ERBP Guideline on management of diabetics with advanced CKD

ERBP Mission

improve the outcome of patients with kidney disease in a sustainable way, through enhancing the accessibility of knowledge on patient care, in a format that stimulates its use in clinical practice.

Outline

- Is intensive glycemic control as measured by HbA1C advantageous in diabetic patients with CKD 3b-5d?
- What oral agent should be preferred as first line agent in patients with CKD 3b-5d with impaired glucose tolerance/diabetes

Some of the factors that influence HbA1c and its measurement*. Adapted from Gallagher et al (*24*)

1. Erythropoiesis Increased HbA1c: iron, vitamin B12 deficiency, decreased erythropoiesis. Decreased HbA1c: administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease.
2. Altered Haemoglobin Genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF, methaemoglobin, may increase or decrease HbA1c.
3. Glycation Increased HbA1c: alcoholism, chronic renal failure, decreased intra-erythrocyte pH. Decreased HbA1c: aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH. Variable HbA1c: genetic determinants.
4. Erythrocyte destruction Increased HbA1c: increased erythrocyte life span: Splenectomy. Decreased A1c: decreased erythrocyte life span: haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone.
5. Assays Increased HbA1c: hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use. Variable HbA1c: haemoglobinopathies. Decreased HbA1c: hypertriglyceridaemia.

Adjusted mortality rate in ESRD and DM: HbA1c

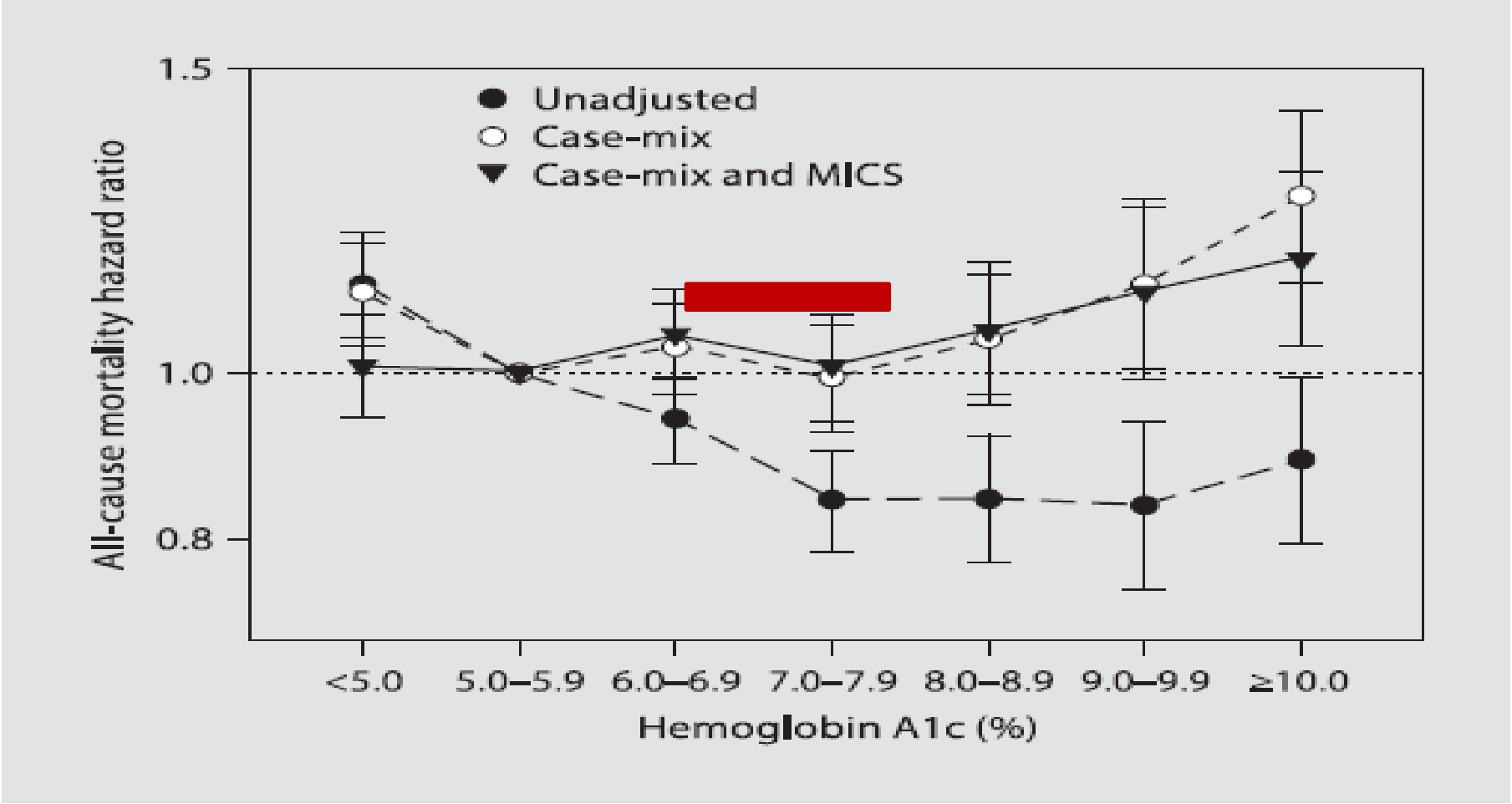


Fig. 5. Mortality rate adjusted for case mix and malnutrition-inflammation complex syndrome (MICS).

Adjusted mortality rate in ESRD and DM: HbA1c

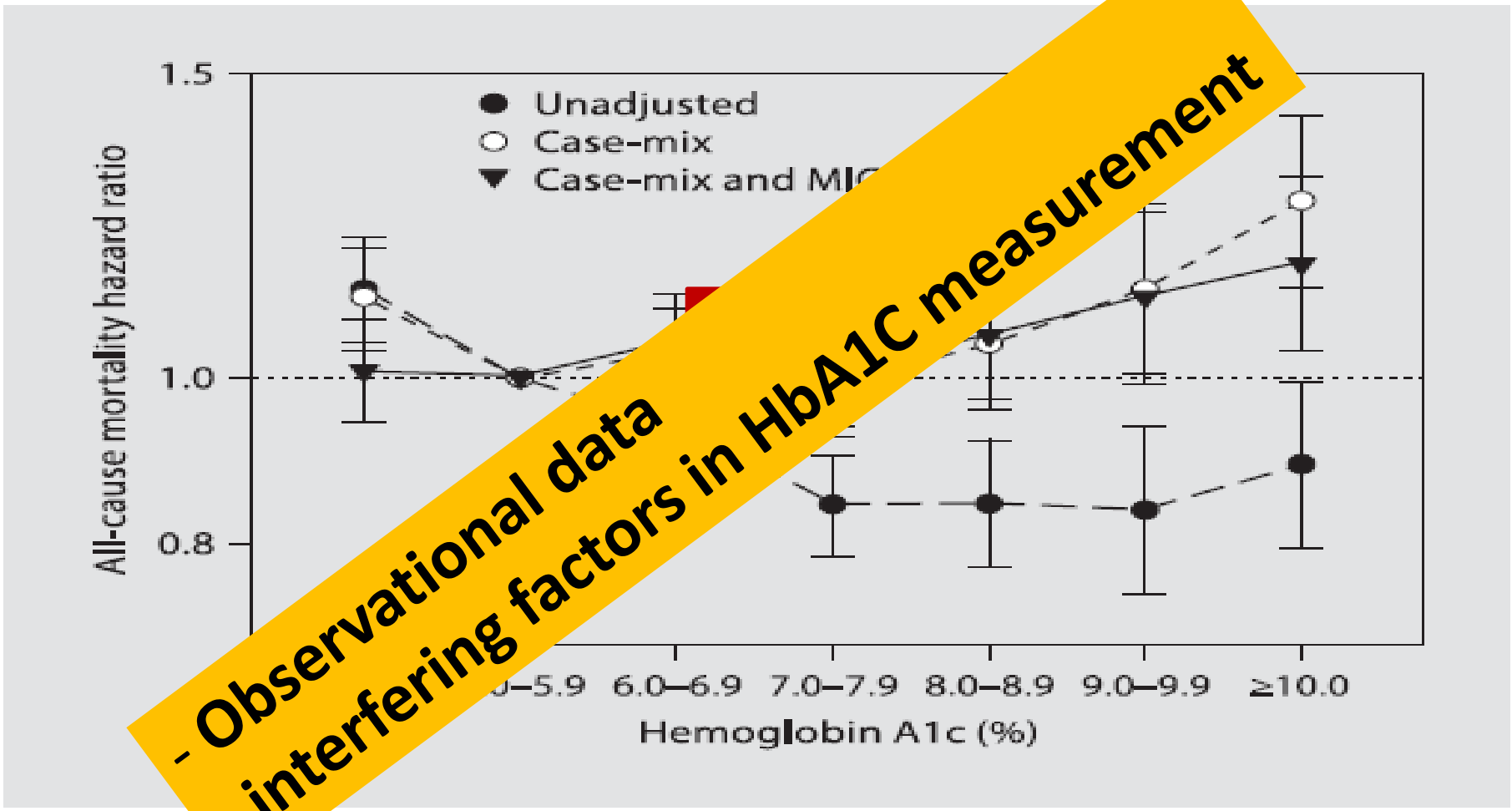


Fig. 5. Mortality rate adjusted for case mix and malnutrition-inflammation complex syndrome (MICS).

Considerations in advanced CKD patients

Increased risk of hypoglycemia

- **Decreasing renal mass leads to impaired gluconeogenesis and glycenolysis**
- **Decreased renal clearance of insulin**
- **Decreased clearance of hypoglycemic drugs**
- **comorbidity and co-medication**

Increasing impaired glucose tolerance

- **Peripheral insulin resistance in CKD from counter-regulatory hormones, electrolyte abnormalities, uremic acidosis, and accumulation of uremic toxins**

Shortened life expectancy

Increased cardiovascular risk +++

Cochrane review Hemmingsen et al, BMJ, 2011

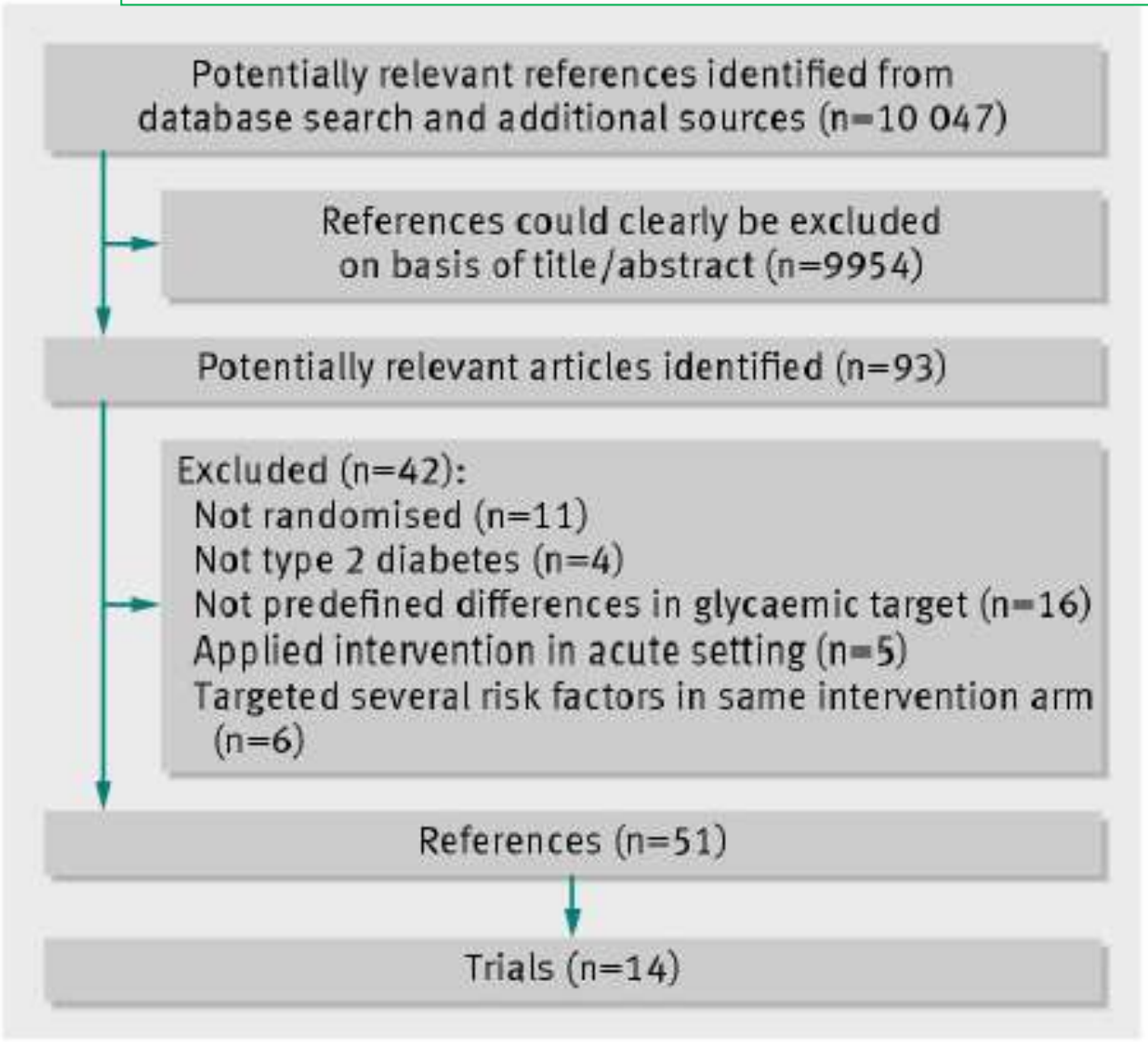


Fig 1 Flow diagram of identification of randomised trials for inclusion

Cochrane review Hemmingsen et al, BMJ, 2011

Study	No of events/total: Intensive control	No of events/total: Conventional control	Risk ratio (Mantel-Haenszel, random) (95% CI)	Weight (%)	Risk ratio (Mantel-Haenszel, random) (95% CI)
UGDP 1978	52/204	52/210		8.6	1.03 (0.74 to 1.44)
Service 1983	0/10	0/10		0.0	Not estimable
VA CSDM 1995	5/75	5/78		0.8	1.04 (0.31 to 3.45)
Jaber 1996	0/23	0/22		0.0	Not estimable
UKPDS 1998	539/3071	213/1138		25.9	0.94 (0.81 to 1.08)
Kumamoto 2000	3/55	6/55		0.6	0.50 (0.13 to 1.90)
Bagg 2001	0/21	0/22		0.0	Not estimable
ACCORD 2008	257/5128	203/5123		20.4	1.26 (1.06 to 1.51)
ADVANCE 2008	498/5571	533/5569		30.7	0.93 (0.83 to 1.05)
REMBO 2008	4/41	4/40		0.7	0.98 (0.26 to 3.64)
IDA 2009	0/51	0/51		0.0	Not estimable
VADT 2009	102/892	95/899		12.3	1.08 (0.83 to 1.41)
Total (95% CI)	1460/15 142	1111/13 217		100.0	1.02 (0.91 to 1.13)

Test for heterogeneity: $\tau^2=0.01$, $\chi^2=10.07$, df=7, P=0.18, $I^2=30\%$

Test for overall effect: z=0.33, P=0.74

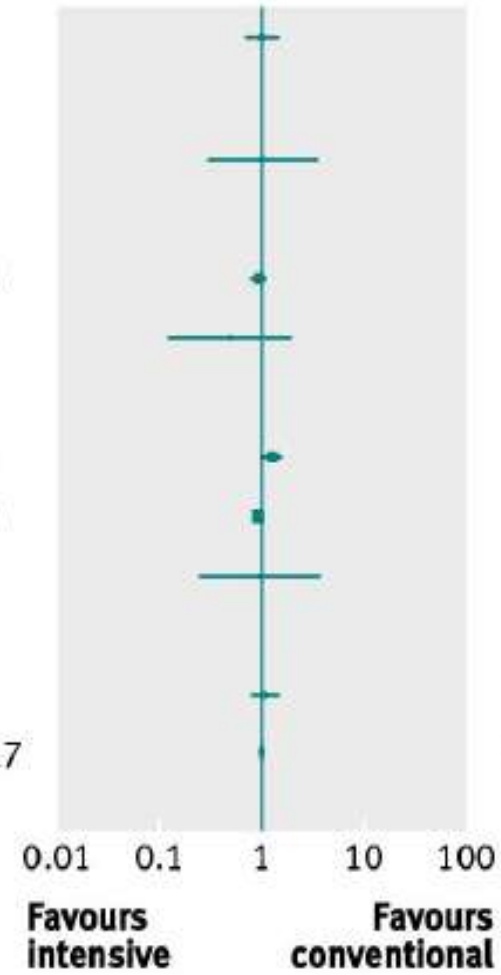


Fig 2 Forest plot for all cause mortality

Cochrane review Hemmingsen et al, BMJ, 2011

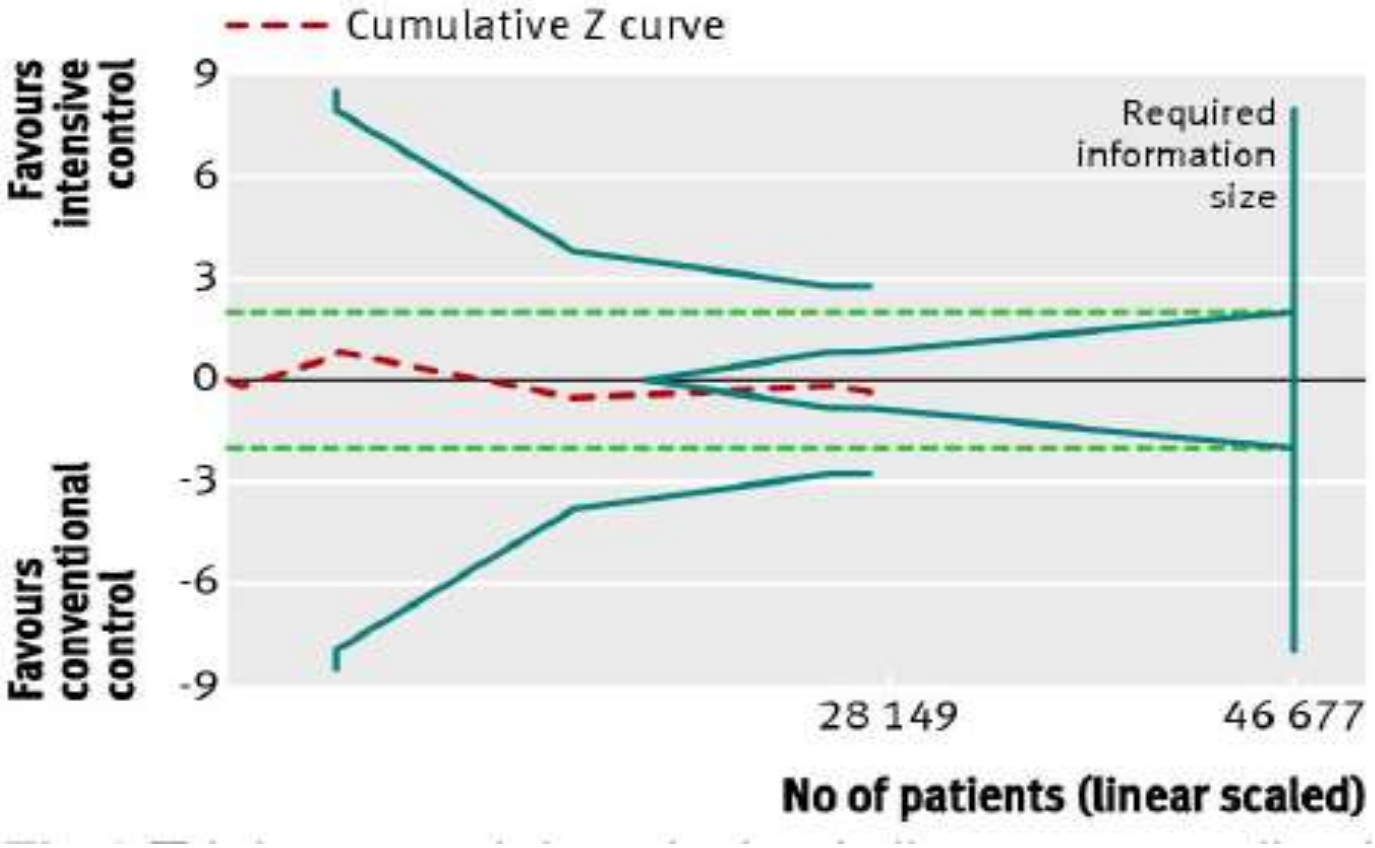


Fig 3 Trial sequential analysis of all cause mortality. Heterogeneity adjusted required information size of 46 677 participants calculated on basis of proportion of mortality of 8.4% in conventional glucose control group, relative risk reduction of 10%, α=5%, β=20%, and I^2=30%. Actually accrued No of participants was 28 149, 60% of required information size. Dashed red cumulative Z curve does not cross solid blue trial sequential monitoring boundaries for benefit or harm, but boundaries for futility (blue inner wedge boundaries) are crossed. Horizontal dotted green lines illustrate traditional level of statistical significance (P=0.05)

Cochrane review Hemmingsen et al, BMJ, 2011

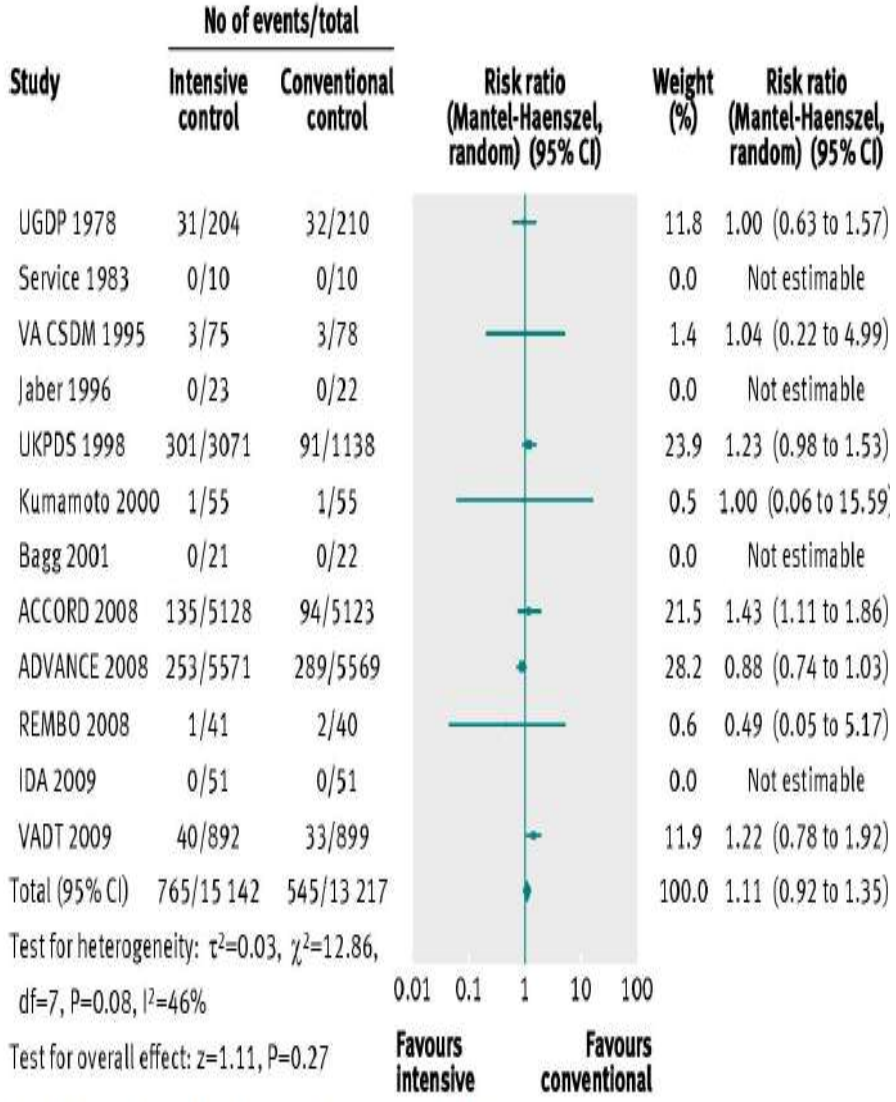
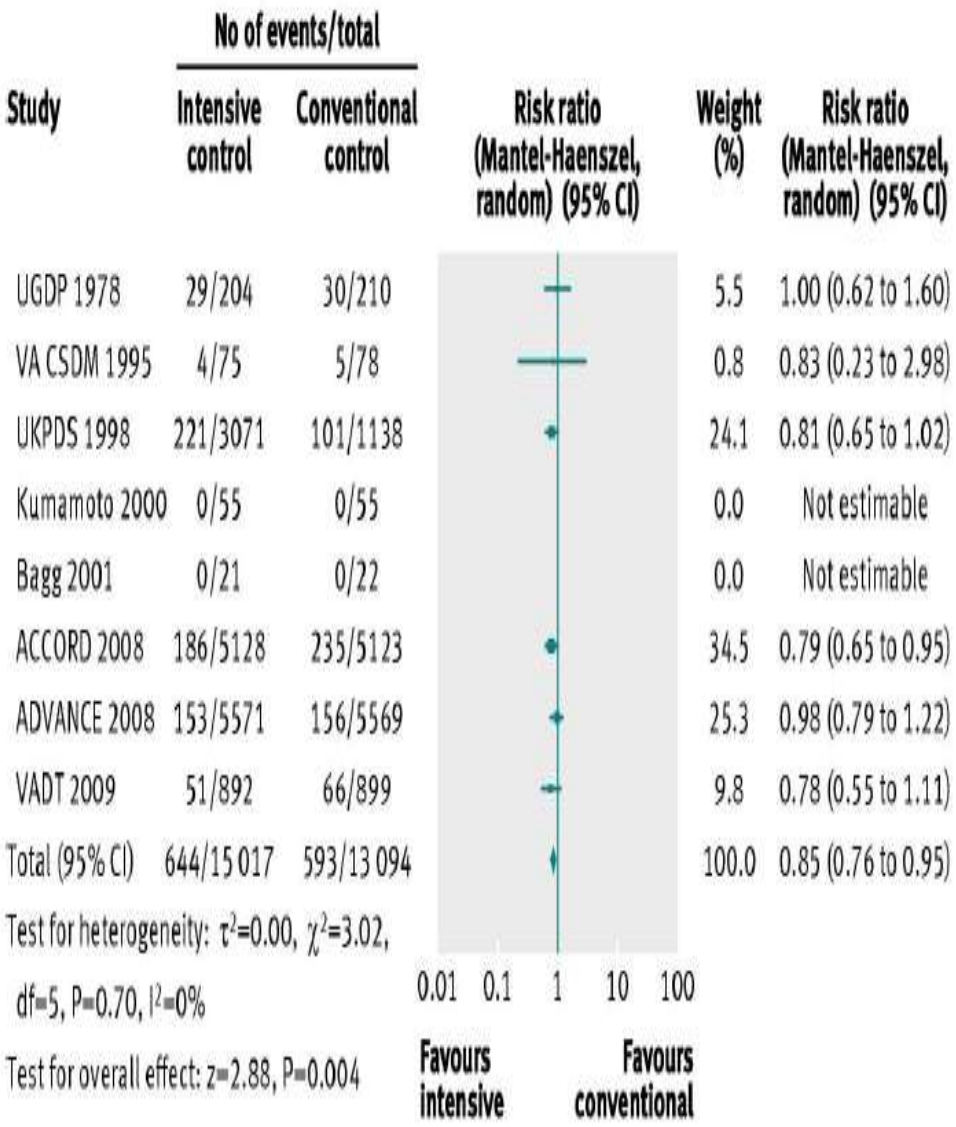


Fig 4 Forest plot for cardiovascular mortality



Non fatal myocardial infarction

Cochrane review Hemmingsen et al, BMJ, 2011

Study	No of events/total: Intensive control	No of events/total: Conventional control	Risk ratio (Mantel-Haenszel, random) (95% CI)	Weight (%)	Risk ratio (Mantel-Haenszel, random) (95% CI)
UKPDS 1998	249/3071	121/1138		18.8	0.76 (0.62 to 0.94)
ACCORD 2008	556/5128	586/5123		40.8	0.95 (0.85 to 1.06)
ADVANCE 2008	526/5571	605/5569		40.4	0.87 (0.78 to 0.97)
Total (95% CI)	1331/13 770	1312/11 830		100.0	0.88 (0.79 to 0.97)

Test for heterogeneity: $\tau^2=0.00$, $\chi^2=3.61$, df=2, P=0.16, $I^2=45\%$

Test for overall effect: z=2.46, P=0.01

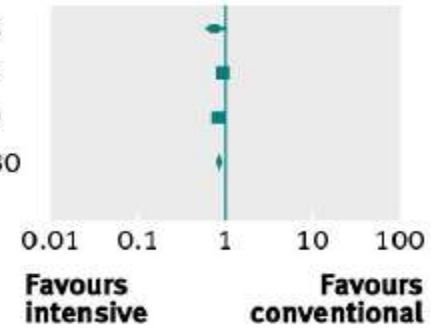
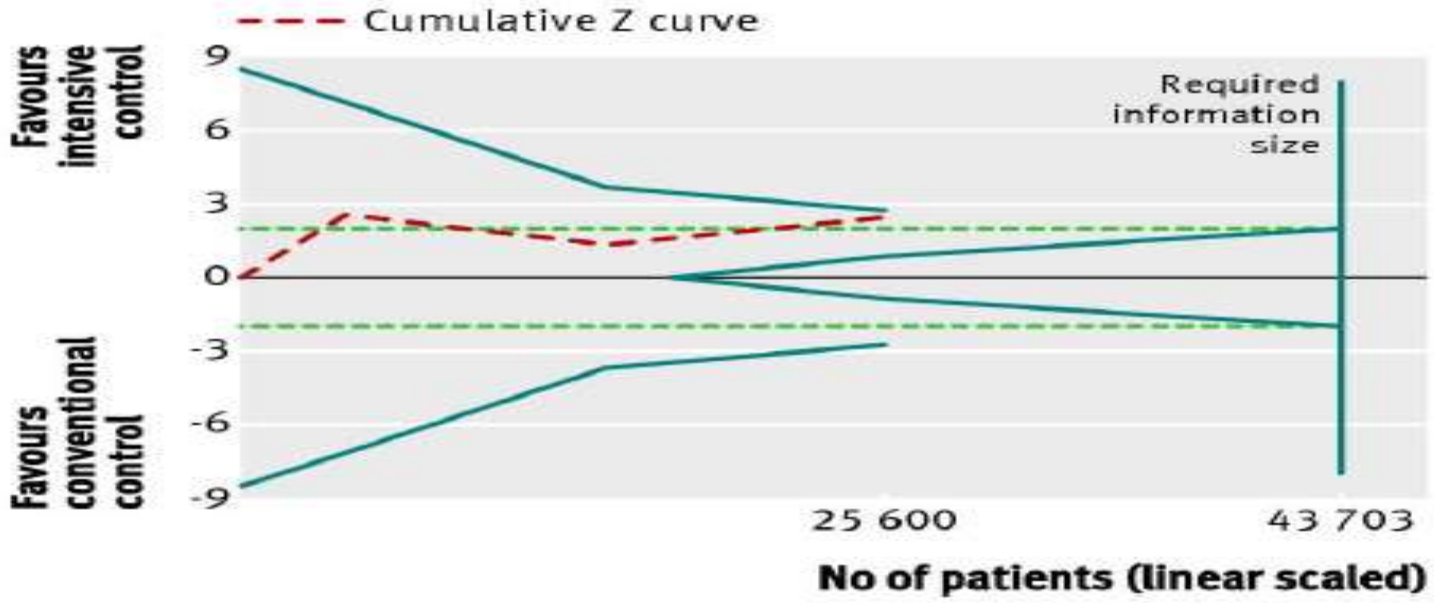


Fig 8 Forest plot for composite microvascular outcome



Cochrane review Hemmingsen et al, BMJ, 2011

Study	No of events/total: Intensive control	No of events/total: Conventional control	Risk ratio (Mantel-Haenszel, random) (95% CI)	Weight (%)	Risk ratio (Mantel-Haenszel, random) (95% CI)
VA CSDM 1995	5/75	2/78		3.8	2.60 (0.52 to 12.99)
Jaber 1996	0/23	0/22		0.0	Not estimable
UKPDS 1998	33/3071	8/1138		12.3	1.53 (0.71 to 3.30)
Kumamoto 2000	0/55	0/55		0.0	Not estimable
Bagg 2001	0/21	0/22		0.0	Not estimable
ACCORD 2008	830/5128	261/5123		33.0	3.18 (2.78 to 3.63)
ADVANCE 2008	150/5571	81/5569		28.5	1.85 (1.42 to 2.42)
IDA 2009	0/51	0/51		0.0	Not estimable
VADT 2009	76/892	28/899		22.4	2.74 (1.79 to 4.18)
Total (95% CI)	1094/14 887	380/12 957		100.0	2.39 (1.71 to 3.34)

Test for heterogeneity: $\tau^2=0.08$, $\chi^2=15.01$, df=4, P=0.005, $I^2=73\%$

Test for overall effect: z=5.10, P<0.001

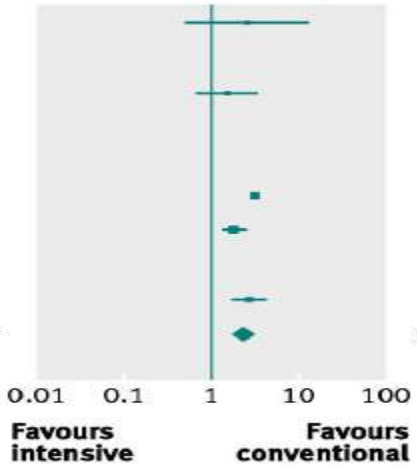
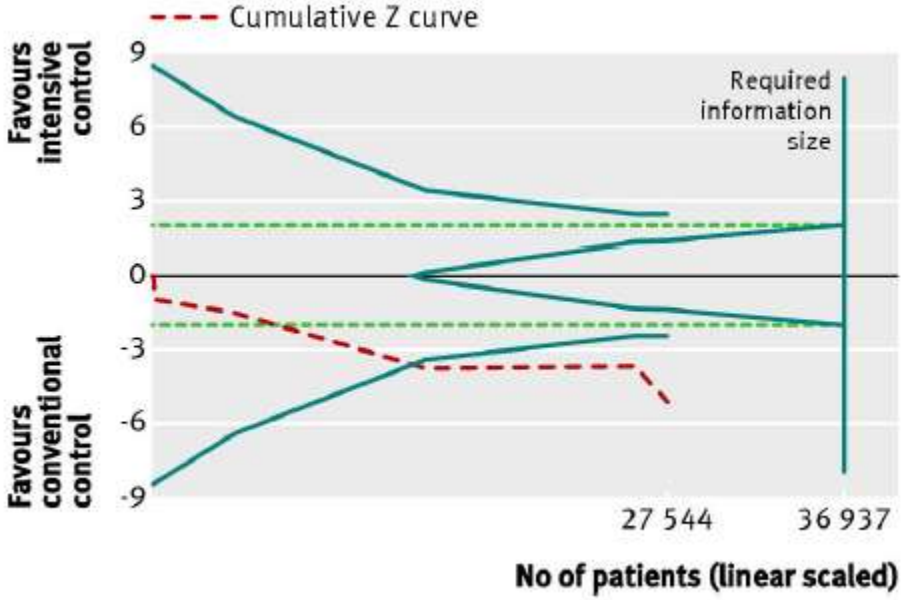


Fig 13 Forest plot for severe hypoglycaemia



Conclusions

Hard evidence for LACK of impact on all cause mortality by actively lowering HbA1C

Insufficient evidence for a 10% relative risk reduction in cardiovascular mortality and non-fatal myocardial infarction

Insufficient evidence for reduction in microvascular disease (combination of retinopathy, nephropathy

STRONG evidence for increased risk of severe hypoglycaemia

Conclusions

Hard evidence for LACK of impact on all cause mortality by actively lowering HbA1C

Insufficient evidence for a 10% relative risk reduction in cardiovascular mortality and non-fatal myocardial infarction

Insufficient evidence for reduction in microvascular disease (combination of retinopathy, nephropathy

At least in studies with an overwhelming majority of non advanced CKD patients!!!!!!

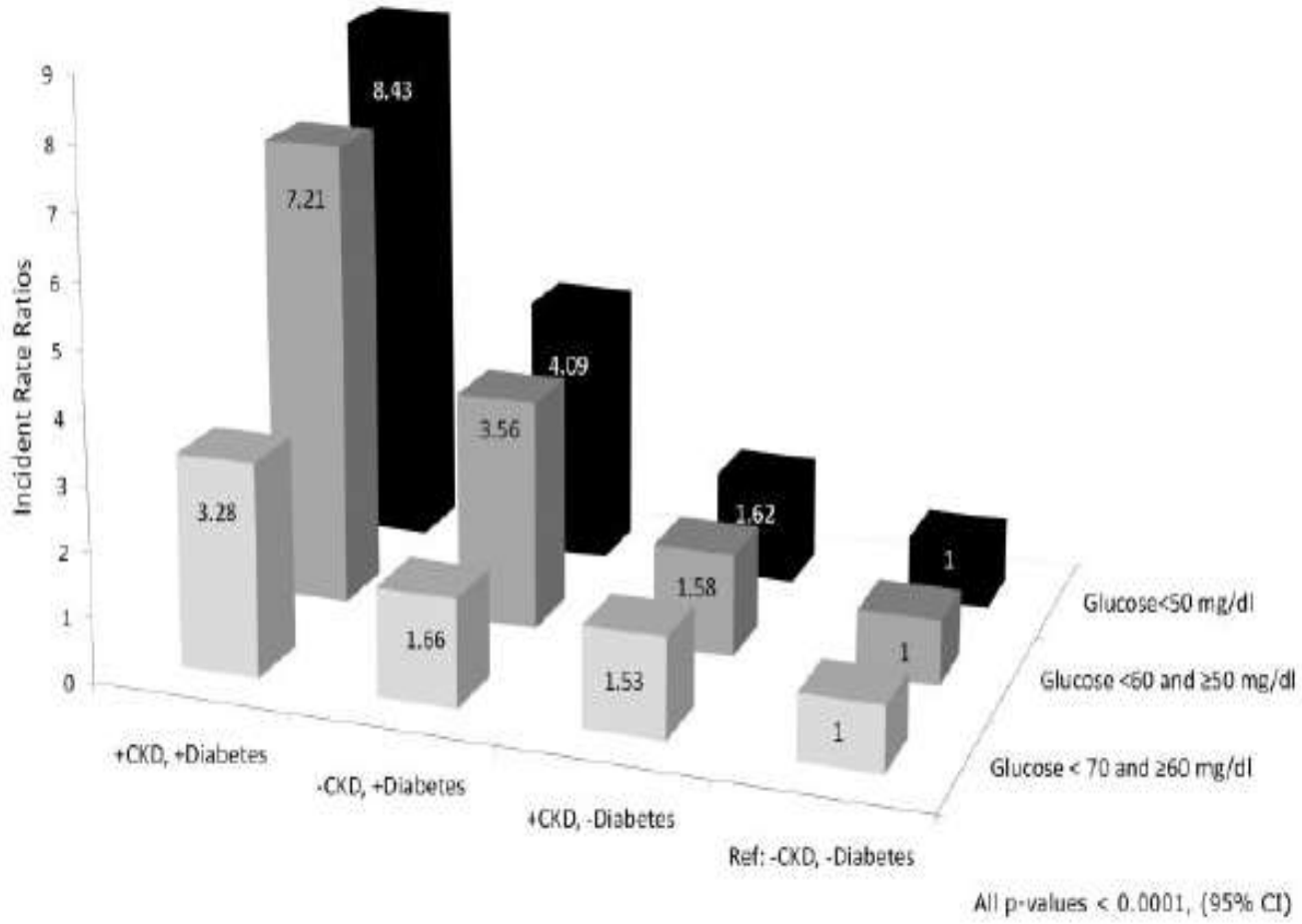
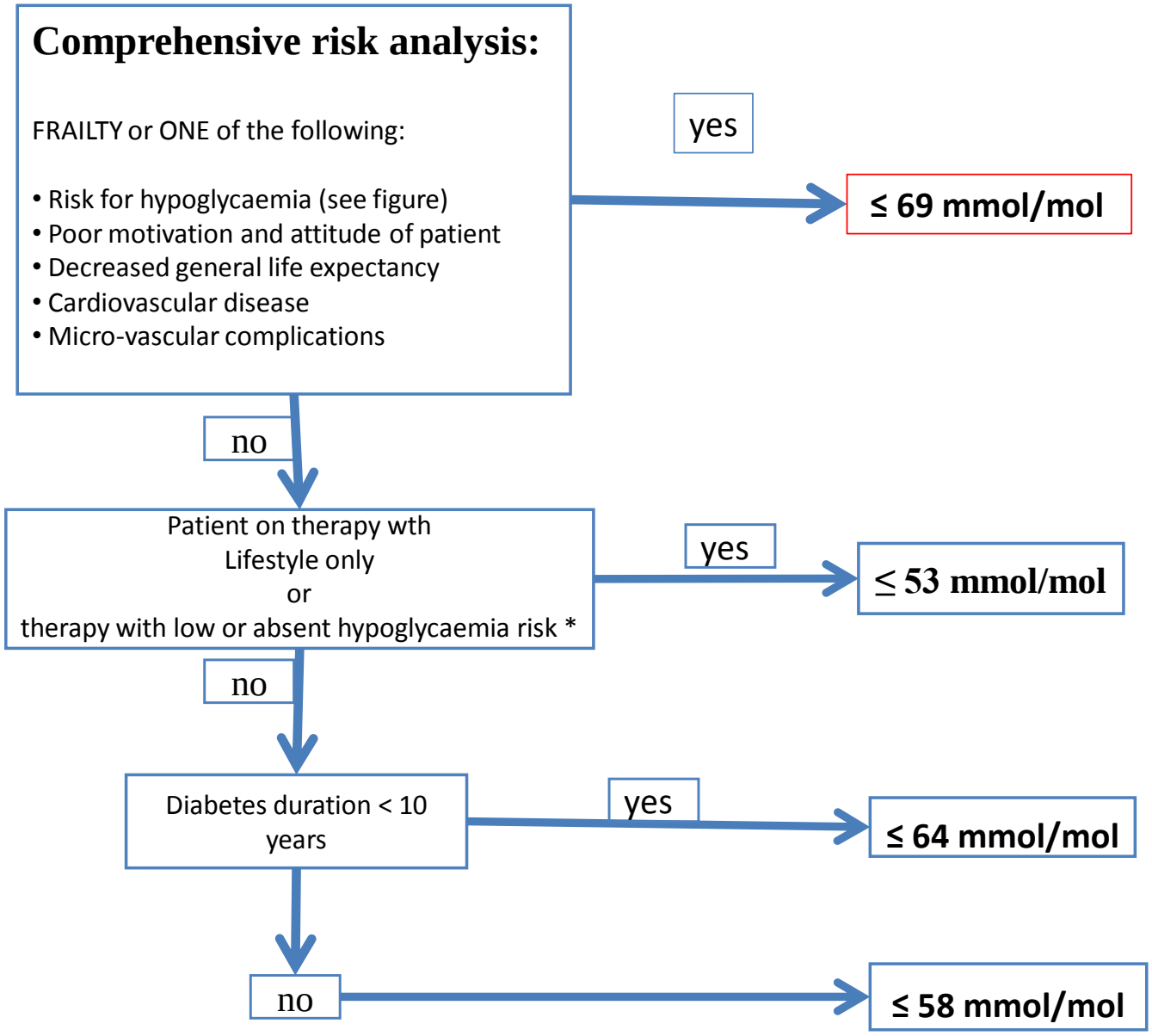
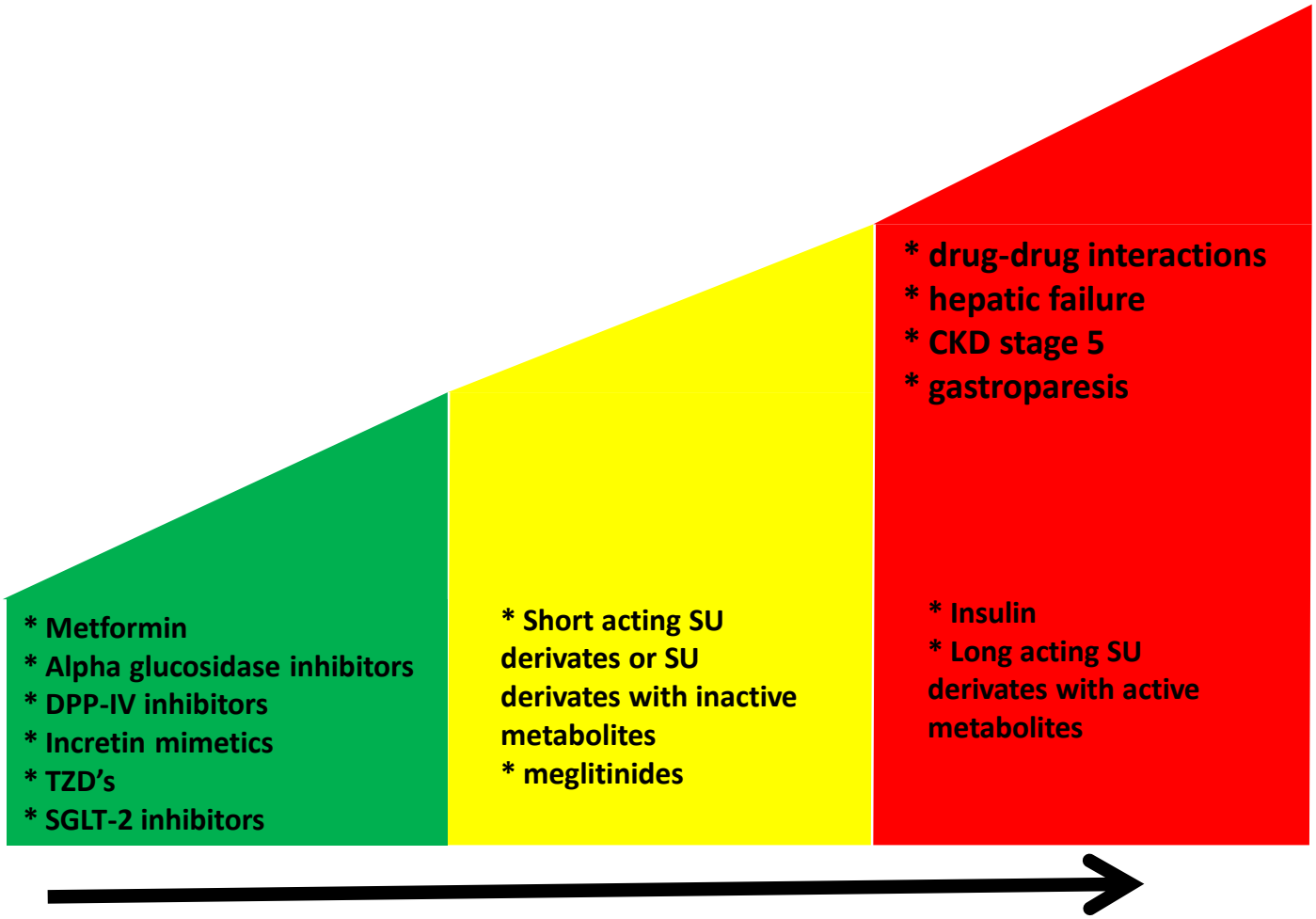


Figure 1. Risk for hypoglycemia of varying severity and expressed as an adjusted incidence rate ratio in veterans classified by presence or absence of chronic kidney disease (CKD) and diabetes. Reference group are veterans without CKD or diabetes. Rates adjusted for race, gender, age, Charlson comorbidity index, cancer, diabetes, and cardiovascular disease (all rate ratios $P < 0.0001$).

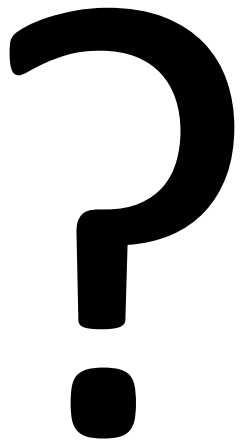
Conclusions

- **First concern: avoid hypoglycemia**
- **If no hypoglycemia's and HbA1C>7%: try to intensify hypoglycemic treatment**
- **Take into consideration comorbidity and age of patients**

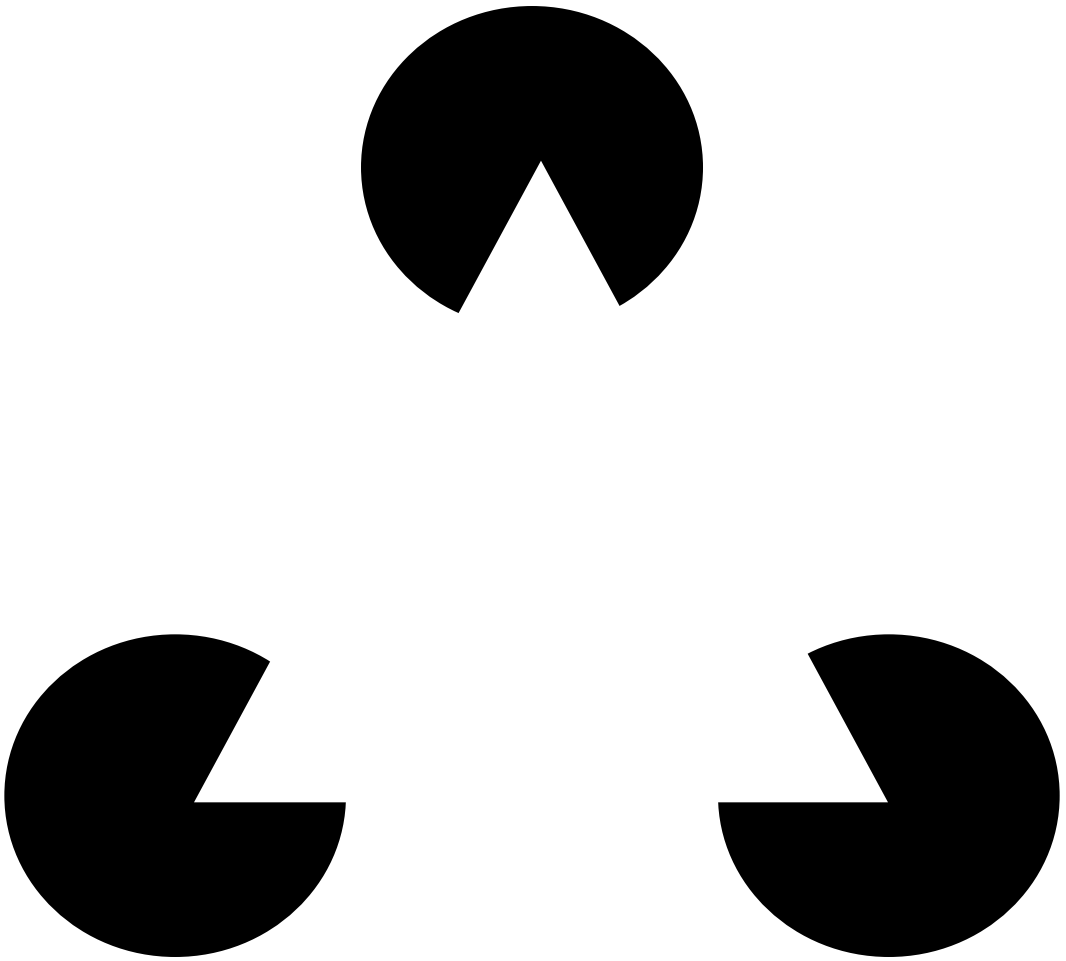

Comprehensive risk analysis:
FRAILTY or ONE of the following:
• Risk for hypoglycaemia (see figure)
• Poor motivation and attitude of patient
• Decreased general life expectancy
• Cardiovascular disease
• Micro-vascular complications
yes
≤ 69 mmol/mol
no
Patient on therapy wth
Lifestyle only
or
therapy with low or absent hypoglycaemia risk *
yes
≤ 53 mmol/mol
no
Diabetes duration < 10 years
yes
≤ 64 mmol/mol
no
≤ 58 mmol/mol


* Metformin
* Alpha glucosidase inhibitors
* DPP-IV inhibitors
* Incretin mimetics
* TZD's
* SGLT-2 inhibitors
* Short acting SU derivates or SU derivates with inactive metabolites
* meglitinides
* drug-drug interactions
* hepatic failure
* CKD stage 5
* gastroparesis
* Insulin
* Long acting SU derivates with active metabolites
Hypoglycaemia risk

METFORMIN
in advanced CKD:



Scheen AJ. Metformin and lactate acidosis. Acta Clin Belg 2011, 66 (5): 329-331



METFORMIN

- First drug of choice in all current guidelines
- Cheap
- No hypoglycemic risk
- Weight-neutral or reducing effect
- Lipid- lowering effect
- Well characterized efficacy and safety profile
- Impressive preventive effects with prevention of:
  - Diabetes
  - Micro- and macrovascular complications
  - Major events in patients with heart failure
  - Apoptotic neuron death
  - Cancer
  - Osteopenie
  - Mortality in lactic acidosis not related to to metformin

METFORMIN: LACTIC ACIDOSIS

Figure 1: Various circumstances capable of initiating vicious circles that may conduct to metformin–associated lactic acidosis (MALA). In all circumstances that can provoke severe dehydration, metformin therapy must be interrupted. ACEI: angiotensin converting enzyme inhibitor. ARB: angiotensin receptor blocker. NSAID: nonsteroidal anti-inflammatory drug.

Acta Clinica Belgica, 2011; 66-5

Scheen AJ. Metformin and lactate acidosis. Acta Clin Belg 2011, 66 (5): 329-331

A coctail of risk aversion and WYSIATI effects

Table 1 Predicted absolute number of deaths caused by the life-threatening complications of metformin and sulphonylureas

	Metformin-associated lactic acidosis
Incidence of lactic acidosis or severe hypoglycaemia in type 2 DM (number per 100,000 patient years)	6.3 [4]
Mortality (percentage; most pessimistic available figure)	50% [22]
Predicted absolute no. of deaths (number per 100,000 pt years)	3

Herrington WG, Levy JB. Metformin: effective and safe in renal disease. Int Urol Nephrol 2008; 40: 411-417

A coctail of risk aversion and WYSIATI effects

Table 1 Predicted absolute number of deaths caused by the life-threatening complications of metformin and sulphonylureas

	Metformin-associated lactic acidosis	Sulphonylurea-induced hypoglycaemia	Insulin-induced hypoglycaemia
Incidence of lactic acidosis or severe hypoglycaemia in type 2 DM (number per 100,000 patient years)	6.3 [4]	1,000 [2]	1,800 [2]
Mortality (percentage; most pessimistic available figure)	50% [22]	4.3% [21]	4.3% [21]
Predicted absolute no. of deaths (number per 100,000 pt years)	3	43	77.4

Herrington WG, Levy JB. Metformin: effective and safe in renal disease. Int Urol Nephrol 2008; 40: 411-417

METFORMIN: LACTIC ACIDOSIS

- No firm data that lactic acidosis is more frequent in patients on metformin (Salpeter, Cochrane review)
- Evidence that outcome of lactic acidosis is BETTER in patients on vs not on metformin
- We have to distinguish
  - Lactic acidosis type A: caused by tissue hypoxia/liver damage
  - Lactic acidosis type B: caused by intoxication, eg metformin
- We have to to distinguish:
  - Metformin as CAUSE of the lactic acidosis
  - Metformin as a drug in a patient who develops lactic acidosis because of other reasons
  - Mixed forms

Recommendations

- We recommend metformin in a dose adapted to renal function as a first line agent when lifestyle measures alone are insufficient to get HbA1C in the desired range **(1B)**
- We recommend to add on to meformin a drug with a low risk for hypoglycaemia as a second agent when improvement of glycaemic control is deemed appropriate according to guideline (1D)
- There is insufficient evidence to support insulin over an additional oral agent as add on second line treatment
- We recommend instructing patients to withhold metformin in conditions of pending dehydration, when undergoing contrast media investigations, or when there is a risk for AKI

advice for clinical practice

- Consider to provide patients with credit-card type flyers with instructions on when to temporarily withdraw methformin
- drugs with low risk for hypoglycaemia: (figure)
  - Metformin
  - Alpha glucosidase inhibitors
  - DPP-IV inhibitors
  - Incretin mimetics
  - SGLT-2 inhibitors
- drugs with moderate risk for hypoglycaemia:
  - Short acting SU derivates or SU derivates with inactive metabolites
  - meglitinides
- drugs with high risk for hypoglycaemia:
  - Insulin
  - Long acting SU derivates or derivates with active metabolites
- in patients with diabetes and eGFR <45 who are on metformin, the decision to withhold the drug 48 hours before and after administration of contrast media should be taken by the treating physician, balancing the probability for emergence of contrast induced nephropathy (type and amount of contrast, intravenous vs intra-arterial), and presence of other co-existing factors that might cause sudden deterioration of kidney function (dehydration, use of NSAID, use of inhibitors of the RAAS system) against the potential harms by stopping the drug (which should be considered low in view of the short period that it should be withheld).

FIGURE 2: Suggested use and dose adaptation of glucose-lowering drugs according to the CKD stages (see also Table 1 for details). *1.5 g with eGFR > 45 mL/min and 850 mg with eGFR 30–45 mL/min; **to be temporarily witheld in periods of unstable eGFR.