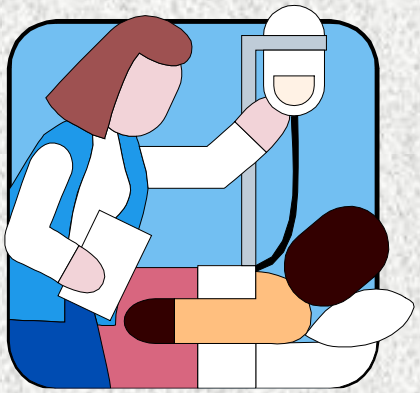
Does Sulfonylurea *Dose-Responsiveness* and/or its *Combination with Metformin* Correlate with Excess Diabetic Cardiovascular Mortality?

?Influence of "Hypoglycemic-Strategy"



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BACKGROUND:- **Studies[1,2,3,4] have implicated sulfonylureas with increased mortality.**

(1)The UGDP[1] showed an increase in cardiovascular deaths of +806 ± 353 per 10,000 tolbutamide-treated patients without a significant increase in total mortality. However, it utilized a high, fixed dose of tolbutamide (4g/day.)

2) The UKPDS[2] data is too confounded to draw reliable conclusions about sulfonylurea-specific toxicity - except in terms of the *initial prescription*. Limited to that perspective, *initial prescription* for sulfonylureas fared no worse than that for dietary therapy or insulin.

3) The study by Garratt *et al*[3] at the Mayo Clinic, limited to diabetic patients undergoing angioplasty for acute myocardial infarction, comprised of 67 patients on sulfonylureas and 118 controls. It was also retrospective and subject to selection bias. Nevertheless, the inpatient mortality was 24% in the sulfonylurea group and 11% in the controls (p =0.02). The relative risk of mortality using the Cox Propotional hazards model was 2.77-fold in the sulfonylurea group. The excess risk of mortality was 1290 ±595 [95% CI 120 to 2450 deaths] per 10,000 patients.

4) The Campbell[4] review of "sulfonylurea-induced hypoglycemia" culled from the world literature 1940-1982 showed 670 reported cases with 56 deaths. Data from Swedish Adverse Drug Reaction Advisory Committee (SADRAC) from 1972 to mid 1981 showed 51 cases of glyburide-induced hypoglycemia and Campbell reviewed an additional 6 cases. The median age was 75 years old and 21% were 85 years old or older. The mean daily dose of glyburide was 10 mg (perhaps the daily equivalent to 2g tolbutamide.) Twenty-four patients had protracted hypoglycemia of 12-72 hours duration and 10 died. The mortality risk for glyburide-induced hypoglycemia was calculated to be 1,754 [95% CI 875 to 2990 deaths] per 10,000 afflicted patients or 19 [95% CI 7.22 to 30.7] per 10,000 treated patients or 3.32 [95% CI 0.126 to 0.539] deaths per 100,000 patient-years.)

METHODOLOGY - *Review and summarize available clinical trial data to answer*:-

1) Is there any data available that either sulfonylureas or sulfonylurea-metformin combination or both might contribute to excess total or cardiovascular mortality? If so, might hypoglycemia be a contributing factor?

2) Are sulfonylureas associated with hypoglycemia? When added to metformin, is there a significant increase in the risk of hypoglycemia? What is the risk of hypoglycemia with metformin monotherapy?

3) Do sulfonylureas manifest the appearance of dose-responsiveness in terms of total or cardiovascular mortality across any controlled studies?

4) Is there any single agent within any other study which significantly decreases cardiovascular or total mortality as monotherapy?

5) In that study, is metformin - this otherwise safe and effective agent - added to *maximum-doses of sulfonylureas* specifically in order to further tighten glycemic control?

6) Is there a significant risk of hypoglycemia when control is tightened?

7) What is the impact upon cardiovascular or total mortality of this metformin + sulfonylurea combination (specifically administered to test the effect of even tighter control?)

8) Does viewing total and cardiovascular excess mortality by "hypoglycemic-strategy" - where Stratum 1 represents "treat but *avoid hypoglycemia*" and Stratum 2 "treat to *achieve tighter control*" - shed any additional light?

9) Are there any interactions which could be viewed as "treatment-by-*strategy*?

10) Are there any trials in which tightened control [and increased hypoglycemic-strategy] improves survival? If so, under which circumstances?

11) Overall, what impact does just metformin+SFU combination Rx have upon survival?

1a) Is there any data available that either sulfonylureas or sulfonylurea-metformin combination or both might contribute to excess total or cardiovascular mortality?

Malmo Surveillance Study[7]

Odds Ratios for Mortality of Combination Rx versus SFU Monotherapy

Cause of mortality	Multiple causes OR (95% CI)	Underlying cause OR (95% CI)
Ischemic Heart Disease	1.82 (1.31 to 2.53)	1.73 (1.17 to 2.55)
Stroke	2.06 (1.23 to 3.45)	2.33 (1.17 to 4.63)
Other causes		1.39 (0.95 to 2.02)
Non IHD, non-stroke	1.17 (0.73 to 1.89)	
Overall	1.63 (1.27 to 2.09)	1.63 (1.27 to 2.09)

sulfonylurea monotherapy	n=741 with 195 missing data
sulfonylurea + metformin	n=169 with 30 missing data

Bezafibrate Infarct Prevention Trial[8]

"The study sample comprised 11,440 ***patients with a previous myocardial infarction and/or stable anginal syndrome***, aged 45-74 years, who were screened, but not included in the Bezafibrate Infarction Prevention study. Among them, 9,045 were nondiabetics and **2,395 diabetics**. The diabetic patients were divided into four groups on the basis of their therapeutic regimen at screening….All NIDDM groups were similar with regard to age, gender, hypertension, smoking, heart failure, angina and prior myocardial infarction. Crude mortality rate was lower in the nondiabetic group (11.21 vs. 21.8%; $p < 0.001$)."

	diet alone	sulfonylureas	metformin	sulfonylurea and metformin
n	990	1,041	78	266
All-cause Mortality	18.5%	22.5%	25.6%	31.6%
Excess (all-cause) mortality	0	+4.0±1.79% 0 -	+7.16±5.10% - 0	+13.1±3.11% +9.10±3.13% +5.94±5.71%
(95%CI)	-	(+0.49 to +7.5%) - -	(-2.83 to +17.81%) - -	(+7.01 to +19.2%) (+2.97 to +15.2%) (-5.25 to +17.1%)

US Clinical Trials for Metformin[5]

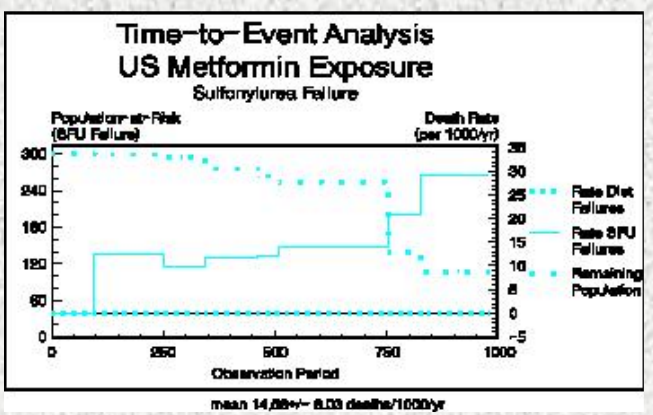
The New England Journal of Medicine

The data submitted for the approval of metformin for use in the United States were from two 29-week clinical trials involving patients with non-insulin-dependent diabetes mellitus (Type 2 diabetes), reported by DeFronzo et al. (31Aug 1996), (1) and one 2-year, unreported, open-enrollment study. (2) One of the clinical trials was placebo-controlled, with 143 patients assigned to receive metformin and 146 to receive placebo. In the second trial, 210 patients were assigned to monotherapy with metformin, 213 to metformin plus glyburide, and 209 to glyburide alone.

Six hundred two of these patients chose to enroll in the open study to receive metformin with or without a sulfonylurea drug: 75 patients from the placebo group, 142 from the glyburide group, 217 from the metformin groups, and 168 from the metformin-plus-glyburide group. With the open study, the total duration of metformin treatment during all U.S. open and controlled studies was increased to 1136 patient-years.

There was one death in the controlled trials, and there were six additional deaths in the open study. All seven deaths occurred among the patients who had initially been assigned to metformin therapy; no deaths occurred among those initially assigned to glyburide or placebo. A comparison of the survival distributions in the treatment groups by the log-rank test revealed a significant difference from the expected distribution of 4.4 deaths in the metformin group and 2.6 deaths in the control group (P = 0.04). Moreover, all seven deaths occurred among 423 patients (1.7 percent) randomly assigned to therapy with metformin in the second study. The shortest duration of treatment resulting in a death was 97 days, and the longest was 825 days (mean [±SD], 463±242 days).

Time-to-Event Analysis in the US Pivotal Trial Data for Metformin[6].

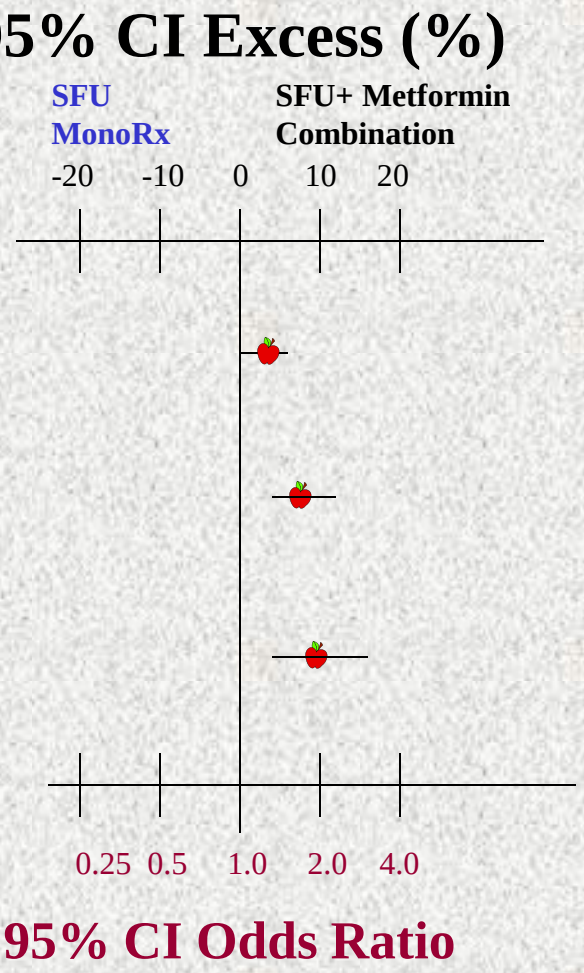


The *sulfonylurea-failure excess risk was 1.65% with a 99% CI of 0.0545 to 3.26%.* A Kaplan-Meier analysis revealed that the event rate was enriched at the end of observation to its maximum of 29.22 deaths/ 1000/year. [Over the entire observation period the mortality rate averaged 14.58 ± 8.03 deaths/ 1000/year.] Considering that 1 death was due to cancer and another to suicide, then excluding these deaths from analysis reveals a mean treatment difference of 1.17% with a 95% CI of 0.151% to 2.20%

Total Mortality of Metformin-SFU Combination vs SFU Alone in Different Studies[6,7,8]

Study	TM † Excess(Rate)
US Pivotal Data[6]	**1.17%**
Malmo Surveillance[7]	**1.63***
BIPS Screening[8]	**9.1%**

*Odds Ratio



1b) If so, might hypoglycemia be a contributing factor to this increase in mortality?

?Hypoglycemic Biases[6,7]

There was a distinct selection bias seen in the US open-enrollment[6] with more of the poorly controlled patients from the control (glyburide) group entering the study [and more of the better controlled metformin patients electing to continue therapy.]

Did Glyburide Randomized Patient Enter Open Enrollment?	n	HbA1c
No	68	7.10
Yes	142	9.47
P	-	P<0.01
Difference (95%CI)	74	+2.37±0.45 (+1.47 to +3.27)

Against the notion of hypoglycemic predisposition **is the Malmo study[7] from 2 counties in Sweden prompted by the excess mortality found in the UKPDS early randomization study [of sulfonylurea patients to combination with metformin.] In this study the group analyzed on metformin plus sulfonylurea combination had a hemoglobin A1c of 8.3% (n=169 with 30 missing data) as opposed to the sulfonylurea group who had a hemoglobin A1c of 7.3% (n=741 with 195 missing data.) The average fasting sugars of the groups were 185 and 158 mg/dl, respectively.**

2) Are sulfonylureas associated with hypoglycemia? When added to them, does metformin significantly increase that risk of hypoglycemia? What is metformin's inherent "*hypoglycemic potential*" when administered as *monotherapy*?

Risks of Sulfonylurea-Induced Hypoglycemia

According to Campbell's review of published data[4] as well as surveillance information from the Swedish Adverse Drug Reaction Advisory Committee (SADRAC) for 1972 to mid 1981:

...the mortality risk for glyburide-induced hypoglycemia was calculated to be 1,754 [95% CI 875 to 2990] deaths per 10,000 afflicted patients or 19 [95% CI 7.22 to 30.7] deaths per 10,000 treated patients or 3.32 [95% CI 0.126 to 0.539] deaths per 100,000 patient-years.)

US Clinical Trials - "Hypoglycemic" Events in Patients on SFU-Metformin[6]

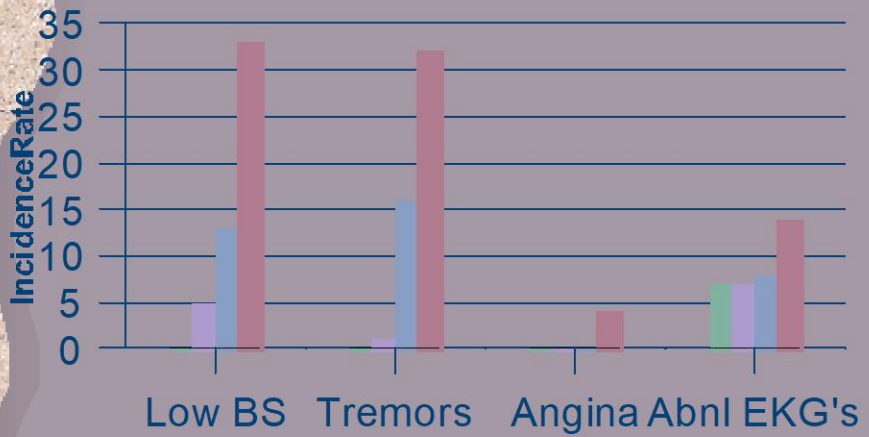
There was a highly significant increase in hypoglycemia manifested by patients taking combined metformin-sulfonylurea therapy in all controlled trials submitted in this NDA. Combined therapy had an 14.5% excess in hypoglycemia *when compared with glyburide monotherapy controls* for which the 99% CI was 7 to 22.

AE/IME	*total*	*mild*	*moderate*	*severe*
Diaphoresis	15	6	8	1
Glucose_blood_decreased	6	4	2	0
Hunger_abnormal	1	0	0	1
Hypoglycemia	124	80	42	2
Hypoglycemic_reaction	24	14	0	0
Irritability	1	0	1	0
Jitteriness	1	0	1	0
Night_sweat	4	3	1	0
Shakiness	10	8	2	0
Sweating_increased	17	10	7	0
Tension_nervous	14	3	10	1
Tingling	7	6	1	0
Tremor	25	17	8	0
Tremulousness	3	2	1	0
TOTAL	252	153	94	5

Patients over age 65 (n=69) vs those under age 65 (n=495) reported more:

- **AE's/IME's (52% vs 43%)**
- **asthenia (22% vs 11%)**
- **hypoglycemia (12% vs 7%)**

Incidence of Hypoglycemia (among other ADR's) in US Pivotal Trials[6]



Placebo	0	0	0	7
Metformin	5	1	0	7
Glyburide	13	16	0	8
Combinati	33	32	4	14

3) Do sulfonylureas manifest the appearance of dose-responsiveness in terms of total or cardiovascular mortality across any controlled studies?

Total and Cardiovascular Mortality in Low "*Hypoglycemic-Strategy*" Trials[9,10,11]

Table 7 Low Hypo-Glycemic Potential Low-Dose Tolbutamide <=1.5g/day	**Controls**			**Treated**		
Average Observation Period 10.48 years	n	CV Deaths	Total Deaths	n	CV Deaths	Total Deaths
Bedford	125	19	27	123	16	25
Serafinerlasarettet	83	16	16	95	13	13
Malmohus	98	30	68	49	7	24
Totals	**306**	**65**	**111**	**267**	**36**	**62**

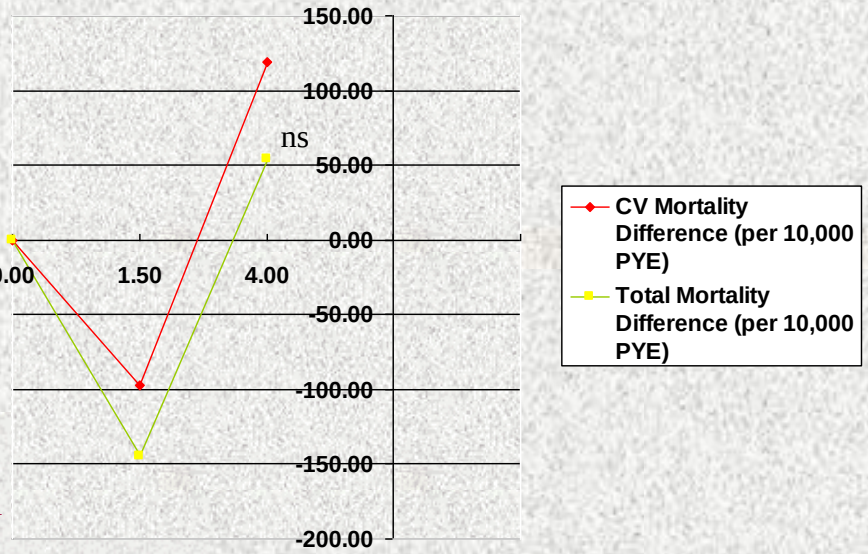
CV mortality difference = -776 ± 314/10,000 patients
95%CI (-161 to –1390) /10,000 patients
TM difference = -1310 ± 377/10,000 patients
95%CI (-566 to -2040) /10,000 patients

Total and Cardiovascular Mortality in High "*Hypoglycemic-Potential*" Trials[1]

Table 8 High Hypo-Glycemic Potential High-Dose Tolbutamide >=4g/day	**Controls**			**Treated**		
Study duration Average 8.1 years	N	CV Deaths	Total Deaths	n	CV Deaths	Total Deaths
UGDP	64	3	7	204	26	30

CV mortality difference = +806 ± 353/10,000 patients
95%CI (+115 to +1500) /10,000 patients
TM difference = +377 ± 462/10,000 patients
95%CI (-529 to +1280) /10,000 patients

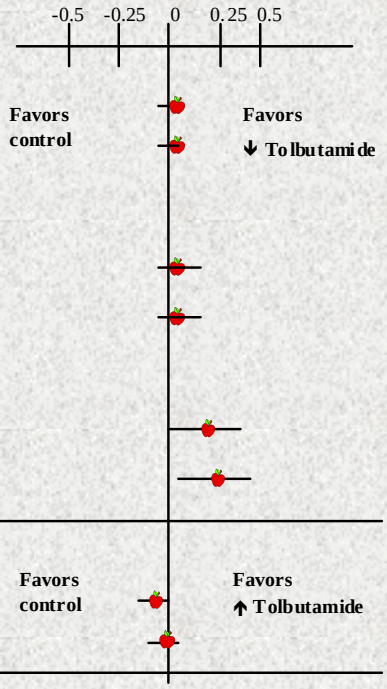
Tolbutamide Mortality Dose-Responsiveness



Total and Cardiovascular Excess Mortality for Low and High Doses of Tolbutamide[1,9,10,11]

95% CI

Study	max dose	duration	control	↓tolbutamide
Bedford[9]	1.0g/d*	8	125	123
CV †Rate			13.0	20.3
TM †Rate			15.2	21.6
Serafinerlasarettet[10]	1.0g/d*	3	83	95
CV † Rate			19.3	13.7
TM † Rate			19 3	13.7
Malmohus County[11]	1.5g/d*	20	98	49
CV † Rate			30.6	14.3
TM † Rate			69.4	48.7
UGDP	4.0g/d**	7	64	204
CV † Rate			3	26
TM † Rate			26	30
			control	↑tolbutamide

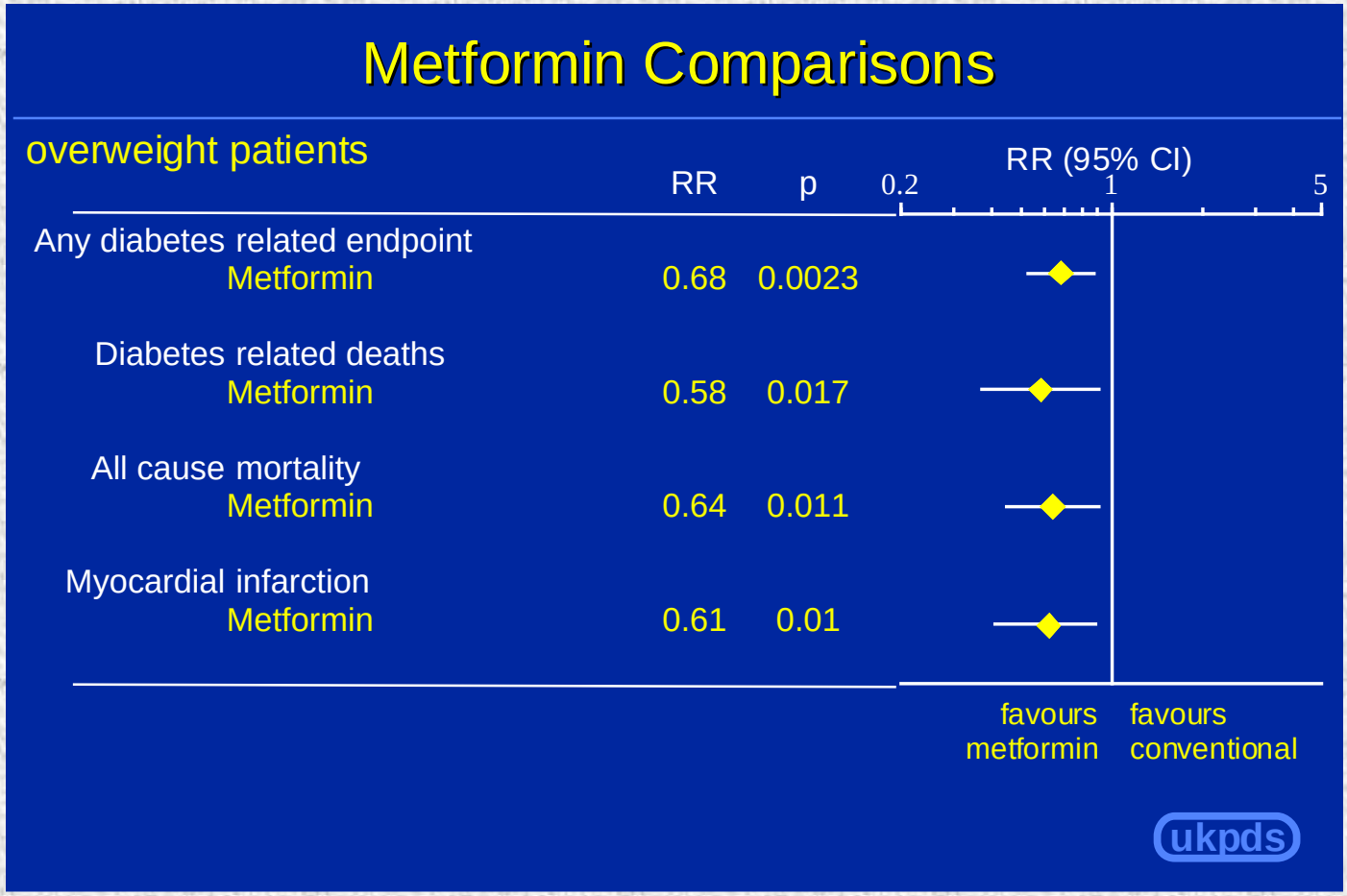


*titrated to max dose without hypoglycemia

**fixed dose

4) Is there any single agent within any other study in actual type 2 diabetes patients which significantly decreases cardiovascular or total mortality as monotherapy?

Total and Cardiovascular Mortality in UKPDS Low "*Hypoglycemic-Strategy*"[12]



Total and Cardiovascular Mortality in UKPDS Low "*Hypoglycemic-Strategy*"[12]

Table 9 Low Hypo-Glycemic Potential Metformin vs Conventional Rx	**Conventional Rx**			**Metformin**		
	N	CV Deaths	Total Deaths	n	CV Deaths	Total Deaths
UKPDS 34	411	53	89	342	26	50

CV mortality difference = -529 ± 219/10,000 patients
95%CI (-100 to –958) /10,000 patients
TM difference = -703 ± 279/10,000 patients
95%CI (-157 to -1250) /10,000 patients

5) In that study, is this same agent, metformin, added to *maximum-doses of sulfonylureas* specifically to further tighten glycemic control?

“If tight control is good, then even tighter control is better….”[2]

Sulphonylurea plus Metformin

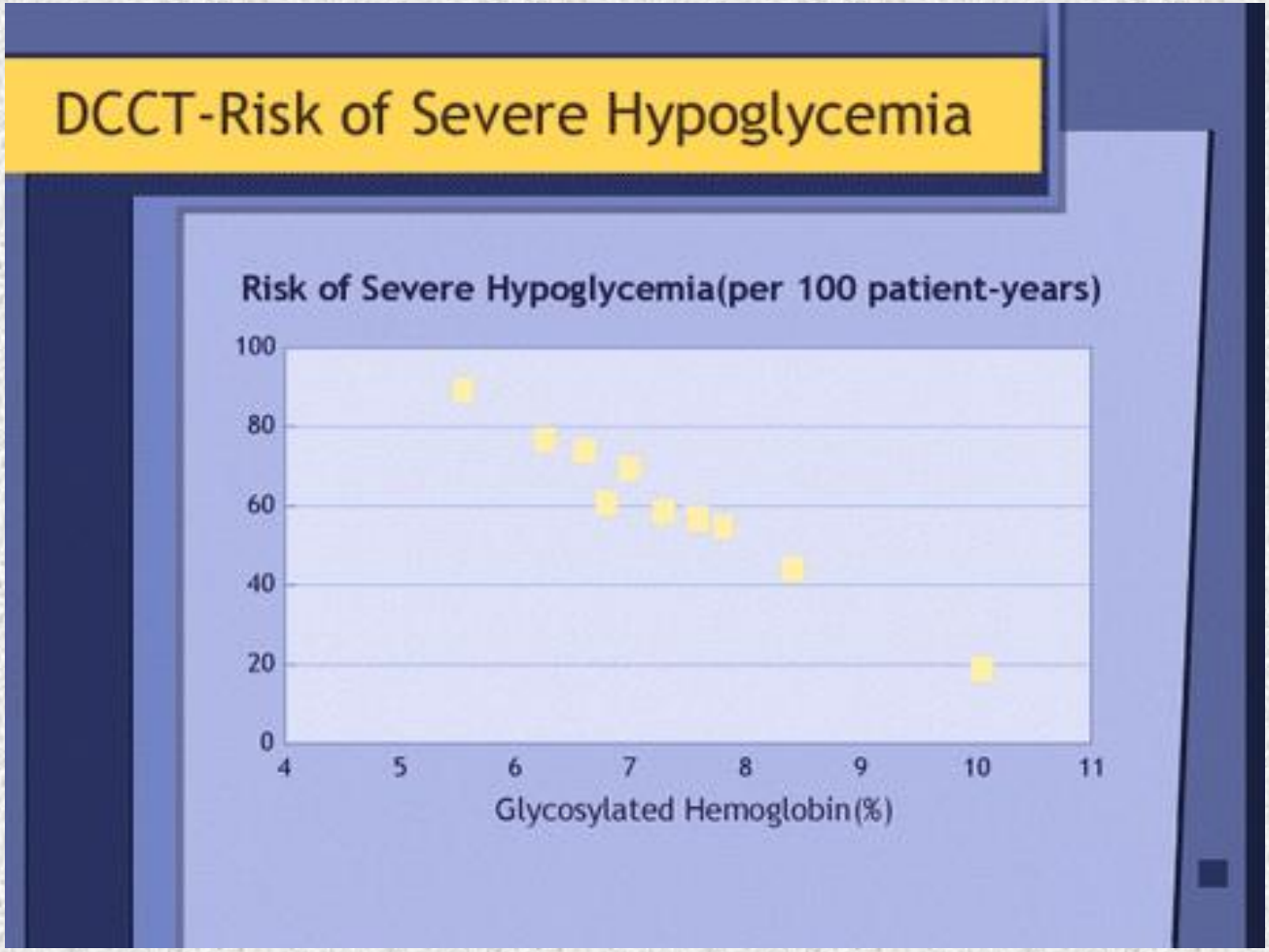
- patients primarily randomised to intensive therapy with sulphonylurea were not given additional metformin until their fpg was >15 mmol/L or they developed hyperglycaemic symptoms

- in view of the progressive hyperglycaemia in these patients, a protocol modification was made to secondarily randomise the subset of patients who were on maximum sulphonylurea therapy and had fpg >6 mmol/L to earlier addition of metformin

ukpds

6) Is there a significant risk of hypoglycemia when control is tightened?

Very ***Tight Control*** and Risk of ***Severe*** Hypoglycemia



7) What is the effect upon cardiovascular or total mortality of this metformin + SFU combination *[specifically administered to test the impact of even tighter control*?]

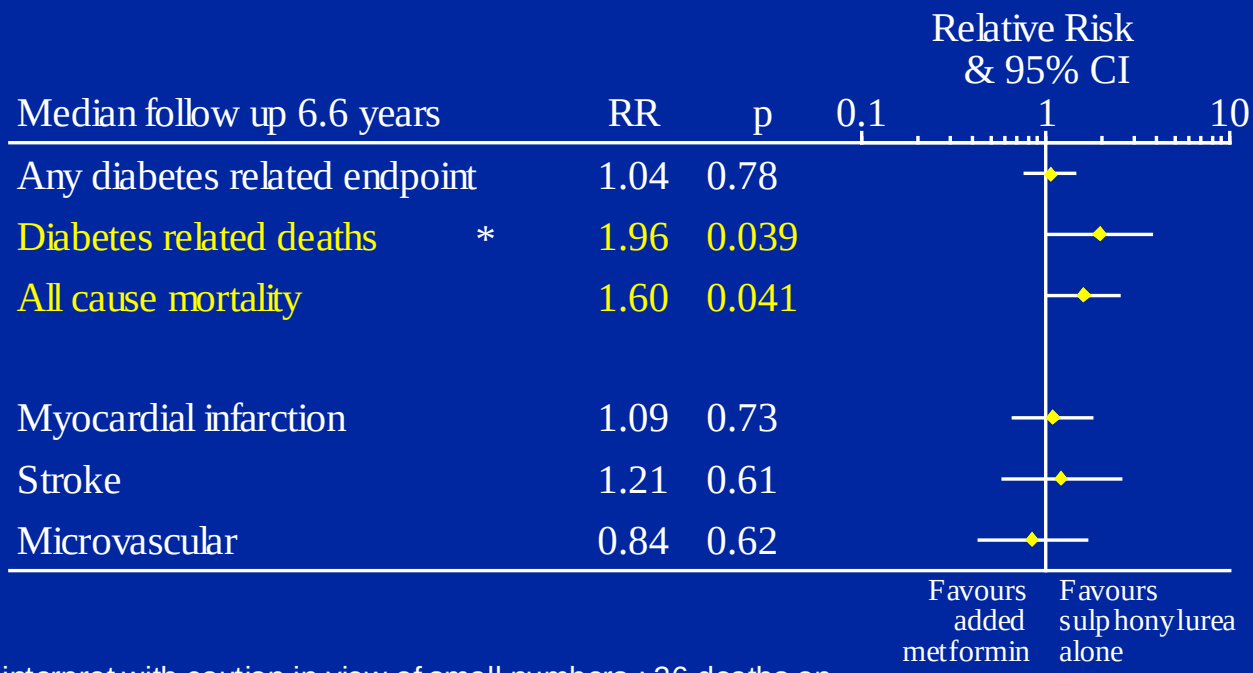
Total and Cardiovascular Mortality in UKPDS High "*Hypoglycemic-Strategy*"[2]

Table 10 **High Hypo-Glycemic Potential** SFU vs Combination SFU + metformin	**SFU**			**SFU + metformin Combination Rx**		
	n	CV Deaths	Total Deaths	n	CV Deaths	Total Deaths
UKPDS 34	269	13	31	268	25	47

CV mortality difference = +450 ± 221/10,000 patients
95%CI (+17 to +882) /10,000 patients
TM difference = +601 ± 303/10,000 patients
95%CI (+7 to +1200) /10,000 patients

Total and Cardiovascular Mortality in UKPDS High "*Hypoglycemic-Strategy*"[2]

Aggregate Endpoints



* interpret with caution in view of small numbers : 26 deaths on sulphonylurea plus metformin versus 14 deaths on sulphonylurea alone

ukpds

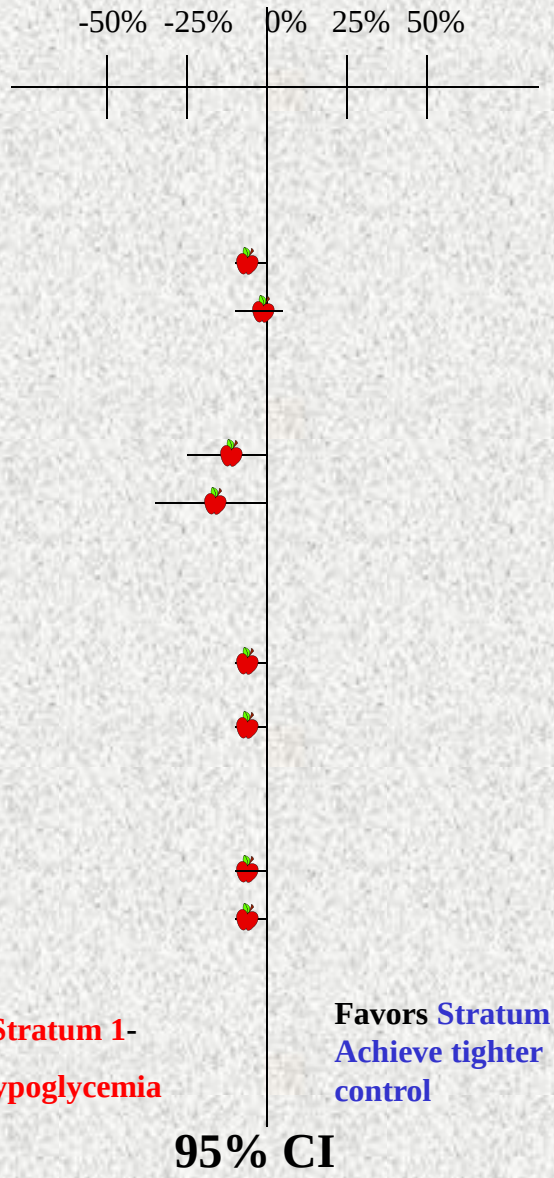
8) Does viewing total and cardiovascular excess mortality by "hypoglycemic-strategy" - where Stratum 1 represents "treat but *avoid hypoglycemia*" and Stratum 2 "treat to *achieve tighter control*" - shed any additional light?

Total and Cardiovascular Excess Mortality by Strata

Stratum 1 - Rx to avoid hypoglycemia

Stratum 2 -Rx to achieve tighter control [1,2,11,12]

Study	duration	Stratum 1	Stratum 2
UGDP[1]	7	64	204
CV † Rate		4.7	10.9
TM † Rate		12.7	14.7 (ns)
Malmohus County[11]	20	98	49
CV † Rate		30.6	14.3
TM † Rate		69.4	48.7
UKPDS Obesity[12]	9	342	411
CV † Rate		7.6	12.9
TM † Rate		14.6	21.7
UKPDS Tight Control[2]	9	269	268
CV † Rate		4.8	9.3
TM † Rate		11.5	17.5



9) Are there any treatment-by-*strategy* Interactions?

Treatment-by-*Strategy* Interactions[1,2,8,9,10]

•The high *hypoglycemic-strategy* Metformin + Sulfonylurea stratum showed a highly significant **cardiovascular mortality** excess over the low *hypoglycemic strategy Metformin monotherapy* stratum of +979 ± 12 deaths per 10,000 treated patients or +99 ± 1.21 deaths/10,000 patient-years.

The high *hypoglycemic-strategyl* Metformin + Sulfonylurea stratum showed a highly significant **all-cause mortality** excess over the low *hypoglycemic-strategy Metformin monotherapy* stratum of +1300 ± 16 deaths per 10,000 treated patients or +131.5 ± 1.60 deaths/10,000 patient-years.

These data appear quite robust in that the cardiovascular mortality difference in the tolbutamide studies across (different hypoglycemic strategies) of +1578 ± 24 deaths per 10,000 treated patients [over an average of 9.73 years] compares favorably to the +979 ± 12 deaths per 10,000 treated patients [over an average of 10 years] seen across strata in the the UKPDS analyses. Likewise, the all-cause mortality difference in the tolbutamide studies across (different hypoglycemic strategies) of +1687 ± 3 deaths per 10,000 treated patients [over an average of 9.73 years] compares favorably to the +1300 ± 16 deaths per 10,000 treated patients [over an average of 10 years] seen across strata in the the UKPDS analyses.] **(This represents an excess CV mortality of about 1%/year and excess total mortality of about 1.3%/year)**

Are there any conditions in which tightened control [and increased hypoglycemic-strategy] improves survival?

Q:-Does Tightening *Glycemic Control* Over the <u>Short</u>-Term in Any Setting Have A Long-Term Impact Upon Cardiovascular Disease or Mortality?

- A:- Well, only by insulin and only in the setting of acute MI…. (DIGAMI)

Glycometabolic State at Admission: Important Risk Marker of Mortality in Conventionally Treated Patients With Diabetes Mellitus and Acute Myocardial Infarction (*Circulation.* 1999;99:2626-2632.)

Long-Term Results From the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study

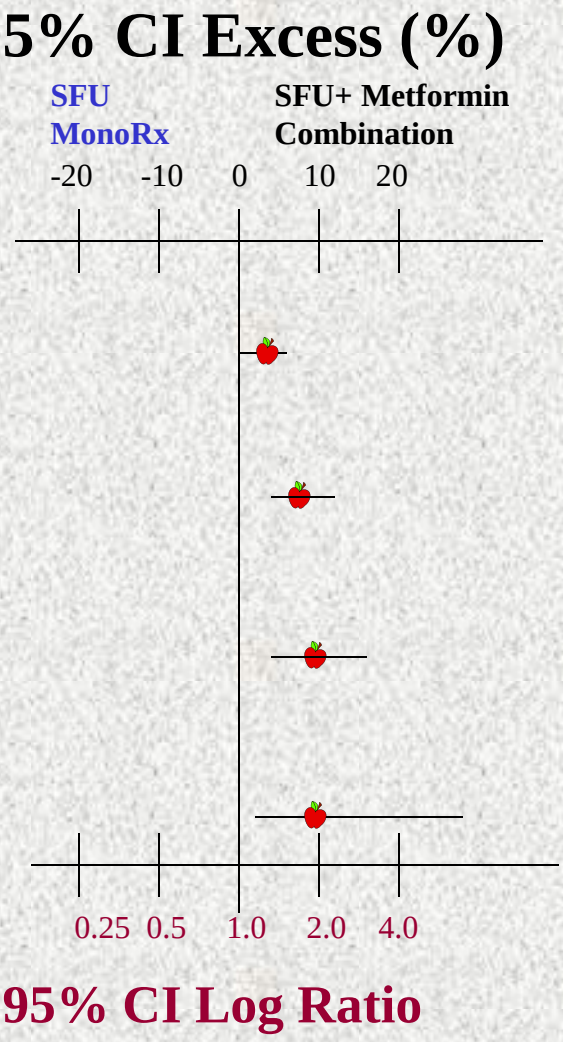
Klas Malmberg, MD, PhD; Anna Norhammar, MD; Hans Wedel, PhD; Lars Rydén, MD, PhD

"***Mortality in diabetic patients with AMI is predicted by age, previous heart failure, and severity of the glycometabolic state at admission but not by conventional risk factors or sex. <u>Intensive insulin treatment reduced long-term mortality despite high admission blood glucose and Hb A_{Ic}</u>.***"

11) Overall, what impact does just the metformin+SFU combination, *per se,* have upon survival?

Total Mortality of Metformin-SFU Combination vs SFU Alone *Across* Different Studies

Study	TM † Excess(Rate)
US Pivotal Data[6]	**1.17%**
Malmo Surveillance[7]	**1.63***
BIPS Screening[8]	**9.1%**
UKPDS[2]	**1.96****



*Odds Ratio

**Relative Risk

CONCLUSIONS:- Low-dose tolbutamide therapy in IGT patients in the Malmohus County study showed significantly improved 20 year cardiovascular survival, whereas high dose tolbutamide in diabetic patients in the UGDP showed significantly increased 7 year cardiovascular mortality.

US clinical trials submitted to FDA for metformin initial regulatory approval showed significantly increased mortality of patients randomized to metformin on combination metformin plus sulfonylureas.

Obervational data from Malmo show increased mortality in diabetic patients taking combination metformin plus sulfonylureas. Data from the Bezafibrate Infarction Prevention Trial show an increased cardiovascular mortality from patients on combination metformin plus sulfonylureas.

Initial randomization to (low hypoglycemic-potential) metformin monotherapy significantly improved cardiovascular survival in the UKPDS. Initial randomization to (high hypoglycemic-potential) metformin + sulfonylurea combination therapy significantly increased cardiovascular mortality in the same UKPDS.

Long-term pharmacologic *strategies* to very tightly control type 2 diabetes with (1) high-dose sulfonylureas or (2) metformin + sulfonylurea combination are ineffective in improving survival. To the contrary, they both probably contribute to excess morbidity and mortality (of ~1%/year.)

The NIH ACCORD trial -Prevention of Cardiovascular Disease in Diabetes Mellitus ("Action to Control Cardiovascular Risk in Diabetes" - currently underway to test the "extremely tight control hypothesis" should also therefore be 2-tailed and the informed consent so revised.

References

1.University Group Diabetes Program, A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes Diabetes (1975) 24 (Suppl 1):65-184

2. Turner R. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet (1998) Loc. Cit.[LancetOnline]

3. Garratt KN, Brady PA, Hassinger NL, D Grill DE, Terzic A and Holmes DR Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction. J Am Coll Cardiol (1999) 33:119-124

4. Campbell IW. Metformin and the sulfonylureas: the comparative risk. Horm Metab Res (1985) Suppl 15:105-11

5. Innerfield R.J. Metformin-Associated Mortality in U.S. Studies. New Eng J Med (1996) 334:1611-1613

6. Innerfield RJ. Medical officer safety review of an NDA submission. Metformin. (NDA 20-357.) (On file at FDA, Bethesda, Md., May 1994 [FOI].)

7. Olsson J., Lindberg G., Gottsäter M., Lindwall K., Sjöstrand Å., Tisell A., .Melander A. Increased mortality in Type II diabetic patients using sulphonylurea and metformin in combination: a population-based observational study Diabetologia (2000) 43:558-560

8. Fisman EZ, Tenenbaum A, Benderly M, Goldbourt U, Behar S, Motro Mn . Antihyperglycemic treatment in diabetics with coronary disease: increased metformin-associated mortality over a 5-year follow-up. Cardiology (1999) 91(3):195-202

9. Jarrett RJ, McCartney P, Keen H; The Bedford Survey:Ten year Mortality rates in Newly Diagnosed Diabetics, Borderline Diabetics and Normoglycemic controls and Risk Indices for Coronary Heart disease in Borderline Diabetics Diabetologia (1982) 22:79-84

10. Paasikivi J. Long-term tolbutamide treatment after myocardial infarction. A clinical and biochemical study of 178 patients without overt diabetes. Acta Med Scand Suppl 1970;507:1-82

11. Knowler WC, Sartor G, Melander A, Schersten B, Glucose tolerance and mortality, including a substudy of tolbutamide treatment. *Diabetologia* (1997) **40**:680-686

12. UK Prospective Diabetes Study (UKPDS) Group, Effect of Intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) *Lancet* (1998) **352**:854-865

13. Klas Malmberg, MD, PhD; Anna Norhammar, MD; Hans Wedel, PhD; Lars Rydén, MD, PhD Glycometabolic State at Admission: Important Risk Marker of Mortality in Conventionally Treated Patients With Diabetes Mellitus and Acute Myocardial Infarction (*Circulation.* 1999;99:2626-2632.)