How to prevent iatrogenic risk with antidiabetics in older people

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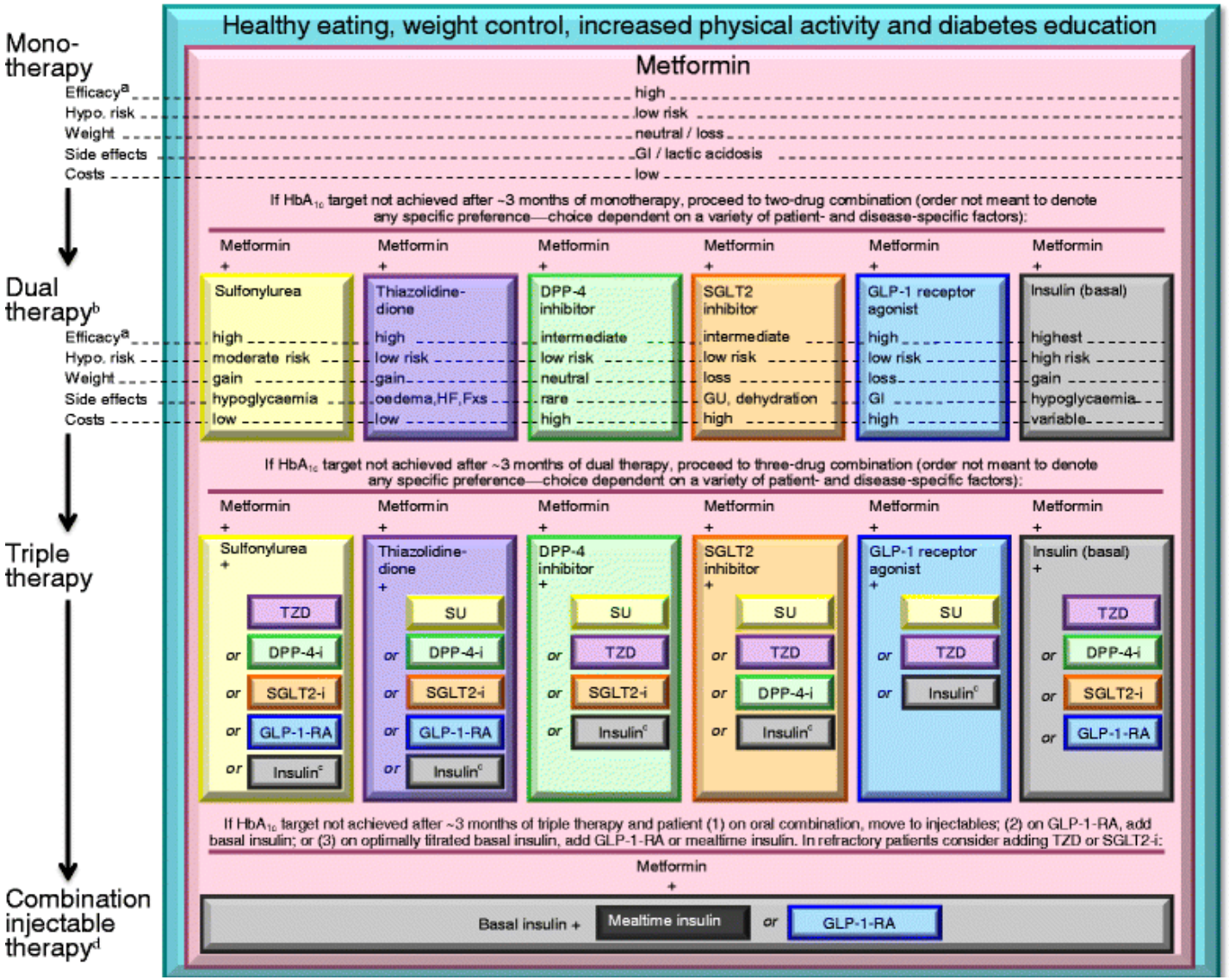
CONFLICT OF INTEREST DISCLOSURE

I have the following potential conflicts of interest to report

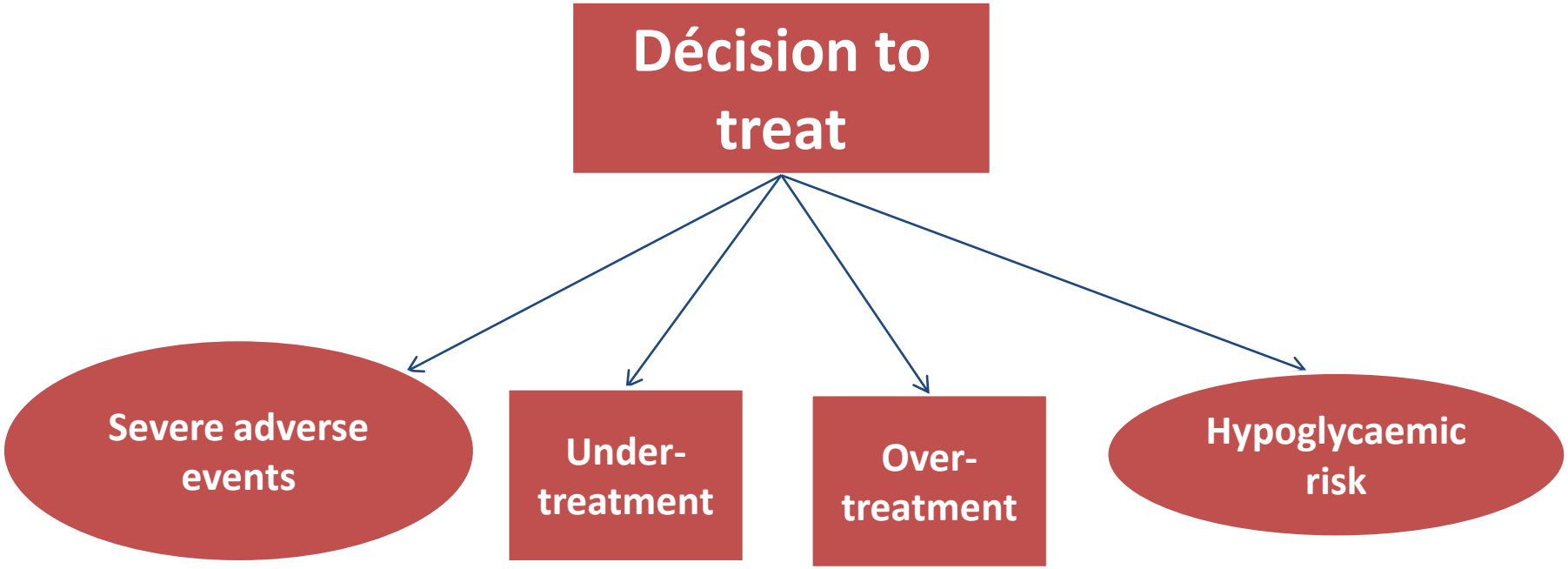
- Conference in symposia from pharmaceutical compagnies
  Sanofi, Novo Nordisk, Novartis, Merks, Boerhinger
- Scientific advise
  Sanofi, Lilly
- Investigator and / or writer in clinical trial / scientific review
  - Novartis, Nutricia, Sanofi

Treatment decision in type 2 diabetes



In frail older people
No triple therapy
No association insulin + sulfonylureas

ADA / EASD; Inzucchi SE, Diabetologia. 2015 Mar;58(3):429-42


Décision to treat
Severe adverse events
Under-treatment
Over-treatment
Hypoglycaemic risk

Decision to treat in T2DM

- In all older people
  - drug contra-indications / side-effects more frequent
  - Limitations due to comorbidities and polymedication
- In frail older people
  - mono or dual therapy only
  - Insulin use more frequent

Metformin: the first line therapy

- Effective
  - Glucose-lowering
  - Cardio-vascular prevention
- Low hypoglycemia risk
- Low-cost
- Few side-effects
- Remaining questions
  - Metformin-Associated Lactic Acidosis
  - Appetite and weight regulation
  - Mental effects

Metformin-associated lactic acidosis: MALA

MALA is rare but serious adverse event: high mortality

- 13.8 cases/year/100,000 metformin-treated diabetics with 50% survival, Mariano F, Blood Purif 2017;44:198-205
- Are MALA episodes really MALA ??
  - Metformin dosage should be done and physiopathology of the event analysed : Lalau J-D, Diabetes Obes Metab. 2017;1–11.
- Few epidemiological evidence for an increase risk of acidosis among metformin users as compared to others
  - Epidemiology is not the good tool to analyse metabolic adverse event
- Under-declaration of MALA: lacking registries
- Two main contra-indications to the use of metformin
  - Hypoxemic diseases
  - Renal failure
    - Stop prescription if GFR < 30ml/min
    - Caution if GFR < 45ml/min

- Precaution: limiting the dosage of metformin to the lowest necessary to achieve blood glucose

Metformin: Anorectic effect

- (inhibition of neuropeptide Y expression) Duan Y, Neural Regen Res. 2013 Sep 5; 8(25): 2379–2388
- (decreased perceived hunger in children) Adeyemo MA, Diabetes, Obesity and Metabolism 17: 363–370, 2015.

- Effect of DOSAGE ?
- No published data about the weight loosing effect in older or frail people

- Precaution: limiting the dosage to the minimum necessary to achieve blood glucose control target

Metformin, long term use and mental health

- Protective ?
  - Cognition
    - Ng TP, J Alzheimers Dis. 2014;41(1):61-8
  - Depression
    - Wang CP, J Diabetes Complications. 2017;31(4):679-86
- Deleterious ?
  - Cognition
    - Longitudinal: long term use of metformin increased SLIGHTLY the risk of developping AD: AOR = 1.71, 95% CI = 1.12–2.60. Imfeld P, J Am Geriatr Soc 60:916–921, 2012
    - Cross-sectional: more cognitive impairment with metformin treatment, in part due to vitamin B12 deficiency, Moore EM, Diabetes Care 36:2981–2987, 2013
  - Depression
    - Vitamin B12 deficiency increased the risk of depression in metformin users Biemans E, Acta Diabetol. 2015 Apr;52(2):383-93.

- Role of vitamin B12 deficiency ?
- Interest of Calcium supplementation to improve Vitamin B12 absorption metformin diminishes through calcium-dependent ileal membrane antagonism, an effect reversed with supplemental calcium Bauman WA, Diabetes Care 2000 Sep; 23(9): 1227-1231.
- Importance of dosage ?
- Precautions
  - limiting the dosage of metformin to the lowest necessary to achieve blood glucose
  - Monitoring of Vitamin B12 at steady state of treatment

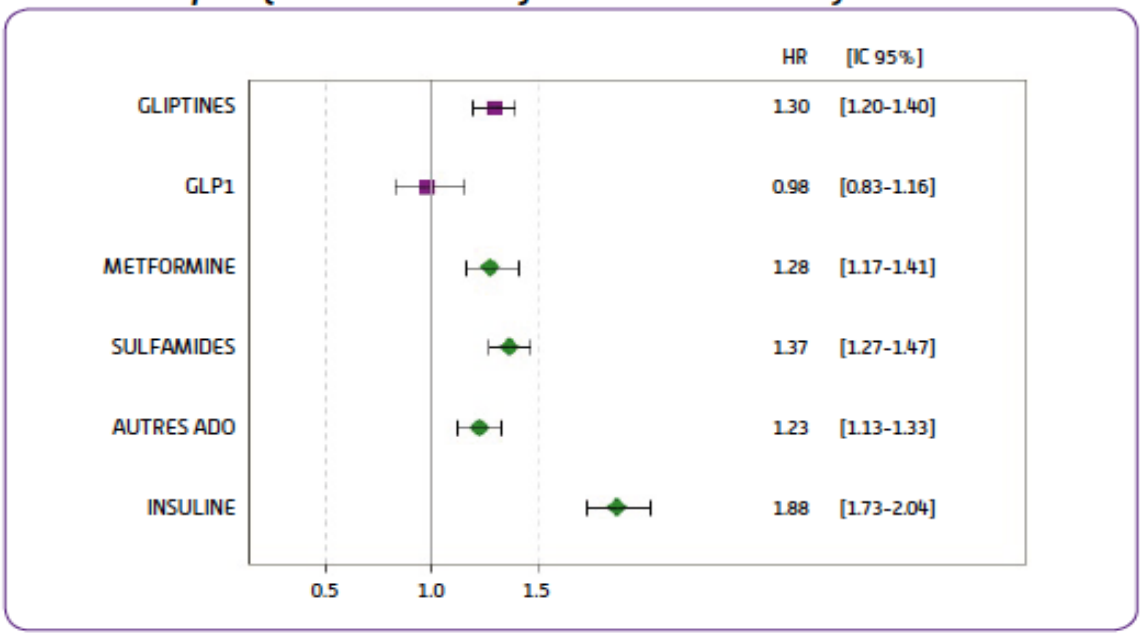
Gliptin

- Second line treatment in frail older patients in dual therapy (or monotherapy in case of contra-indication to metformin)
- Low hypoglycemic risk
- Efficiency estimated as moderate
- High cost
- Precautions: dosage decrease in case of renal insufficiency
- Side-effects ? Class and molecule effects
  - Cardiovascular: increase hospitalization for heart failure
  - Cancer
  - pancreatitis, risk of renal failure, bile duct and gall blader diseases, peripheral oedema (older people, co prescription of ACE or Sartan), hypersensitivity reaction, bullous pemphigoid

Pancreas cancer risk

- ANSM (France) report using Health insurance data base, 2010-2013, Avenin
http://ansm.sante.fr/var/ansm_site/storage/original/application/56e803c82049d20c6336eb5a2a8b4bdc.pdf

Figure 1. Risque du cancer du pancréas associé aux différents antidiabétiques (Hazard Ratios ajustés* et IC à 95 %)



* Ajustement sur âge, sexe, utilisation autres antidiabétiques, diabète compliqué, antécédent pancréatite, antécédent ulcère, antécédent lithiase, antécédent hépatite, tabac, alcool et obésité

Thiazolidinediones

- Second line treatment in frail older patients in dual therapy in case of contra-indication to DPP4-
- Low hypoglycemic risk
- Efficiency estimated as moderate
- Moderate cost
- Precautions: dosage decrease in case of renal insufficiency
- Side-effects ? Class and molecule effects
  - Increased risk for baldder cancer
  - Cardiovascular: increased hospitalizations rate for heart failure
  - Fractures
- Exit from the French market

GLP1 Analogs ANSM report 2015

- Main problems in older
  - Weight loss when unwilling
  - Dehydration and renal failure
  - Other side effects: pancreatitis, biliary ducts effects, cutaneous effects

Alpha-glucosidase inhibitors

- Low efficiency
- Low hypoglycaemic risk
- Digestive side-effects

SGLT2 inhibitors

- Second line therapy in adults
- Few assessed in older than 70y
- Effective ?
- High cost
- Low hypoglycaemic risk
- Energy lost in urine decreasing blood glucose and inducing weight loss
- Side effects:
  - Acido-ketosis in type 2 diabetes; Risk x 7 / DPP4- of acidosis, 71% euglycemic ketoacidosis, Blau JE, Diabetes Metabolism Research Review in press
  - Mycosis urinary infections
- Not in the French market (cost)
- Probably not the preferred drug in > 75y

Sulfonylureas and glinides

- Second line therapy
- Efficient
- Low cost
- Drug interactions: numerous
- Hypoglyceamic risk: high or very high (glibenclamide)
- Cardiovascular risk for sulfonylureas
  - Controversies but no specific studies in > 75y
- Glinides can be prescribed in case of renal failure
  - In older and in case of renal insufficiency the half-life is long

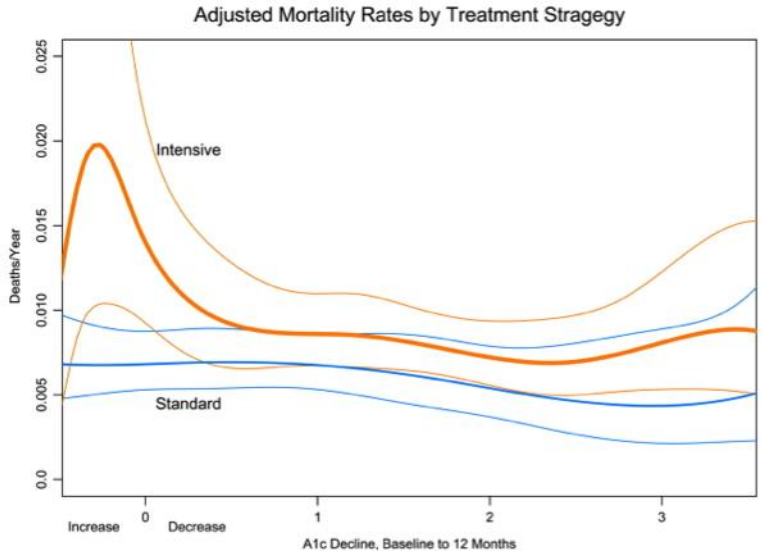
Insulin (s)

- Third line therapy or first line in malnutrition
- Efficient
- Various costs depending on the ability of subjects for self-injections
- No drug interaction, no contra-indications
- Hypoglyceamic risk: very high particularly in association with sulfonylureas (to strictly avoid in frail olders)
- Risk of non adapted insulin schema (hypoglycaemia/hyperglycaemia alternately)

The iatrogenic cost of treatment intensification

- Comment from ACCORD trial
  - Systematic intensification of glucose lowering treatment lead to 42% subjects with 3 or > oral treatment (+ insulin in 25%) in intervention arm
  - As compared with 19% usual care arm
  - The cost of lowering HbA1c with polyprescription was excess mortality

Curves displaying all-cause mortality rates by treatment for the whole period of follow-up, over a range of decreases in A1C from baseline in the 1st year of treatment (as a percentage of A1C).



- Riddle MC, Diabetes Care 2010;33:983–90, comments Charbonnel B, Diabetes Research and Clinical Practice, 2012: 3-5

Overtreatment in older possible improvements

Figure 1. Achieved Glycemic Control Among Older US Adults With Diabetes Mellitus Across 3 Health Status Categories

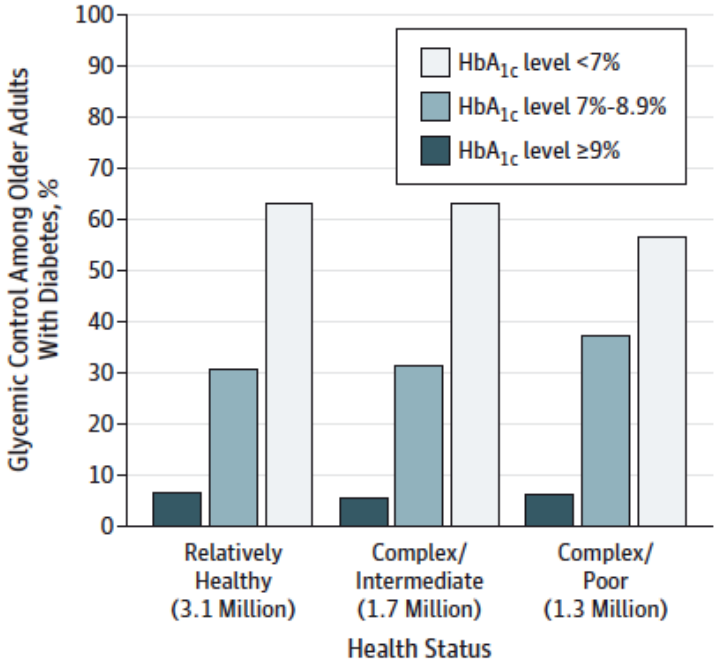
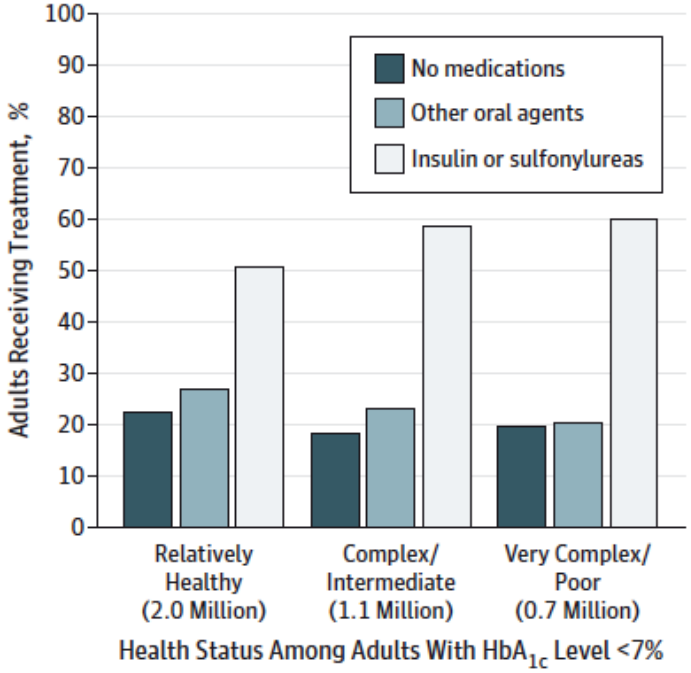


Figure 2. Treatment of Older US Adults With Diabetes Mellitus With an HbA_{1c} Level of Less Than 7% Across Health Status Categories



Lipska KJ, JAMA Intern Med. 2015;175(3):356-362

New older patient with diabetes stable situation

Assessment: CGA
Mental, comorbidities, function, social
Nutrition, dietary intake
Abilities to self manage
Global health status

Assessment:
Nutrition, dietary intake
Abilities to self manage
History of drug-side effects
Renal function

Initial visit → Nutrition/physical activities → Follow-up → Nutrition/PA Targets not achieved add-on metformin → Follow-up →

Targets for global care
Targets for blood glucose (interval)
Shared targets with patient and GP
Education patient/care-givers

Education patient/care-givers

Education patient/care-givers

Older patient with diabetes stable situation-follow-up

Assessment:
Nutrition, dietary intake
Abilities to self manage
History of drug-side effects
Renal function

Follow -up

Nutrition/physical activities
Targets not achieved
add-on second oral agent

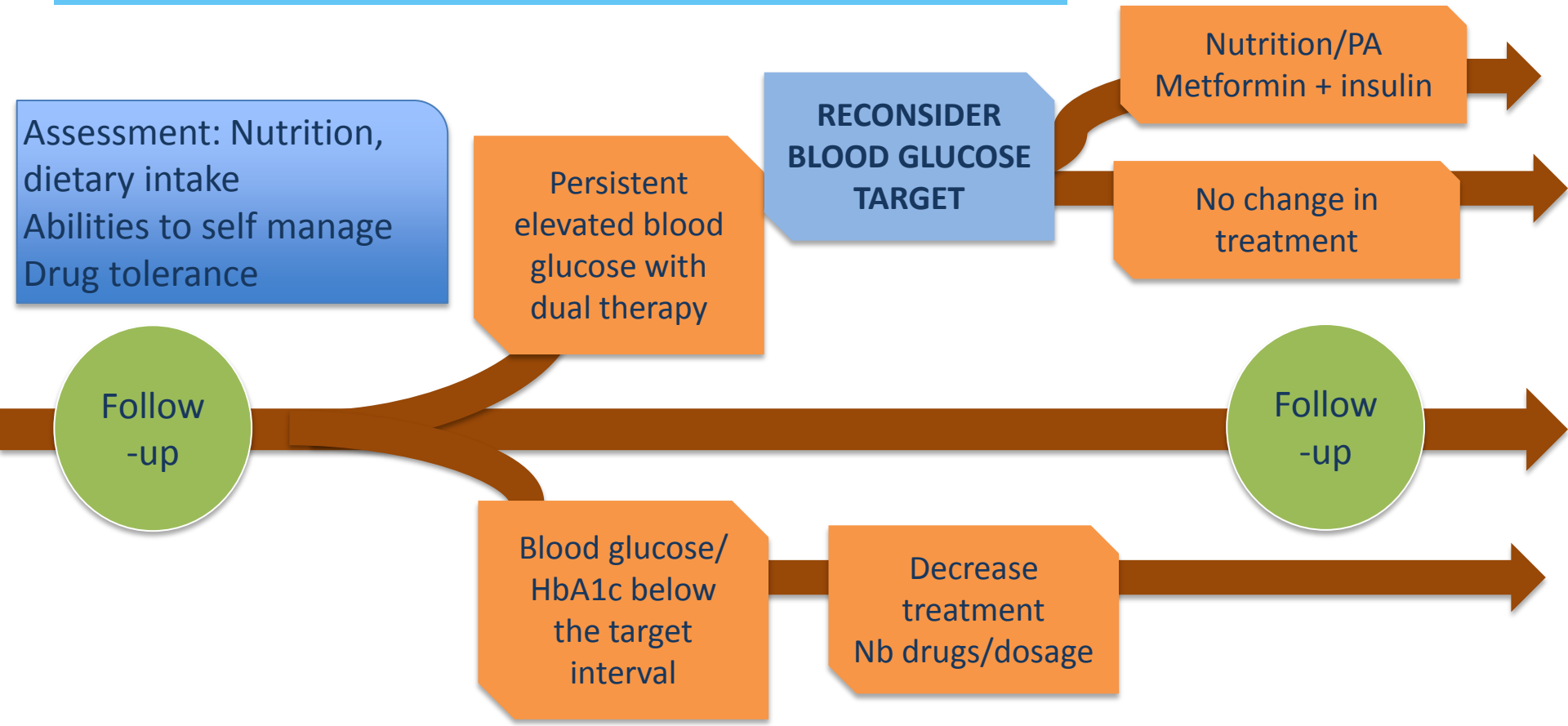
Follow -up

Education patient/care-givers

Education patient/care-givers

Education patient/care-givers

Older patient with diabetes stable situation-follow-up

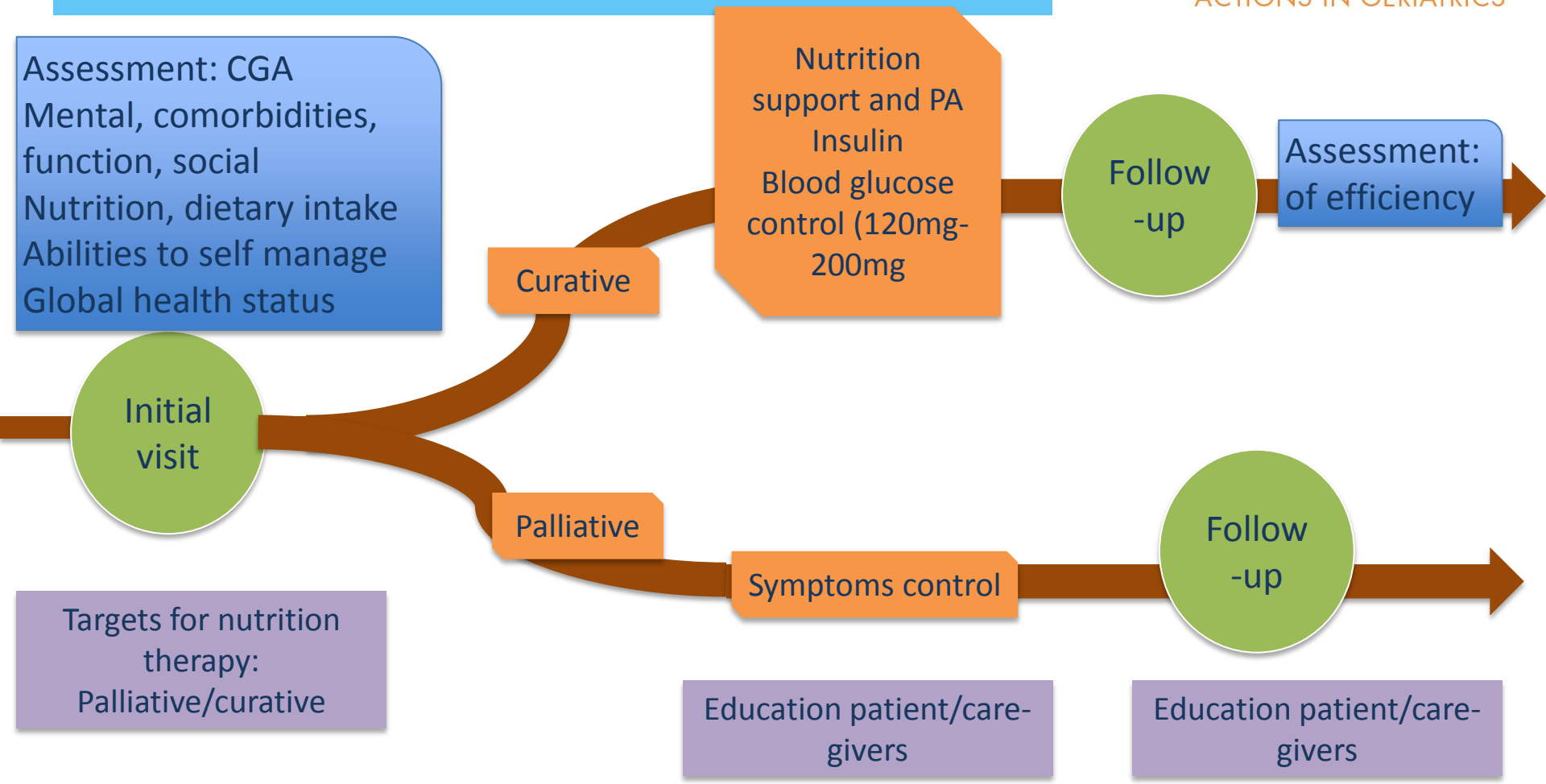


Targets not achieved with dual therapy

CGA: Research for occurrence of new health event

Education patient/care-givers

Older patient with diabetes and malnutrition



Older patient with diabetes
Acute care

Assessment:
Nutrition, dietary intake
Severity of disease/
hypoxia/renal function

Assessment:
Nutrition, dietary intake
Abilities to self manage
History of drug-side effects
Renal function

Admission

Nutrition/early mobilistion
Stop metformin
Blood glucose control 120-200mg
Insulin when required

Discharge

Targets for global care
Targets for blood glucose (interval)
Shared targets with patient and GP
Education patient/care-givers

Consider risk under and overtreatment

Follow -up

Watch the 2-week post-discharge period

Conclusions

- Assessment (CGA)
- Targets for global care
- Targets for blood glucose control
- Attention to drug side-effects and hypoglycaemic risk
- Education patient / care giver
- Watching
- Reconsider targets during treatment intensification
- Reconsider treatment when blood glucose < target interval