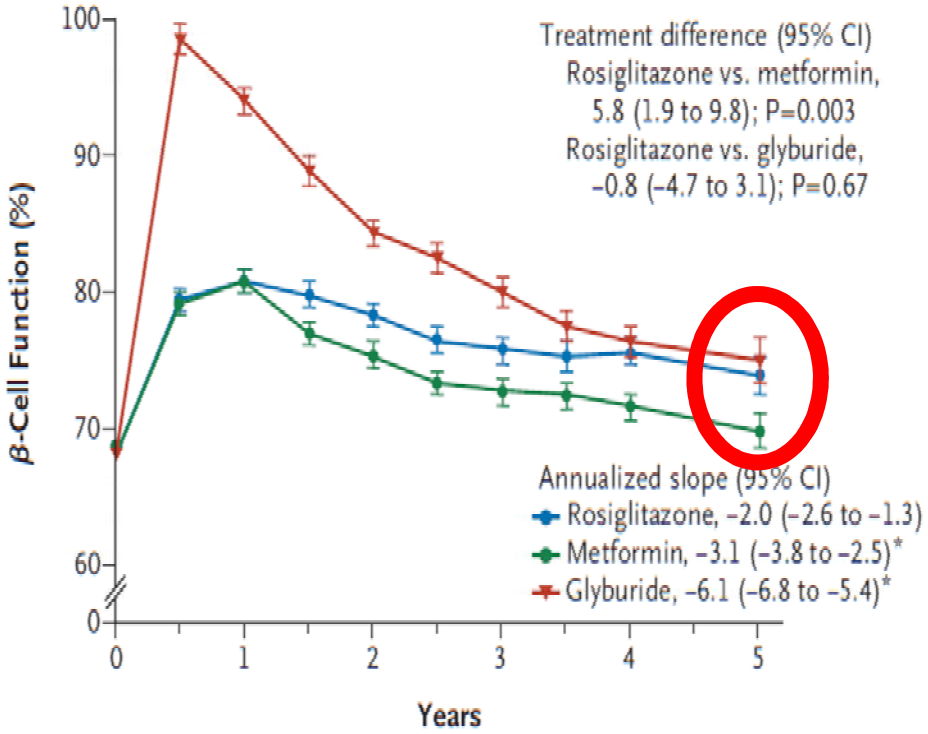


Many clinical study have shown the similar change of A1c curve like **big drop at the beginning, and then it goes up significantly**

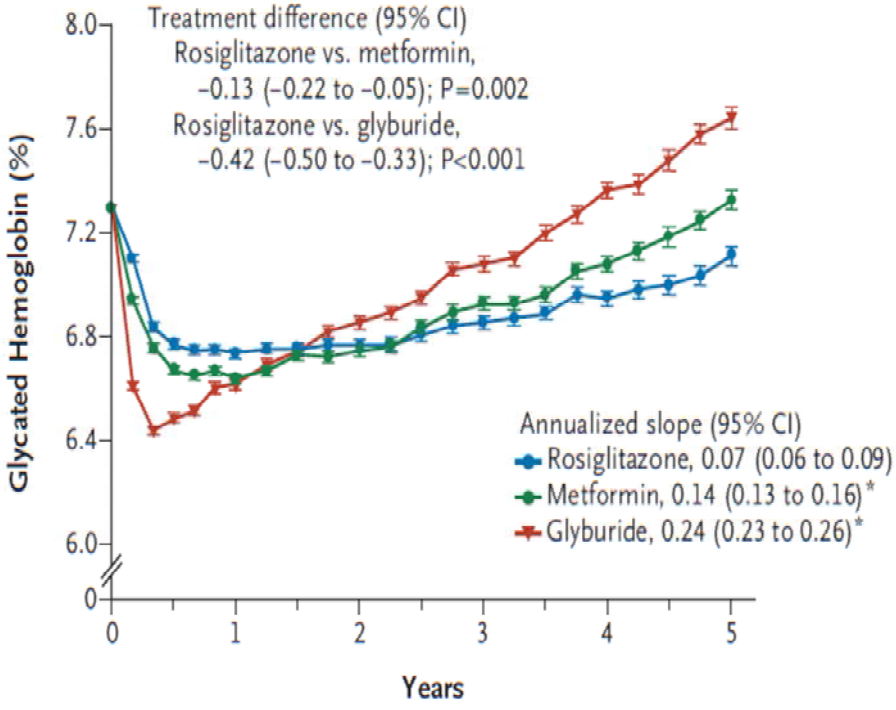
β-cell function declines as a natural course of diabetes progression (SU vs. Metformin vs. TZD)

Similar result was observed in ADOPT study. However, the beta-cell function at the end of trial in SUA was still higher than Rosig and Mef

Changes of β-cell function



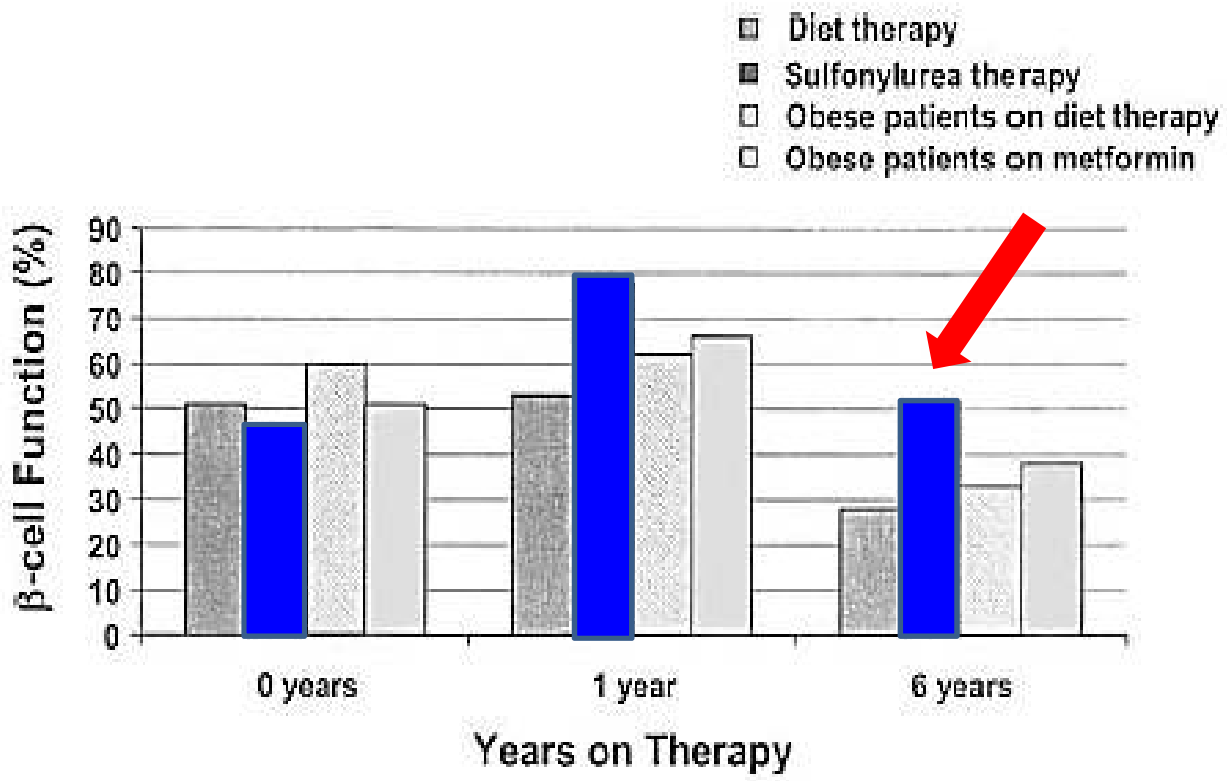
Changes of HbA1c



ADOPT. N Engl J Med 2006;355:2427-43

β-cell function declines as a natural course of diabetes progression (SU vs. Metformin)

After 6 years of sulfonylurea therapy,
Pancreatic function was greater than after diet therapy or treatment with metformin

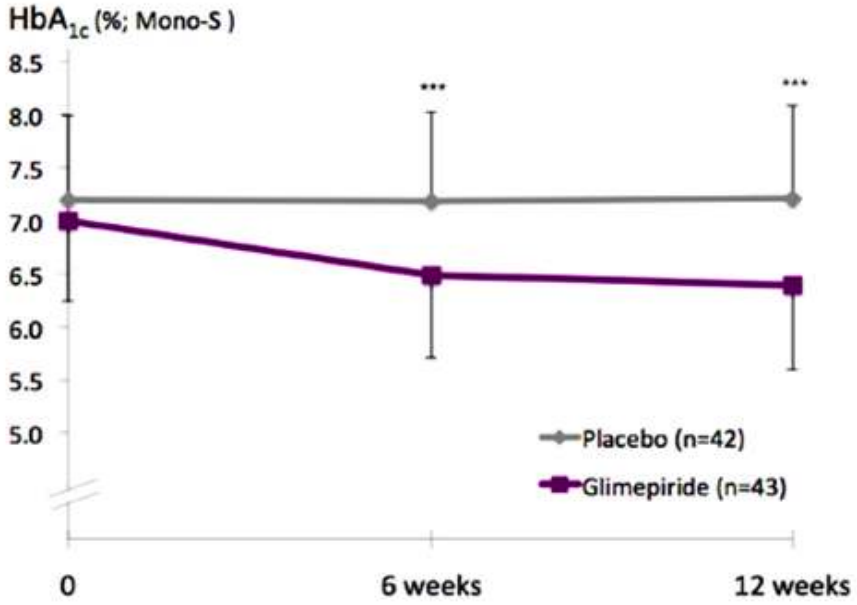


Also in UKPDS Group (UKPDS 16), Diabetes, 1995 44 (1249-1258)

Glimepiride is effective in T2DM with declined β-cell function - 10+yrs on diabetes -

Design: A randomized, placebo-controlled, double-blind, cross-over study

Patients: Type 2 diabetes ≥ 10 years who had been treated with metformin (median 1700 mg) and insulin (all regimens) for at least 1 year.



β-cells still remain responsive to SU even after many years of diabetes leading to significant HbA1c lowering and reducing the need for exogenous insulin

At the end of the study, placebo group showed no change in HbA1c, while a decrease of 0.6%(P < 0.001) was observed with glimepiride.

Diabetes Res Clin Pract. 2014 Jan 8. pii: S0168-8227(14)00023-0.

To summarize the role of Sulfonylurea for Metabolic Karma!

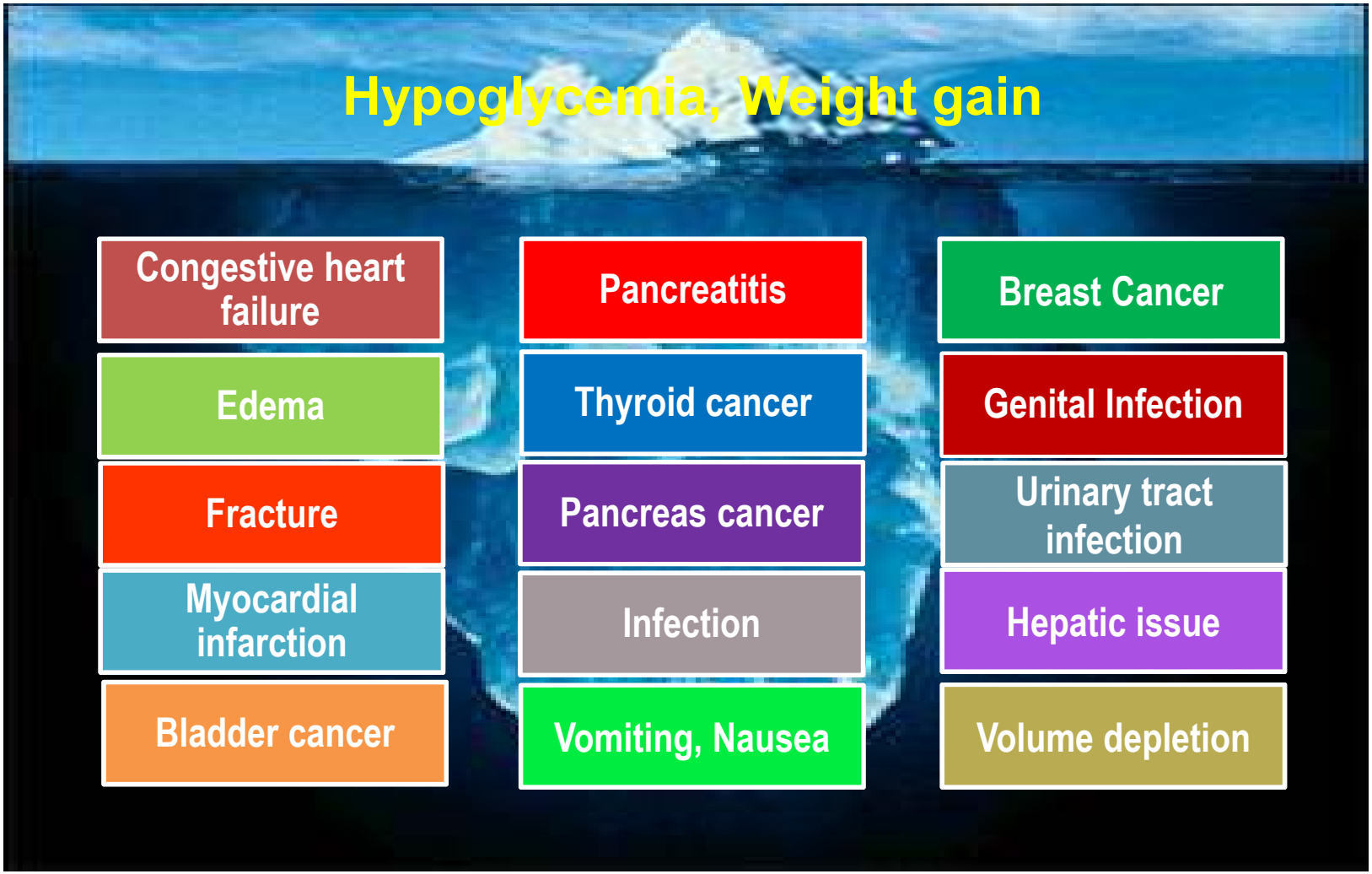
Benefits

- Fast/Powerful efficacy
- Long history of use
- Well known safety profile

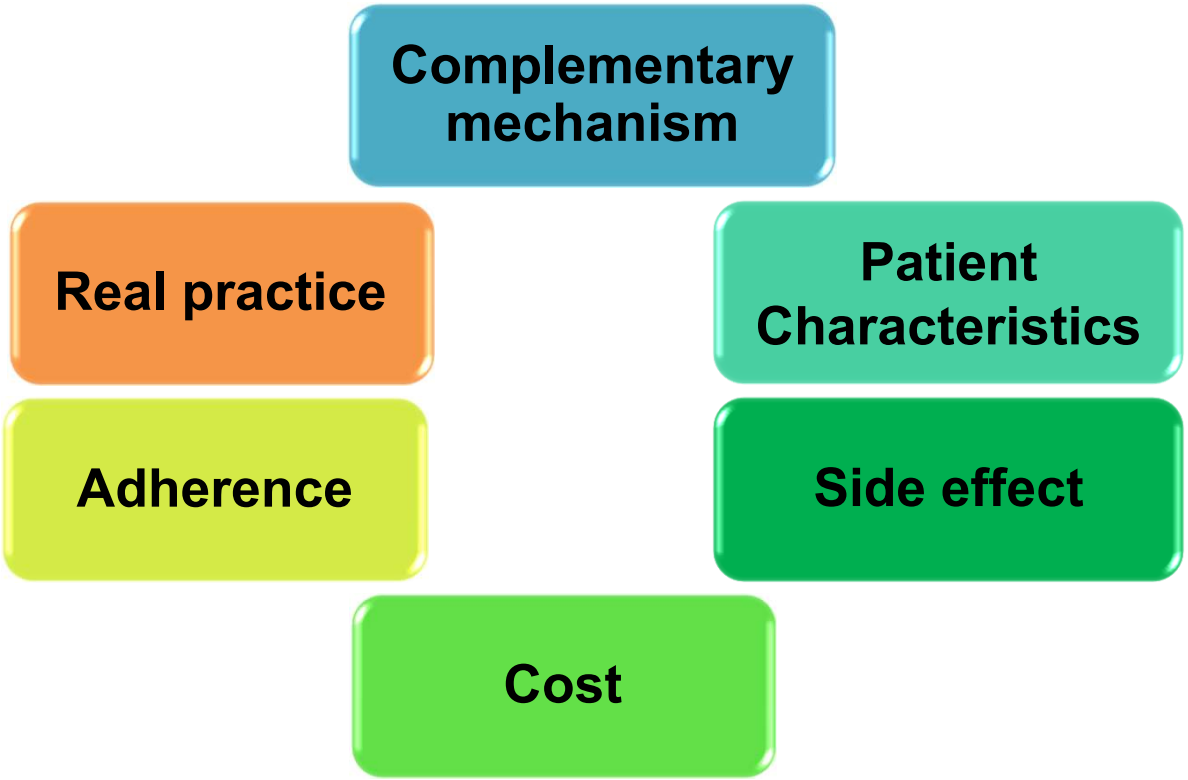
Limitations

- Hypoglycemia
- Weigh gain
- Limited durability

OLD & Brand NEW classes of anti-diabetic agent have more uncertain safety issues compare to sulfonylurea



What is your most important concern for the choice of anti-diabetics?



Adapted from Diabetes Care. 2012 Jun;35(6):1364-79

Clinicians must select from these features to develop individualized therapy regimens

Beyond Metformin: Safety Considerations in the Decision-Making Process for Selecting a Second Medication for Type 2 Diabetes Management Reflections From a Diabetes Care Editors' Expert Forum

Recently an important paper reviewed the safety evidence for six major diabetes drug classes was published :
Insulin, SUs, TZDs, GLP-1 RA, DPP4-i, and SGLT2-i.

Those about which we know the most-MET, SUs, insulin, and TZDs-are efficacious in most patients and can be placed into a basic initial algorithm.

However, these agents leave some clinical needs unmet.
Selecting next steps is a more formidable process involving newer agents that are understood less well and for which there are unresolved questions regarding risk versus benefit in certain populations.
The most important message of this study is that
"Choosing a specific agent is not as important as implementing some form of early intervention and advancing rapidly to some form of combination therapy as needed"
for the successful treatment and good glycemic legacy.

Cefalu WT, et al. Diabetes Care. 2014 Sep;37(9):2647-59.

Conclusion

- **What goes around?**

→ **Intensive early glycemic control**

- **What comes around?**

→ **Reduced diabetic complication risk**

Glimepiride is the 3rd class SU with low side effect. It can provide intensive glucose control with relatively safer (and known) profile as a option of add-on therapy

Thank You
for your attention!