Unleash Metformin: Reconsideration of the Contraindication in Patients with Renal Impairment

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Learning Objectives

1. Explain the role, benefits, and limitations of metformin in the treatment of type 2 diabetes
2. Describe the pathophysiology of lactic acidosis and the controversy associated with metformin
3. Apply current guidelines regarding metformin dosing in renal impairment
4. Evaluate the evidence available and come to your own conclusion concerning safety of metformin in renal impairment

TYPE 2 DIABETES

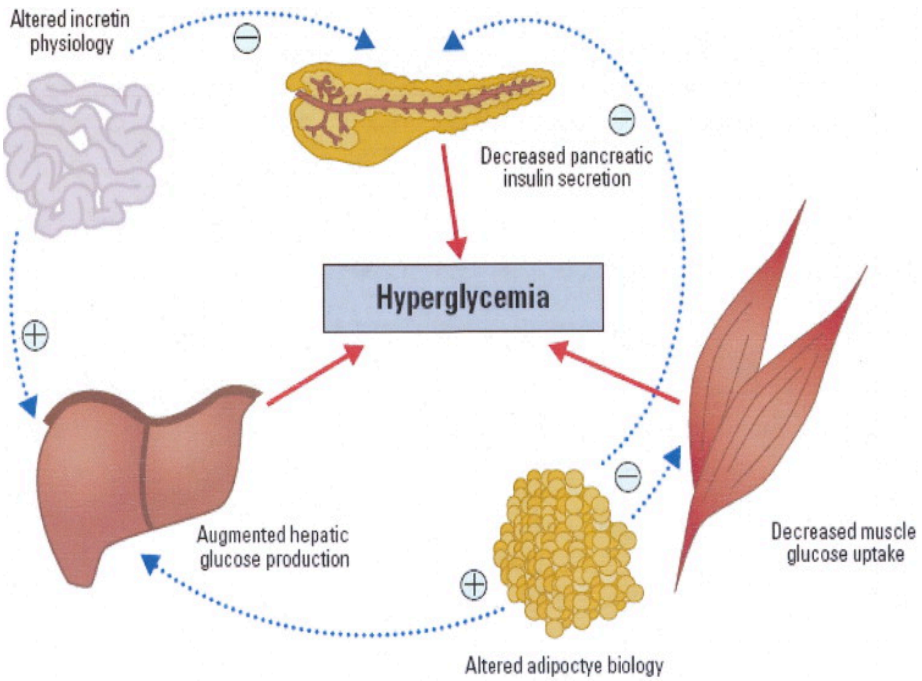
I. Epidemiology[1]
   a) 25.8 million Americans with type 2 diabetes; 8.3% of the U.S. population in 2011
   b) 79 million Americans with prediabetes; 35% of the U.S. population in 2011

II. Health Care Costs Impact[1, 2]
   a) $174 billion in 2007
   b) $116 billion in total medical expenditures, including medications and office visits, in addition to the hospital costs, and $58 billion in reduced national productivity
   c) One of every five health care dollars is spent caring for someone with diabetes

III. Complications[1]
   a) Leading cause of new cases of blindness, non-traumatic lower-limb amputations, and end-stage renal disease
   b) Major cause of cardiovascular disease and stroke
   c) The seventh leading cause of death in the U.S.

IV. Pathogenesis of Type 2 Diabetes[3]
   a) Inadequate insulin secretion from pancreatic β-cells
   b) Increased glucagon secretion from pancreatic α-cells
   c) Insulin resistance in target tissues
   d) Increased hepatic glucose production
   e) Abnormalities in the incretin system

Figure 1: Pathogenesis of Type 2 Diabetes



Adapted from Masoudi and Inzucchi. *American Journal of Cardiology* 2009;99(4) Supplement 19:113-32

ROLE OF METFORMIN IN TYPE 2 DIABETES

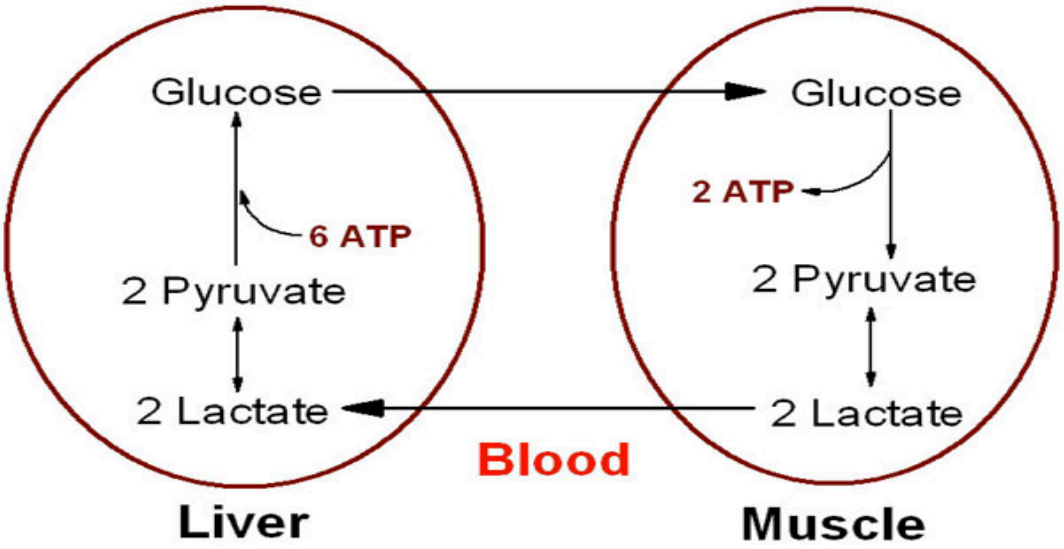
I. Metformin Mechanism of Action[4, 5]
   a) Suppresses hepatic gluconeogenesis
   b) Enhances glucose uptake mainly by muscle and adipose tissue
   c) Delays intestinal glucose absorption
   d) Increases fatty-acid oxidation
   e) Decreases hepatic synthesis of very-low-density lipoprotein[6]
      i. Decreases in plasma triglyceride: 5-10%
      ii. Small increases in high-density lipoprotein

II. Benefits of Metformin[3]
   a) A1c (glycosylated hemoglobin) reduction: 1 to 2%[7]
   b) Weight neutral and even weight loss
      i. May reduce adipose-tissue mass: preferred in obese patients
   c) No hypoglycemia
   d) Low cost
   e) Greater reduction of cardiovascular disease and all-cause mortality compared to sulfonylurea and insulin[8, 9, 10]
   f) Reduction of all-cause mortality and readmission related to heart failure[11, 12]

III. Metformin as the First Line of Treatment in Type 2 Diabetes (see Appendix A, Page 19)
   a) Initial drug monotherapy
   b) Backbone for combination therapy

IV. Limitations of Metformin[5]
   a) Contraindications
      i. SCr (serum creatinine) ≥1.5 mg/dL in males or ≥1.4 mg/dL in females
      ii. Abnormal creatinine clearance from any cause, including shock, acute myocardial infarction, or septicemia
      iii. Acute or chronic metabolic acidosis with or without coma, including diabetic ketoacidosis
   b) Warnings/Precautions
      i. **U.S. Black Boxed Warning**: metformin associated lactic acidosis
      ii. Use cautiously in heart failure, hepatic impairment, iodinated contrast, surgical procedures, ethanol use, and the elderly
   c) Adverse reactions
      i. Gastrointestinal side effects
      ii. Reduced vitamin B12 levels

Figure 2: The Cori Cycle



http://themedicalbiochemistrypage.org/gluconeogenesis.php

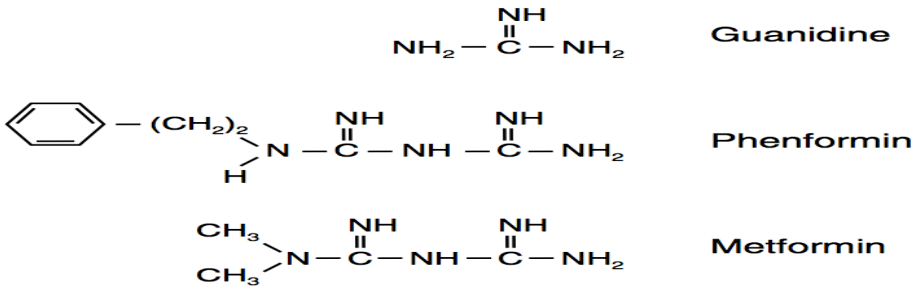
I. Definitions[13]
   a) Normal blood lactate concentration: 4.5 to 18 mg/dL
   b) Hyperlactatemia:
      i. 18 to 36 mg/dL without metabolic acidosis
      ii. Can occur in the setting of adequate tissue perfusion, intact buffering systems, and adequate tissue oxygenation
   c) Lactic acidosis:
      i. >45 mg/dL with metabolic acidosis
      ii. Associated with major metabolic dysregulation, tissue hypoperfusion, the effects of certain drugs or toxins, and congenital abnormalities in carbohydrate metabolism

II. Etiology and Risk Factors[13]
   a) Type A Lactic Acidosis
      i. Poor tissue perfusion or oxygenation of blood – most frequent cause
      ii. Overproduction of lactate: circulatory, pulmonary, and hemoglobin transfer disorder
      iii. Underutilization of lactate: liver disease, gluconeogenesis inhibition, thiamine deficiency
   b) Type B Lactic Acidosis
      i. Poor tissue perfusion or oxygenation not the primary etiology
      ii. Type B1
         • Renal and hepatic failure, diabetes, pancreatitis, seizures, infection, and malignancy
      iii. Type B2
         • Drugs and toxins
      iv. Type B3
         • Congenital defects of metabolism – glucose-6-phosphatase deficiency

III. Prognosis
   a) Serum lactate level > 23 mg/dL associates with an increase in mortality rate as high as 50%[15]
   b) Serum lactate level > 45 mg/dL and a pH of < 7.35 associate with a mortality rate of 75%[13]
   c) The median survival for patients with lactic acidosis and shock is 28 hours[13]

I. Mechanism of Phenformin Associated Lactic Acidosis[13]
   a) Induces conversion of glucose to lactate by the intestinal mucosa
   b) Enhances anaerobic metabolism
   c) Suppresses hepatic gluconeogenesis
   d) Impairs renal excretion of lactate

Figure 3: Structures of Guanidine, Phenformin, and Metformin



Adapted from Bailey CJ, Turner RC. Metformin. *N Eng J Med* 1996;334:574-579.

II. Metformin versus Phenformin

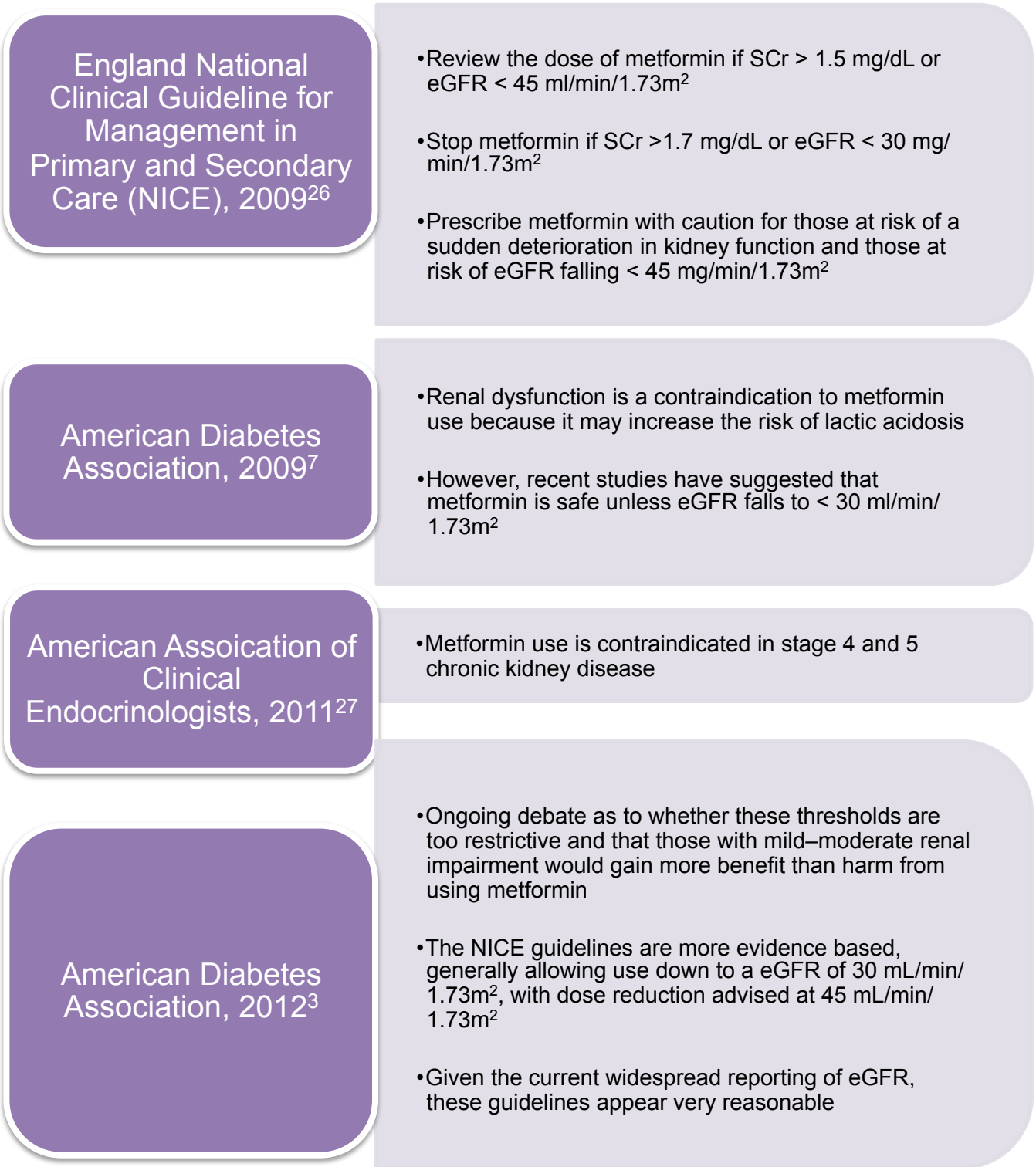
Table 1: Pharmacological Differences between Metformin and Phenformin[16]

	Metformin	Phenformin
Inhibition of glucose oxidation	Absent	Present
Interference with lactate turnover	Absent	Present
Metabolism	Not metabolized/ excreted unchanged	Inactive hydroxylated derivative
Hydroxylation polymorphism	Absent	Present in 10% of Caucasians[17]
Plasma half life	1.5 – 4.9 hours	12 hours
Elimination	Renally eliminated	Renally and hepatically eliminated

III. Evidence from Case Reports and Epidemiological Data
   a) The rate of lactic acidosis in the general population: 9.7 to 16.9 cases per 100,000 patient years[18]
   b) Phenformin related lactic acidosis: 25 to 100 cases per 100,000 patient years[16]
   c) Metformin related lactic acidosis: 0 to 16.7 cases per 100,000 patient years[19, 20]
   d) Neither metformin nor lactate concentrations were prognostically related to mortality[21]
   e) The median plasma metformin concentration was 3 times higher in patients who survived[22]
   f) Plasma concentrations of metformin were not related to increased lactic acid concentration[23]
   g) Emslie-Smith, et al[24]
      i. 24.5% of patients receiving metformin, in Scotland between 1993 to 1995, had contraindications to its use, including renal impairment
      ii. One episode of lactic acidosis occurred in 4,600 patient years – a 72 year old patient with acute myocardial infarction

IV. Serum Creatinine Level versus Estimated Glomerular Filtration Rate
    a) Shaw, et al[25]
        i. Calculated eGFR (estimated Glomerular Filtration Rate) using MDRD (Modification of Diet in Renal Disease) formula that corresponded to SCr of 1.4 mg/dL (female) or 1.7 mg/dL (male) of 12,482 patients
        ii. Few patients with the SCr above cut-offs had an eGFR < 30 ml/min/1.73m^2 (Stage 4)
        iii. Most had an eGFR between 30 and 59 ml/min/1.73m2 (Stage 3)
        iv. SCr of > 1.4 mg/dL corresponds with an eGFR cut-off of 49 ml/min/1.73m^2 for males and 36 ml/min/1.73m^2 for females
        v. SCr of > 1.7 mg/dL corresponds with an eGFR cut off of 41 ml/min/1.73m^2 for males and 30 ml/min/1.73m^2 for females
        vi. Using eGFR results in more equal distribution of males and females with renal impairment compared to using SCr results in more males than females with renal impairment

Figure 4: Guideline Recommendations of the Use of Metformin in Renal Impairment



<table>
<tr><th colspan="2">Rachmani, et al. Metformin in patients with type 2 diabetes mellitus: reconsideration of traditional contraindications. European Journal of Internal Medicine 2002; 13: 428[28]</th></tr>
<tr><td>OBJECTIVE</td><td>• To evaluate the safety of continued use of metformin in patients with contraindications to this agent</td></tr>
<tr><td>DESIGN</td><td>• Prospective randomized controlled trial</td></tr>
<tr><td>STATISTICAL ANALYSIS</td><td>• Intention-to-treat
• Annual values within the groups were compared by t-tests for paired data (two-tailed); linear regression models were used for comparison of continuous variables between the groups
• The effect of continued metformin treatment was examined by analysis of covariance, including the effect of baseline values. All values are given as mean±SD (standard deviation)
• Two-sided, significance defined as p value < 0.05</td></tr>
<tr><td>METHODS</td><td>Subjects:

Table 2
<table>
<tr><th>Inclusion Criteria</th><th>Exclusion Criteria</th></tr>
<tr><td>• 40-75 years old
• Treated with metformin, alone or in combination with other hypoglycemic agents
• Type 2 diabetes diagnosed after age 40
• BMI (body mass index) 24-40 kg/m2
• Presence of one or more traditional contraindications to metformin
a) SCr level of 1.5-2.5 mg/dL
b) CHF (congested heart failure), New York Heart Association classes 3 or 4
c) Abnormal liver function test (twice the upper limit of normal)
d) COPD (chronic obstructive pulmonary disease)
e) Acute coronary syndromes treated conservatively or invasively</td><td>• Liver cirrhosis, an acute myocardial infarction, pulmonary edema within the previous 30 days, and patients with malignant disease</td></tr>
</table>
Treatments:
• To continue or to stop metformin

Follow-up:
• Annually or more frequently if clinically indicated for a total of 4 years
• Baseline and annual values for each patient were the means of three determinations carried out over a period of 2 weeks.</td></tr>
<tr><td>ENDPOINTS</td><td>• Changes in BMI, A1c, SCr, lactic acid levels, urinary albumin/creatinine ratio, LDL (low-density lipoprotein), HDL (high-density lipoprotein)
• Incidences of lactic acidosis and cardiovascular diseases</td></tr>
</table>

RESULTS

Baseline demographics:

- N=393
- There were no differences in any of the baseline parameters between the two groups

Table 3

	Metformin stopped N=198	Metformin continued N=195
Age (years)	64±64	65±64
Gender (M/F)	102/96	103/92
Duration of diabetes (years)	14±4	15±3
BMI (kg/m2)	28.4±0.6	28.7±0.7
A1c (%)	8.6±0.4	8.6±0.5
SCr (mg/dL)	1.82±0.1	1.84±0.08
Serum lactic acid (mg/dL)	13.5±2.7	13.5±3.6
Urinary albumin/creatinine ratio (mg/g)	46±11	48±9
Admission diagnosis		
Coronary heart disease	137	129
CHF	48	46
COPD	47	44
Liver disease	24	27
Amputations	3	2
Peripheral vascular disease	29	32

Outcomes:

Figure 5

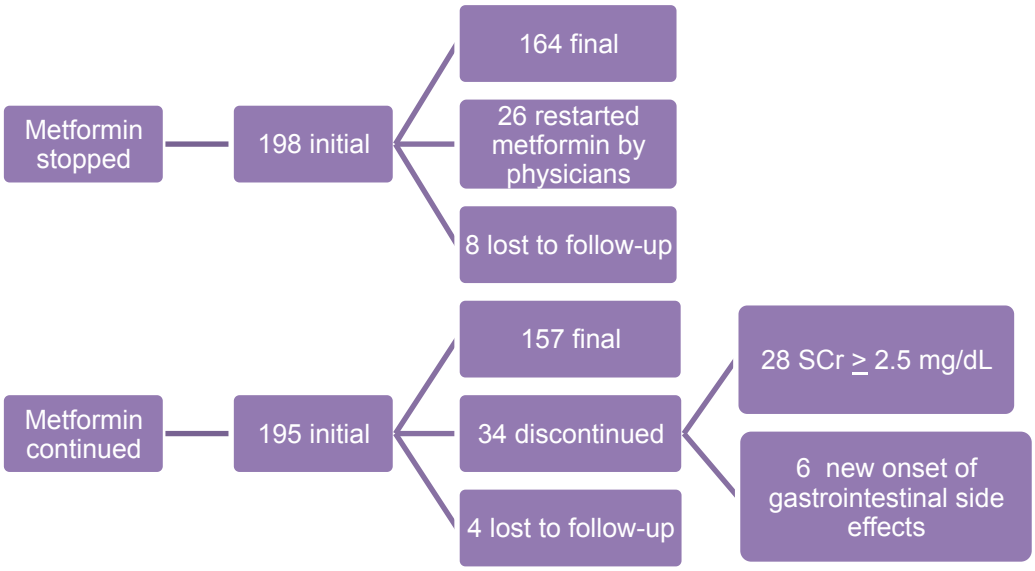


Table 4: Outcome parameters: initial, final, and percent of change in the patients who stopped metformin and in those who continued the drug

	Metformin Stopped				Metformin Continued				
	Initial	Final	% of change	P_1	Initial	Final	% of change	P_1	P_2
BMI (kg/m2)	28.4	29.6	4.2	<0.05	28.7	29.1	1.3	NS	<0.001
A1c (%)	8.6	9.1	5.8	<0.01	8.6	8.8	2.3	NS	<0.01
SCr (mg/dL)	1.82	2.1	16	<0.01	1.84	2.02	10	<0.01	NS
Serum lactic acid (mg/dL)	13.5	14.68	9	<0.01	13.5	14.95	11	<0.01	NS
Urinary albumin/ creatinine ratio (mg/g)	46	57	24	<0.001	48	55	15	<0.001	NS
LDL (mg/dL)	139	142	2.2	NS	138	137	-0.6	NS	<0.05
HDL (mg/dL)	40.5	40.5	0	NS	37.8	40.5	7	<0.05	<0.05

P1, significance of change between initial and final values
P2, significance of difference between final values of the two groups

- Not a single case of lactic acidosis occurred in either group
- 126 patients died during the study period of 4 years
  a) 64 (34%) among those who stopped metformin
  b) 62 (32%) among those who continued to use the drug
- There was no difference between the two groups in the incidence of myocardial infarction, all cardiovascular events, cardiovascular mortality, or total mortality

AUTHOR'S CONCLUSION

- "This prospective, randomized observational study renders further support to the cross-sectional reports that have failed to observe lactic acidosis or an increase in other complications of metformin in patients with the traditional contraindications to this agent."

CRITIQUE

Strengths:

- Randomized controlled trial
- Included a selective group of hospitalized diabetic patients with one or more contraindications to metformin and significant comorbidities (including those that can increase the risks for lactic acidosis)
- Measured changes of serum lactic acid and other laboratory values
- Measured incidence of lactic acidosis and cardiovascular events

Weaknesses:

- Relatively small size
- Single center
- Did not provide metformin dose or plasma metformin concentration

IMPLICATIONS

- The first randomized controlled trial that evaluated patients with SCr > 1.5 mg/dL
- No incidence of lactic acidosis or significant differences in lactate levels observed in SCr levels of 1.5 to 2.5 mg/dL
- Continuation of metformin was associated with significantly less weight gain and less rise in A1c values but no significant changes in SCr levels

Salpeter, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Archives of Internal Medicine* 2003; 163: 2594-2602[29]	
OBJECTIVE	• To assess the risk of fatal and nonfatal lactic acidosis associated with metformin use in persons with type 2 diabetes mellitus compared with placebo or other antihyperglycemic therapies
DESIGN	• Meta-analysis
STATISTICAL ANALYSIS	• Poisson statistics with 95% CI (confidence intervals) to calculate the probable upper limits for the true incidence of lactic acidosis
METHODS	Article search: • Searched of the Cochrane Library (including Cochrane Controlled Trials Database), MEDLNE, OLDMEDILINE, Database of Abstracts of Reviews of Effectiveness, Reactions, and EMBASE • The search was further augmented by scanning references of identified articles; attempts were made to contact authors to obtain additional information Inclusion criteria: • Published between January 1, 1959 and March 31, 2002 • Prospective clinical trials which evaluated metformin use, alone or in combination with other treatments, compared with placebo or compared with other OHA (oral hypoglycemic agents) • Observational cohort studies which provided the number of patients and duration of treatment • At least 1 month of metformin use
ENDPOINTS	• Fatal and nonfatal lactic acidosis • Blood lactate levels for metformin compared with placebo or other nonbiguanide therapies and compared with phenformin a) Change from baseline to treatment b) Mean lactate levels c) Change in treatment lactate levels from a basal state to peak stimulation with either food or exercise
RESULTS	• 129 studies included in the analysis, 126 prospective comparative trials, 56 prospective cohort studies, 12 retrospective cohort studies • A total of 56,692 participants • Mean duration 2.1 years (range 1 month to 10.7 years) Baseline demographics: • 18,689 participants in the metformin group with a mean±SD age of 57.1±8.9 and 61% were men • 38,003 participants in the nonbiguanide group with a mean±SD age of 57.2±9.1 and 61% were men • No statistically significant differences in baseline demographics Outcomes: • Incidence of lactic acidosis a) No cases of fatal or nonfatal lactic acidosis reported in both the metformin and nonbiguanide groups (no cases were found of the 56 trials excluded from analysis) b) Probable upper limit for the true incidence of lactic acidosis i. Metformin group: 8.1 cases per 100,000 patient years ii. Nonbiguanide group: 9.9 cases per 100,000 patient years c) 44% of the 184 prospective studies allowed inclusion of renal insufficiency and 96% allowed inclusion of at least 1 contraindication

<table>
<tr><td></td><td colspan="2">• Blood lactate levels
a) Net change in lactate levels from baseline
i. No difference comparing metformin with placebo or nonbiguanide therapies
ii. A WMD (weighted mean difference) of 1.0 mg/dL (95% CI, -0.1 to 2.2 mg/dL)
b) Mean treatment lactate levels
i. Metformin: 11.2±2.8 mg/dL
ii. Metformin vs nonbiguanide: WMD 0.5 mg/dL (95% CI, 0 to 1.2 mg/dL)
iii. Metformin vs phenformin: WMD – 6.8 mg/dL (95% CI, -7.9 to -5.9 mg/dL)

• Mean lactate level before and after stimulation by a meal or strenuous exercise
a) Metformin: 20.7±15.3
b) Metformin vs nonbiguanide: WMD 0.8 mg/dL (95% CI, -0.3 to 2.0 mg/dL)
c) Metformin vs phenformin: WMD -3.3 mg/dL (95% CI, -9.5 to 2.9 mg/dL)</td></tr>
<tr><td>AUTHOR'S CONCLUSION</td><td colspan="2">• "No evidence from prospective comparative trials or observational cohort studies to support the hypothesis that metformin treatment is associated with an increased risk of lactic acidosis compared with other antihyperglycemic treatments"</td></tr>
<tr><td>CRITIQUE</td><td>Strengths:
• Included large number of trials and participants
• Evaluated the incidence of lactic acidosis and lactate levels
• Compared outcomes between metformin and phenformin</td><td>Weaknesses:
• Meta-analysis
• Unclear of how many of the participants had renal insufficiency
• Did not provide metformin dose or plasma metformin concentration
• No trial was specifically designed to assess the incidence of lactic acidosis, but adverse events were described</td></tr>
<tr><td>IMPLICATIONS</td><td colspan="2">• The incidence of lactic acidosis with metformin was low and similar to that with nonbiguanide therapies
• No differences in the net change and mean lactate levels comparing metformin and nonbiguanide therapies
• Metformin associated with significantly lower mean lactate levels compared to phenformin</td></tr>
</table>

Ekström, et al. Effectiveness and safety of metformin in 51,675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. *British Medical Journal* Open 2012;2:e001076 doi:10[30]

OBJECTIVE

- To investigate benefits and risks associated with different glucose-lowering medications, in a cohort of 51,675 type 2 diabetes patients in clinical practice and in subgroups of patients with different degrees of renal impairment

DESIGN

- Prospective observational cohort study

STATISTICAL ANALYSIS

Statistical tests:

- Covariance adjustment and propensity scores were used to adjust for baseline risk factors and characteristics at Cox regression
- Cox regression models adjusted for baseline characteristics were used to estimate HR (hazard ratios) for all end points in groups of patients with different glucose-lowering treatments
- HR were estimated in subgroups with different eGFR intervals, for metformin, insulin or other OHA in any combination, with any other glucose-lowering treatment as reference. Adjustment was made for same covariates
- Two-sided, significance defined as p value < 0.05

METHODS

Subjects:

Table 5

Inclusion Criteria	Exclusion Criteria
• Pharmacologically treated type 2 diabetes • Aged ≥ 40 to < 85 years • Registered in the NDR (National Diabetes Register) between July 1 2004 and December 31 2007 • Registered in the NDR 1 year prior to and 1 year following their first prescription of antihyperglycemic treatment • Filled at least 3 prescriptions or 18 fills of multidose dispensed drugs during the 12-month period before baseline	• Treatment with diet only • Glucose-lowering treatment initiated after 2007 • Patient who experienced an end point event between first prescription and baseline were excluded from the analysis of that specific end point

Treatments: 7 treatment groups

Table 6

Treatment group	Number (%)
Metformin only	14,697 (28.0)
Metformin + Other OHA	8807 (17.0)
Metformin + insulin	7109 (14.0)
Insulin only	12,291 (24.0)
Other OHA only	5171 (10.0)
Insulin + other OHA	1365 (2.6)
Metformin + insulin + other OHA	2235 (4.3)

Follow-up:

- Followed from baseline until the occurrence of an end point event, or until censor date of December 31 2010, mean follow-up 3.9 years
- Patients changing treatment during the study were not censored, and end point events were attributed to the initial treatment

ENDPOINTS

- CVD (cardiovascular disease), fatal CVD, acidosis/serious infection, fatal acidosis/serious infection, and all-cause mortality

RESULTS

Baseline demographics:

- N=51,675 patients
- Mean±SD age of 65.3±9.8 years, diabetes duration of 9.4±8.0 years, A1c of 7.3±3.3%, eGFR 78.1±21.9 ml/min/1.73 ^{m2}
- There were statistically significant differences between the groups defined for all variables
- After adjustment with propensity score, all differences in baseline characteristics were erased
  a) Patients on insulin-based treatments presented longer diabetes duration, higher mean A1c, more often microalbuminuria and history of CVD, CHF and serious infections than the population in general
  b) Patients treated with metformin generally presented high eGFR and BMI, were the youngest participants, with the shortest diabetes duration, and had a low mean A1c.
  c) Patients treated with metformin relatively seldom had history of CVD, CHF or serious infections
  d) Patients treated with other OHA in monotherapy presented the highest mean age, the lowest mean A1c and the lowest mean BMI

Outcomes:

Table 7: Adjusted HR with 95% CI in all patients, in each treatment group, and with metformin only as reference

	Metformin only	Insulin only	Other OHA only	Insulin + other OHA	Metformin + other OHA	Metformin + Insulin	Metformin + Insulin + other OHA
Any acidosis /serious infection	Reference	1.37 (1.26-1.50)***	1.16 (1.04-1.28)**	1.31 (1.13-1.51)***	1.04 (0.95-1.14)	1.20 (1.09-1.32)***	1.15 (1.00-1.32)*
Fatal acidosis /serious infection	Reference	1.63 (1.29-2.07)***	1.28 (0.98-1.67)	1.32 (0.91-1.89)	0.94 (0.72-1.23)	1.41 (1.08-1.83)*	1.12 (0.73-1.67)
Any CVD	Reference	1.28 (1.19-1.37)***	1.13 (1.04-1.23)**	1.40 (1.24-1.58)***	1.11 (1.03-1.20)**	1.28 (1.19-1.38)***	1.33 (1.19-1.49)***
Fatal CVD	Reference	1.41 (1.18-1.68)***	1.30 (1.08-1.56)**	1.17 (0.91-1.51)	~	~	1.21 (0.92-1.58)
All-cause mortality	Reference	1.47 (1.35-1.61)***	1.30 (1.18-1.44)***	1.30 (1.12-1.50)***	1.15 (1.05-1.27)**	1.25 (1.13-1.38)***	1.31 (1.14-1.52)***

*p<0.05; **p<0.01; ***p<0.001; **~** Non-proportional hazards, group excluded from analysis

Table 8: Adjusted HR with 95% CI in patients with insulin only and patients with metformin only as reference

	Events/patients (N/N) Insulin only	Events/patients (N/N) Metformin only	HR (95% CI) Insulin only vs metformin only	P Value
Any acidosis /serious infection	1,867/11,860	1,154/14,517	1.28 (1.14-1.43)	<0.001
Fatal acidosis /serious infection	325/12,284	127/14,697	1.45 (1.07-1.97)	0.019
Any CVD	2,389/11,427	1,734/14,317	1.18 (1.07-1.29)	<0.001
Fatal CVD	681/12,285	264/14,696	1.12 (1.91-1.40)	0.29
All-cause mortality	2,002/12,291	971/14,697	1.34 (1.19-1.50)	<0.001

Table 9: Adjusted HR with 95% CI in patients with other OHA only and patients with metformin only as reference

	Events/patients (N/N) Other OHA only	Events/patients (N/N) Metformin only	HR (95% CI) Other OHA only vs metformin only	P Value
Any acidosis /serious infection	623/5,062	1,154/14,517	1.05 (0.94-1.18)	0.41
Fatal acidosis /serious infection	109/5,171	127/14,697	1.13 (0.83-1.53)	0.44
Any CVD	929/4,964	1,734/14,317	1.02 (0.93-1.12)	0.71
Fatal CVD	237/5,171	264/14,696	1.03 (0.84-1.26)	0.80
All-cause mortality	745/5,171	971/14,697	1.13 (1.01-1.27)	0.032

Table 10: Adjusted HR with 95% CI and p-values in patients treated with insulin + other OHA or insulin + metformin, and with insulin only as reference

	Insulin Only	Insulin + other OHA		Insulin + Metformin	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Any acidosis /serious infection	Reference	0.96 (0.84-1.1)	0.5976	0.86 (0.79-0.94)	0.0007
Fatal acidosis /serious infection	Reference	0.82 (0.58-1.13)	0.2413	0.85 (0.68-1.06)	0.1532
Any CVD	Reference	1.10 (0.98-1.23)	0.1154	0.96 (0.89-1.03)	0.2823
Fatal CVD	Reference	0.84 (0.67-1.05)	0.1334	0.90 (0.77-1.05)	0.1687
All-cause mortality	Reference	0.89 (0.78-1.01)	0.0766	0.84 (0.76-0.91)	<0.001

Table 11: Adjusted HR with 95% CI for any acidosis/serious infection in subgroups with different eGFR intervals

	30≤eGFR<45			45≤eGFR<60			eGFR≥60		
	N (%)	**Events (%)**	**HR (95% CI)**	**N (%)**	**Events (%)**	**HR (95% CI)**	**N (%)**	**Events (%)**	**HR (95% CI)**
Any acidosis/serious infection									
Metformin-based treatments	692 (33.9)	143 (28.4)	0.98 (0.79-1.21)	4,000 (57.5)	557 (49.4)	0.85 (0.74-0.97)*	27,618 (67.3)	2,444 (60.6)	0.91 (0.84-0.98)*
Insulin-based treatments	1,302 (63.7)	366 (72.6)	1.34 (1.02-1.76)*	3,406 (48.9)	652 (57.9)	1.07 (0.91-1.26)	17,152 (41.8)	2,057 (51)	1.22 (1.12-1.32)***
Other OHA-based treatments	738 (36.1)	166 (32.9)	~	2,555 (36.7)	379 (33.6)	0.87 (0.75-1.00)	13,852 (33.7)	1,375 (34.1)	1.02 (0.95-1.09)
Total in group	2,044	504		6,960	1127		41,408	4,034	

Table 12: Adjusted HR with 95% CI for any CVD in subgroups with different eGFR intervals

	30≤eGFR<45			45≤eGFR<60			eGFR≥60		
	N (%)	Events (%)	HR (95% CI)	N (%)	Events (%)	HR (95% CI)	N (%)	Events (%)	HR (95% CI)
Any CVD									
Metformin	670 (35.4)	210 (30.7)	1.00 (0.83-1.19)	3,839 (57.7)	849 (51.2)	0.94 (0.84-1.05)	27,083 (67.3)	3,698 (63.4)	0.98 (0.92-1.05)
Insulin	1,180 (62.3)	474 (69.2)	1.30 (1.02-1.64)*	3,201 (48.1)	930 (56.1)	1.24 (1.09-1.42)**	16,718 (41.5)	2,853 (48.9)	1.19 (1.11-1.27)***
Other OHA	702 (37.1)	241 (35.2)	1.03 (0.85-1.26)	2,450 (36.8)	608 (36.7)	1.05 (0.93-1.18)	13,552 (33.7)	2,065 (35.4)	1.03 (0.97-1.09)
Total in group	1,894	685		6,655	1,657		40,239	5,829	

Table 13: Adjusted HR with 95% CI for all-cause mortality in subgroups with different eGFR intervals

	30≤eGFR<45			45≤eGFR<60			eGFR≥60		
	N (%)	Events (%)	HR (95% CI)	N (%)	Events (%)	HR (95% CI)	N (%)	Events (%)	HR (95% CI)
All-cause mortality									
Metformin	715 (33.3)	179 (27)	1.02 (0.84-1.24)	4,079 (56.8)	558 (46.5)	0.87 (0.77-0.99)*	28,015 (67.1)	2,120 (56.9)	0.87 (0.81-0.94)***
Insulin	1,386 (64.6)	468 (70.5)	1.16 (0.91-1.47)	3,550 (49.5)	701 (58.4)	1.12 (0.95-1.31)	17,565 (42.1)	1,921 (51.5)	1.29 (1.19-1.41)***
Other OHA	766 (35.7)	222 (35.7)	0.97 (0.79-1.19)	2,626 (36.6)	429 (35.7)	0.97 (0.84-1.11)	14,049 (33.6)	1,375 (36.9)	1.10 (1.02-1.19)*
Total in group	2,146	664		7,177	1,201		41,756	3,729	

OHA: other hypoglycemic agents
*p<0.05; **p<0.01; ***p<0.001. ~ Non-proportional hazards, group excluded from analysis

AUTHOR'S CONCLUSION

"Metformin was associated with reduced risk of all-cause mortality compared with both insulin and other OHA and for several additional end points compared with insulin. The results were consistent in a subgroup of patients with renal impairment, and no increased risk of acidosis/serious infection was seen."

CRITIQUE

Strengths

- 51,675 patients with type 2 diabetes
- Extensive adjustments for many important covariates
- The NDR database highly represented of clinical practice
- Multiple relevant endpoints investigated and several comparisons made between various possible groups of treatment combination
- Provided median daily dose of metformin

Weaknesses

- Not a randomized double-blinded trial
- Patients who experienced an end point event between first prescription and baseline were excluded from the analysis of that specific end point
- Patients who changed glucose-lowering treatment during the study were not censored
- Did not analyze doses of metformin in each eGFR interval
- Did not provide plasma metformin concentration

IMPLICATIONS	• Metformin in monotherapy showed a significant reduced risk of any or fatal acidosis/serious infection, all-cause mortality, and any CVD compared with insulin in monotherapy • Metformin in monotherapy also showed a significant reduced risk of all-cause mortality compared with other OHA in monotherapy • Metformin-based treatments were not associated with increased risks of any acidosis/serious infection in reduced eGFR a) Reduced risks of acidosis/serious infection and all-cause mortality in patients with eGFR 45–60 ml/min/1.73 m^2 b) Reduced risks of any CVD in patients with eGFR >60 ml/min/1.73 m^2

CONCLUSIONS

I. Literature Review Summary
   a) Metformin was not associated with a significant change in lactate levels compared to other antidiabetic agents
   b) Incidence of metformin related lactic acidosis was low and similar to that of other antidiabetic agents
   c) Use of metformin in renal impairment was not associated with increased risks of lactic acidosis

II. Guidelines Positions
   a) Serum creatinine concentration alone should not be used to assess the level of kidney function
   b) Although current U.S. labeling of metformin warns against the use of metformin in patients with SCr $\geq$ 1.4 mg/dL in females and $\geq$ 1.5 mg/dL in males, the newly published guideline from the American Diabetes Association endorses using eGFR cut-offs

III. Recommendations
   a) Initiating or continuing metformin in patients with renal impairment requires the use of clinical judgment
      i. Presence of comorbid conditions/risk factors
         • Advanced or decompensated heart failure
         • Advanced renal and hepatic disease
         • Sepsis, shock, acidosis, other acute illnesses
         • High risk medications
      ii. Potential benefits and response to therapy
   b) Metformin therapy should be interrupted if acute changes in renal function occur or are anticipated due to an acute major illness
   c) The drug should be stopped before procedures involving the administration of iodinated contrast media, which can acutely alter renal function and may lead to lactic acidosis
      i. Renal function should be reevaluated after the procedure before resuming metformin therapy
   d) Patients currently on metformin
      i. Repeat renal function test one to two weeks after an abnormal SCr to ensure that renal function has not deteriorated
      ii. Review the dose of metformin if eGFR < 45 ml/min/1.73m^2 and consider dose reduction
      iii. Stop metformin if eGFR < 30 ml/min/1.73m^2
   e) Patients not currently on metformin
      i. Metformin is contraindicated in stage 4 and 5 chronic kidney disease
      ii. Initiate metformin with caution for those with eGFR < 60 ml/min/1.73m^2 and at risk of a sudden deterioration in kidney function

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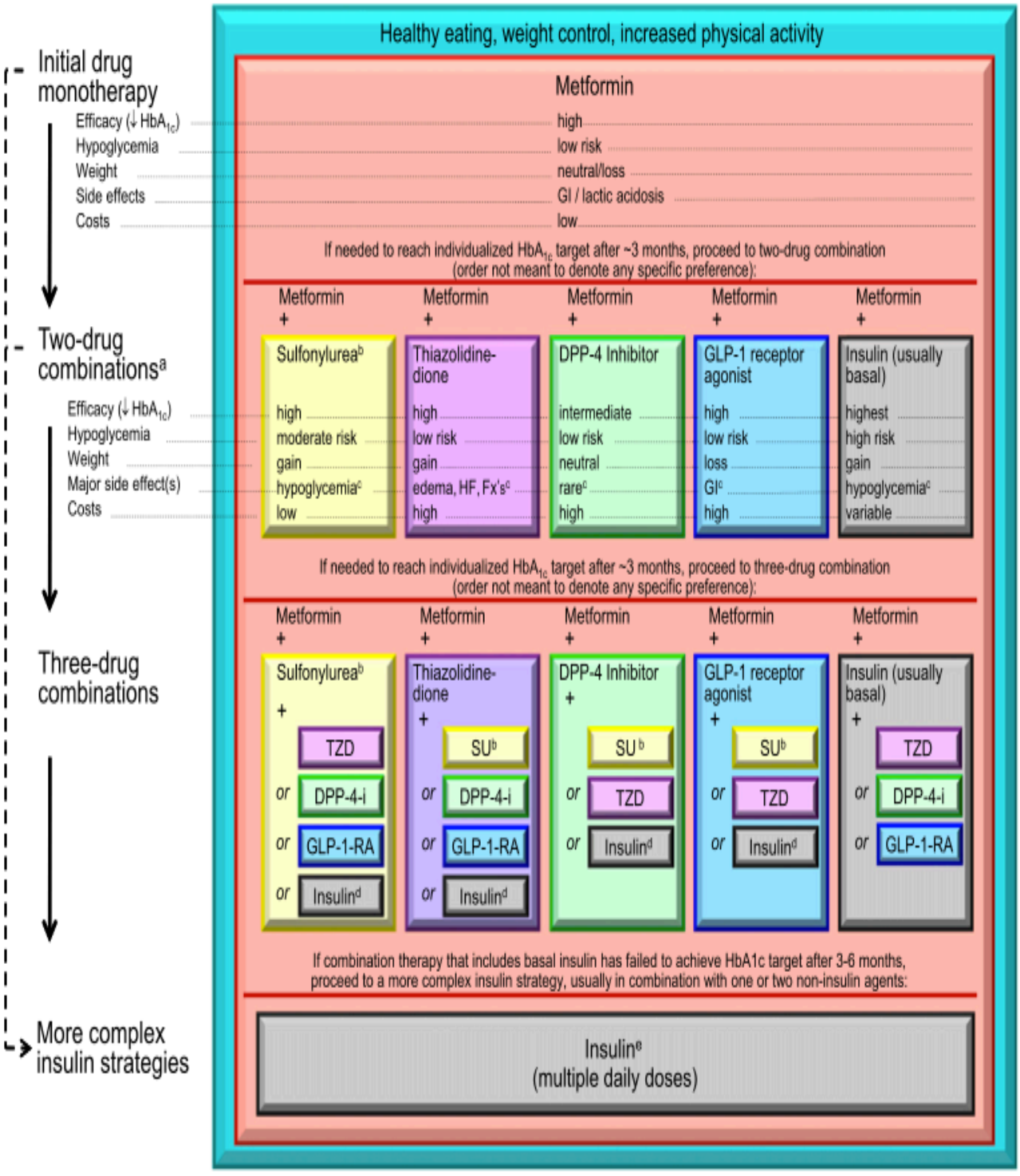
APPENDIX A: ALGORITHM OF ANTIGYPERGLYCEMIC THERAPY IN TYPE 2 DIABETES



Adapted from Inzucchi et al. *Diabetes Care* 2012;35:1364–1379.