CASO CLINICO N° 4

" Un diabete…..un po' ingombrante"

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Caso clinico - Rosa : Anamnesi patologica prossima

- Riferisce che per circa 10 anni ha assunto I.O con scarso controllo glicemico e da 2 anni è in trattamento insulinico intensivo basal-bolus con un compenso a suo dire accettabile (HbA_{1c} : 7.8%).

- Lamenta da allora di essere ingrassata , di sentisi gonfia e di essere diventata ormai "ingombrante" tanto da non riuscire piu' a svolgere le normali attivita' domestiche

. Lo specialista che la segue tuttavia,sostiene che questa insulina debba farla a vita per proteggere l'occhio e il rene dal diabete.

. Con sua insistenza è riuscita a convincere il suo MMG a consultare un altro specialista , perche' lei questa insulina proprio non vuole piu farla!

Caso clinico -Rosa : Anamnesi fisiologica e patologica

- **63 anni,** casalinga, sedentaria, non fumatrice

- **familiarita'** positiva per DM2 e Obesita' (Madre) negativa per CVD

- **Diabetica** tipo2 **ed ipertesa** da 16 anni, in terapia insulinica da 2 anni
- **Obesa da diversi anni** con progressivo incremento ponderale
- **Cardiopatia ischemica** rivascolarizzata mediante **PTCA** (2007)

- **Terapia:**

Levemir 40 UI, Humalog 15-18-20 (93 UI tot = 0.88 UI/kg)
Atorvastatina 20 mg, ASA 100,Pantoprazolo 40 mg,
Bisoprololo 2.5 mg , Valsartan 320 mg, Diuremid

Caso clinico - Rosa : Esami clinici, di laboratorio e strumentali

Peso: 105 kg ; **BMI:** 39 kg/m^2 ; **CV :** 121 cm
PA: 140/75 mmHg; **Fc:** 70 bpm
Es. obiettivo: nulla di patologico

HbA_{1c} 7.8 % **glicemia**: 174 mg/dl
Profilo glicemico: 145/ 178 ; 160/ 195; 154/ 200
LDL 75 mg/dl; **HDL:** 45 mg/dl; **Tg:** 164 mg/dl
Creatinina: 0.9 mg/dl ;**GFR:** CKD epi: 70 ml/min/1.73m2; **AER:** 10 g/dl
Routine normale

F.00: Assente Retinopatia diabetica e ipertensiva
Eco-doppler TSA: Ateromasia TSA 20% stabile, bilaterale
Eco 2d: lieve I.v.sx ed FE conservata

1a DOMANDA

Quale target terapeutico raggiungere?

1. 7.5% ≤ HbA_{1c} ≤ 8.5%
2. HbA_{1c} ≤ 7.0%
3. HbA_{1c} ≤ 7 % in assenza di ipoglicemie

   e ↓ ponderale del 5-10% (del peso iniziale)

1a DOMANDA : commento

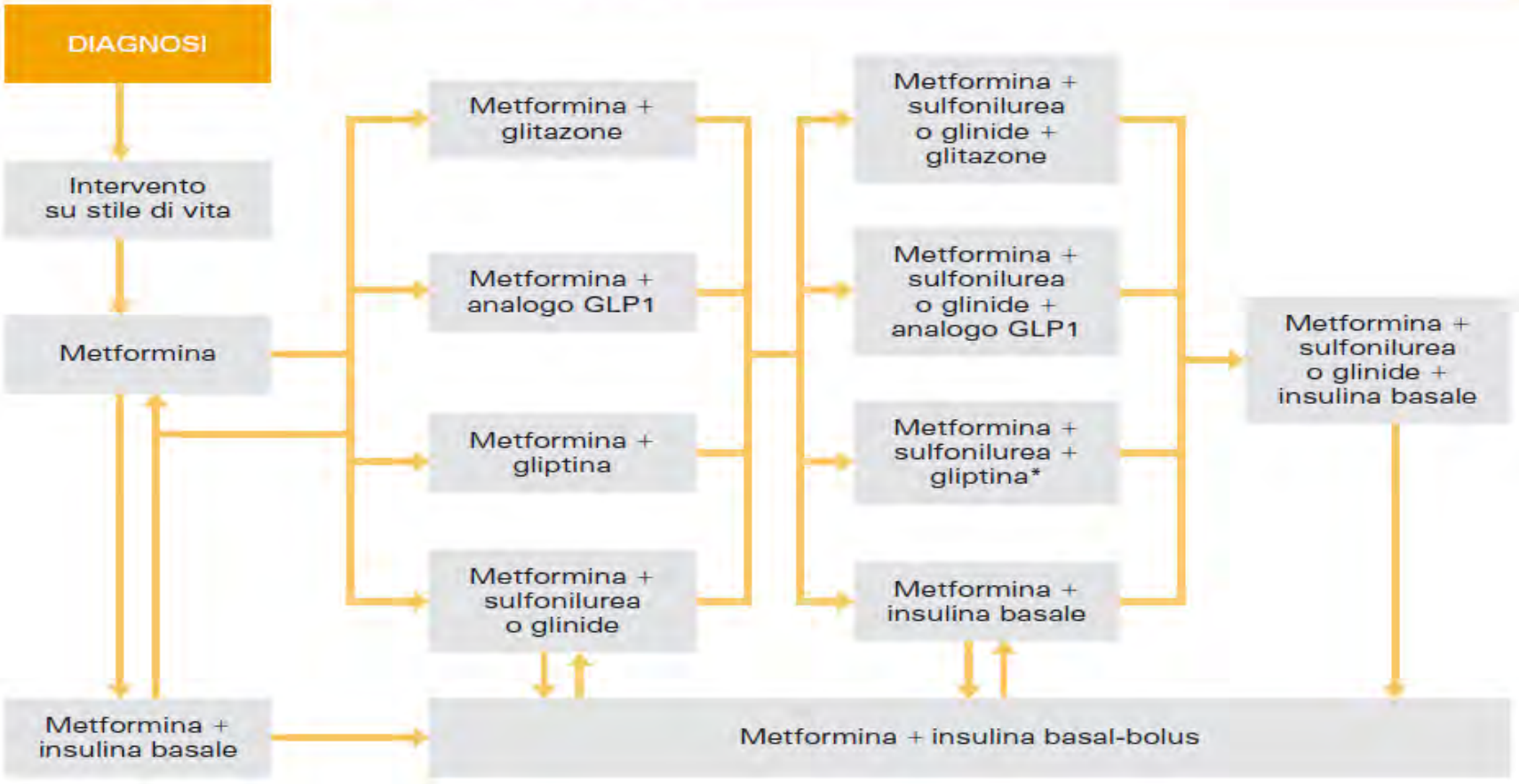
1. Il compenso glicemico **è gia 'ottimale (target : HA1c 7.5 - 8.5%) considerando la cardiopatia ischemica e la durata di malattia**
2. Il compenso glicemico **va ottimizzato (target : HA1c ≤ 7.0%) è assente la microangiopatia nonostante la lunga durata di malattia**
3. **Per ridurre entrambe le complicanze** andrebbe perseguito un **controllo metabolico globale e intensivo (pressorio, lipidico, glicemico , ponderale) con basso rischio di ipoglicemia e un'adeguata riduzione ponderale**
   (HA1c ≤ 7.0% ; riduzione ponderale del 5-10% del peso iniziale)

2a DOMANDA: quale trattamento ?

1. Aggiungo metformina (2 gr/die) e riduco l'insulina prandiale
2. Aggiungo pioglitazone (15 mg/die) e riduco l'insulina prandiale
3. Sostituisco l'insulina prandiale con una solfanilurea
4. Sostituisco gradualmente l'insulina prandiale con l'associazione DPPIV / metformina
5. Altro

Standard Italiani SID-AMD

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



Standard italiani per la cura del diabete mellito 2009-2010

1° step) Aggiungere metformina 2 gr /die e ridurre del 30% l' insulina

Peso: 105 Kg

1 mese : Terapia: Levemir 32 UI + Analogo rapido 8-12-10

Profilo 1 : 92/100; 112/118; 138/142 (62 UI = 0.6UI/kg)

Profilo 2 : 98/ 110; 116/124; 135/136 (40 UI = 0.4UI/kg)

2° step) Stop insulina prandiale

Insulina Basale + metformina 2 gr /die + Gliptina 100 mg/die

Peso : 104 -> 100 Kg

Hb A1c: 7,8 -> 7,4 %

3 mesi : Terapia: Levemir 28 UI + Sita 50/1000 mg bid (28 UI= 0,26 UI/kg)

Profilo: 125/140; 120/138; 128/142

3° step) Stop gliptina

Insulina Basale + metformina 2 gr /die + Analogo GLP1 (1.8 mg/die)

Peso : 100 -> 87 Kg; CV ; 121-> 108 cm

Hb A1c: 7,8 -> 6,7 %

12 mesi : Terapia: Levemir 18 UI + Analogo GLP1 (18 UI= 0,20 UI/kg)

Profilo: 120/130; 114/136; 120/130

Benefici del trattamento: dopo 15 anni di malattia

. Raggiungimento del controllo glicemico ottimale
non gravato da episodi ipoglicemici e stabile nell'arco dell' anno

. Riduzione ponderale di 17 Kg in 1 anno circa

. Controllo metabolico globale ottimale→Prevenzione delle complicanze
(primaria della microangiopatia e secondaria della macroangiopatia

. Riduzione della frequenza dell'automonitoraggio glicemico
(dalla classe 1 alla classe 3) con miglioramento della qualita' di vita

. Riduzione del 40% delle unita di insulina rispetto al basale
con riduzione ponderale e dei costi

Add an agent best suited to the individual (agents listed in alphabetical order):					
Class	**Relative A1C lowering**	**Hypo-glycemia**	**Weight**	**Other therapeutic considerations**	**Cost**
Alpha-glucosidase inhibitor (acarbose)	↓	Rare	neutral to ↓	Improved postprandial control, GI side-effects	$$
Incretin agents: DPP-4 Inhibitors GLP-1 receptor agonists	 ↓↓ ↓↓ to ↓↓↓	 Rare Rare	 neutral to ↓ ↓	 GI side-effects	 $$$ $$$$
Insulin	↓↓↓	Yes	↑↑	No dose ceiling, flexible regimens	$-$$$$
Insulin secretagogue: Meglitinide Sulfonylurea	 ↓↓ ↓↓	 Yes Yes	 ↑ ↑	 Less hypoglycemia in context of missed meals but usually requires TID to QID dosing Gliclazide and glimepiride associated with less hypoglycemia than glyburide	 $$ $
TZD	↓↓	Rare	↑↑	CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect	$$
Weight loss agent (orlistat)	↓	None	↓	GI side effects	$$$

Glycemic Control Algorithm

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

ENTRY A1c < 7.5%

MONOTHERAPY*
- Metformin
- GLP-1 RA
- DPP4-i
- AG-i
- SGLT-2 **
- TZD
- SU/GLN

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

ENTRY A1c ≥ 7.5%

DUAL THERAPY*

MET + (or other first-line agent)
- GLP-1 RA
- DPP4-i
- TZD
- ** SGLT-2
- Basal insulin
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

If not at goal in 3 months proceed to triple therapy

TRIPLE THERAPY*

MET + (or other first-line agent) + 2ND LINE AGENT
- GLP-1 RA
- TZD
- ** SGLT-2
- Basal insulin
- DPP4-i
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

ENTRY A1c > 9.0%

NO SYMPTOMS	SYMPTOMS
DUAL THERAPY OR TRIPLE THERAPY	INSULIN ± OTHER AGENTS

ADD OR INTENSIFY INSULIN

* Order of medications listed are a suggested hierarchy of usage

** Based upon phase 3 clinical trials data

LEGEND

✓ = Few adverse events or possible benefits

! = Use with caution

PROGRESSION OF DISEASE

Algorithm for Adding/Intensifying Insulin

START BASAL (long-acting insulin)

A1c < 8% → **TDD 0.1–0.2 U/kg**

A1c > 8% → **TDD 0.2–0.3 U/kg**

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** > 180 mg/dL: add 4 U
  - **FBG** 140–180 mg/dL: add 2 U
  - **FBG** 110–139 mg/dL: add 1 U
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10% – 20%
  - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after basal insulin started (basal analogs preferred to NPH)

**** Glycemic Goal:**

- For most patients with T2D, an A1c < 7%, fasting and premeal BG < 110 mg/dL in the absence of hypoglycemia.
- A1c and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk.

Glycemic Control Not at Goal**

INTENSIFY (prandial control)

Add GLP-1 RA or DPP4-i

Add Prandial Insulin

TDD: 0.3-0.5 U/kg
50% Basal Analog
50% Prandial Analog
Less desirable: NPH and regular insulin or premixed insulin

Insulin titration every 2–3 days to reach glycemic goal:

- Increase basal TDD as follows:
  - Fixed regimen: Increase TDD by 2 U
  - Adjustable regimen:
    - FBG > 180 mg/dL: add 4 U
    - FBG 140–180 mg/dL: add 2 U
    - FBG 100–139 mg/dL: add 1 U
- Increase prandial dose by 10% for any meal if the 2-hr postprandial or next premeal glucose is > 180 mg/dL
- Premixed: Increase TDD by 10% if fasting/premeal BG > 180 mg/dL
- If fasting AM hypoglycemia, reduce basal insulin
- If nighttime hypoglycemia, reduce basal and/or pre-supper or pre-evening snack short/rapid-acting insulin
- If between meal daytime hypoglycemia, reduce previous premeal short/rapid-acting insulin

Conclusioni

Nei pazienti diabetici con obesita' importante ed elevato fabbisogno insulinico indipendentemente dalla durata di malattia
prima di instaurare un trattamento insulinico intensivo, sarebbe opportuno considerare associare all' insulina basale /metformina un GLP1RA se tollerato o una gliptina, dati i numerosi benefici clinici per il paziente e la riduzione dei costi.

AT DIAGNOSIS OF TYPE 2 DIABETES

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Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

A1C <8.5%	A1C ≥8.5%	Symptomatic hyperglycemia with metabolic decompensation
∨	∨	∨
If not at glycemic target (2-3 mos)	Start metformin immediately	Initiate insulin +/- metformin
∨	Consider initial combination with another antihyperglycemic agent	
Start / Increase metformin		

∨

> If not at glycemic targets <

∨

Add an agent best suited to the individual:

Patient Characteristics	Agent Characteristics
Degree of hyperglycemia	BG lowering efficacy and durability
Risk of hypoglycemia	Risk of inducing hypoglycemia
Overweight or obesity	Effect on weight
Comorbidities (renal, cardiac, hepatic)	Contraindications & side-effects
Preferences & access to treatment	Cost and coverage
Other	Other

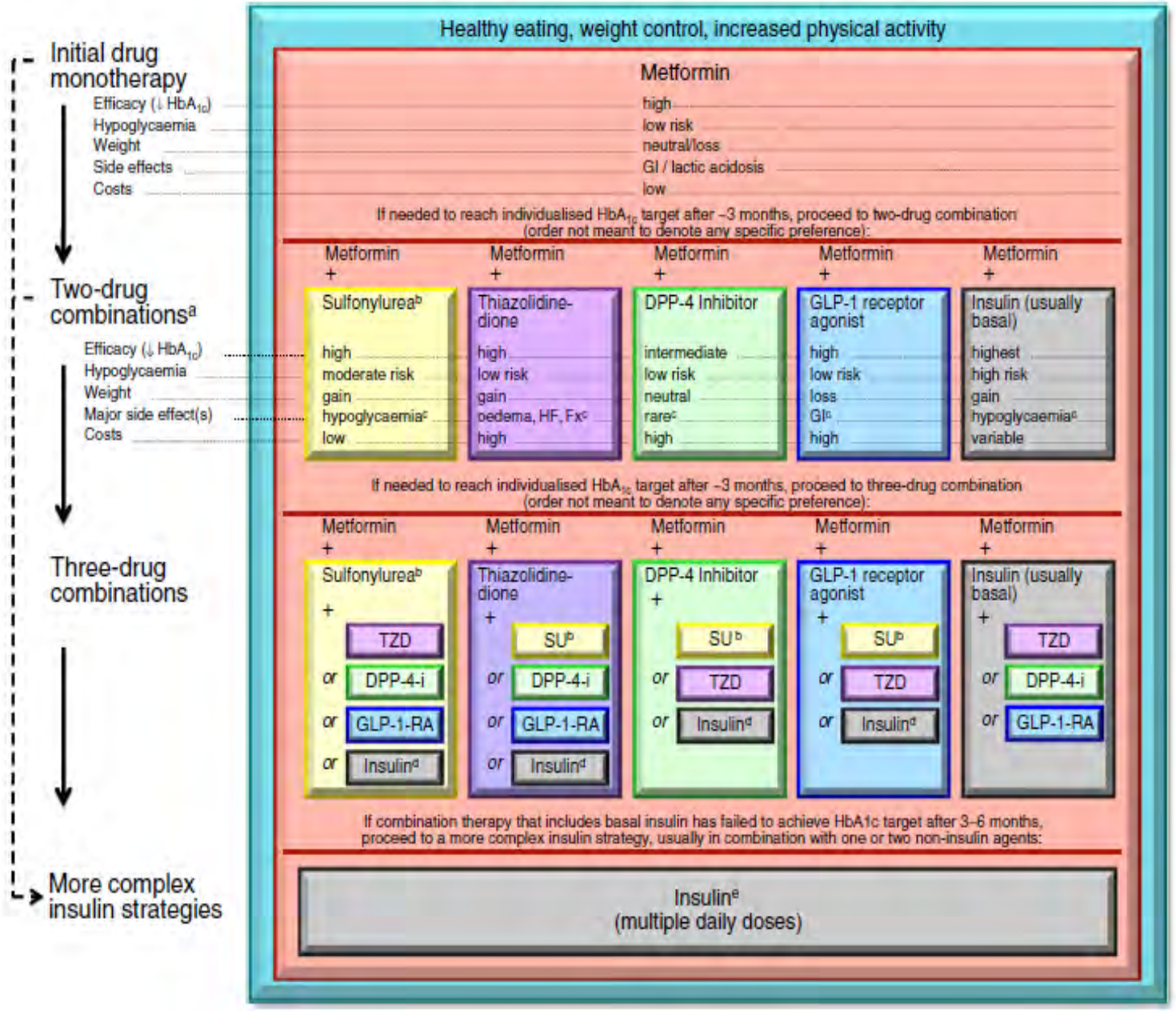
∨

See next page…

L I F E S T Y L E

2013

Position Statement ADA-EASD 2012



Inzucchi SE, et al. Diabetes Care 2012;35:1364-79

Principles of the AACE Algorithm for the Treatment of Type 2 Diabetes

1) Lifestyle optimization is essential for all patients with diabetes. This is multifaceted, ongoing, and engages the entire diabetes team. However, such efforts should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on the response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it.
2) The A1c target must be individualized, based on numerous factors, such as age, co-morbid conditions, duration of diabetes, risk of hypoglycemia, patient motivation, adherence, life expectancy, etc. An A1c of 6.5% or less is still considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate and may change in a given individual over time.
3) Glycemic control targets include fasting and postprandial glucose as determined by self blood glucose monitoring.
4) The choice of therapies must be individualized based on attributes of the patient (as above) and the medications themselves (see *Profiles of Anti-Diabetic Medications*). Attributes of medications that affect their choice include: risk of inducing hypoglycemia, risk of weight gain, ease of use, cost, and safety impact of kidney, heart, or liver disease. This algorithm includes every FDA-approved class of medications for diabetes. This algorithm also stratifies choice of therapies based on initial A1c.
5) Minimizing risk of hypoglycemia is a priority. It is a matter of safety, adherence, and cost.
6) Minimizing risk of weight gain is a priority. It too is a matter of safety, adherence, and cost.
7) The algorithm provides guidance to what therapies to initiate and add, but respects individual circumstances that would make different choices.
8) Therapies with complementary mechanisms of action must typically be used in combinations for optimum glycemic control.
9) Effectiveness of therapy must be evaluated frequently until stable (e.g. every 3 months) using multiple criteria including A1c, SMBG records including both fasting and post-prandial data, documented and suspected hypoglycemia, and monitoring for other potential adverse events (weight gain, fluid retention, hepatic, renal, or cardiac disease), and monitoring of co-morbidities, relevant laboratory data, concomitant drug administration, diabetic complications, and psycho-social factors affecting patient care.
10) Safety and efficacy should be given higher priorities than initial acquisition cost of medications per se since cost of medications is only a small part of the total cost of care of diabetes. In determining the cost of a medication, consideration should be given to monitoring requirements, risk of hypoglycemia and weight gain, etc.
11) The algorithm should be as simple as possible to gain physician acceptance and improve its utility and usability in clinical practice.
12) The algorithm should serve to help educate the clinician as well as to guide therapy at the point of care.
13) The algorithm should conform, as nearly as possible, to a consensus for current standard of practice of care by expert endocrinologists who specialize in the management of patients with type 2 diabetes and have the broadest experience in outpatient clinical practice.
14) The algorithm should be as specific as possible, and provide guidance to the physician with prioritization and a rationale for selection of any particular regimen.
15) Rapid-acting insulin analogs are superior to Regular because they are more predictable.
16) Long-acting insulin analogs are superior to NPH insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency both between subjects and within subjects, with a corresponding reduction in the risk of hypoglycemia.

This document represents the official position of the American Association of Clinical Endocrinologists and the American College of Endocrinology. Where there were no RCTs or specific FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Many details that could not be included in the graphic summary (Figure) are described in the text.