INQUADRAMENTO
e strategie terapeutiche
DELL'ANZIANO DIABETICO

Personalized therapy for type 2 diabetes in old age

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Firenze
23 ottobre 2017
Starhotels Michelangelo

SID
Società Italiana di Diabetologia

La sottoscritta Angela Dardano dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Boehringer Ingelheim

Agenda

1. Epidemiology of type 2 diabetes mellitus in the elderly
2. Pathogenesis of type 2 diabetes mellitus in the elderly
3. Setting the scene: who is the old patient?
4. Older patients: understanding needs
5. Goals of treatment
6. Treatment choices
7. Conclusions

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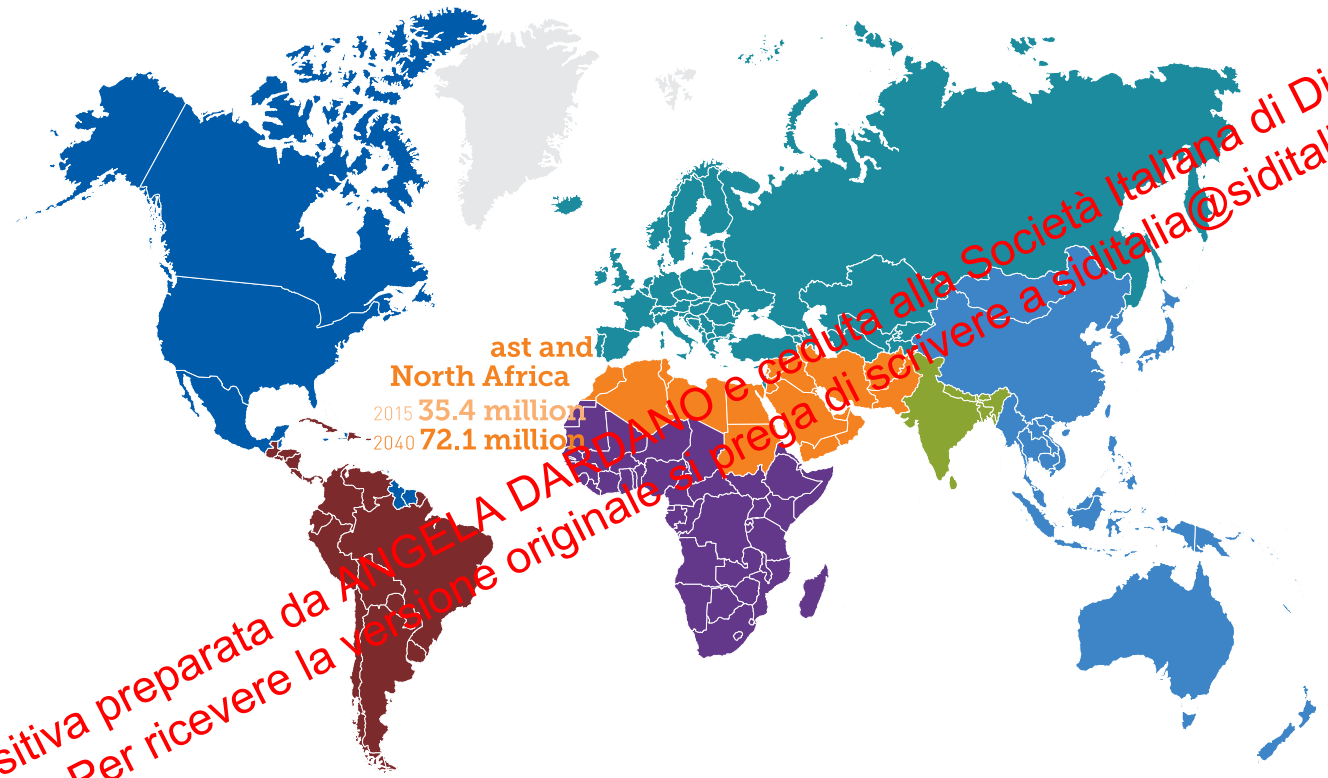
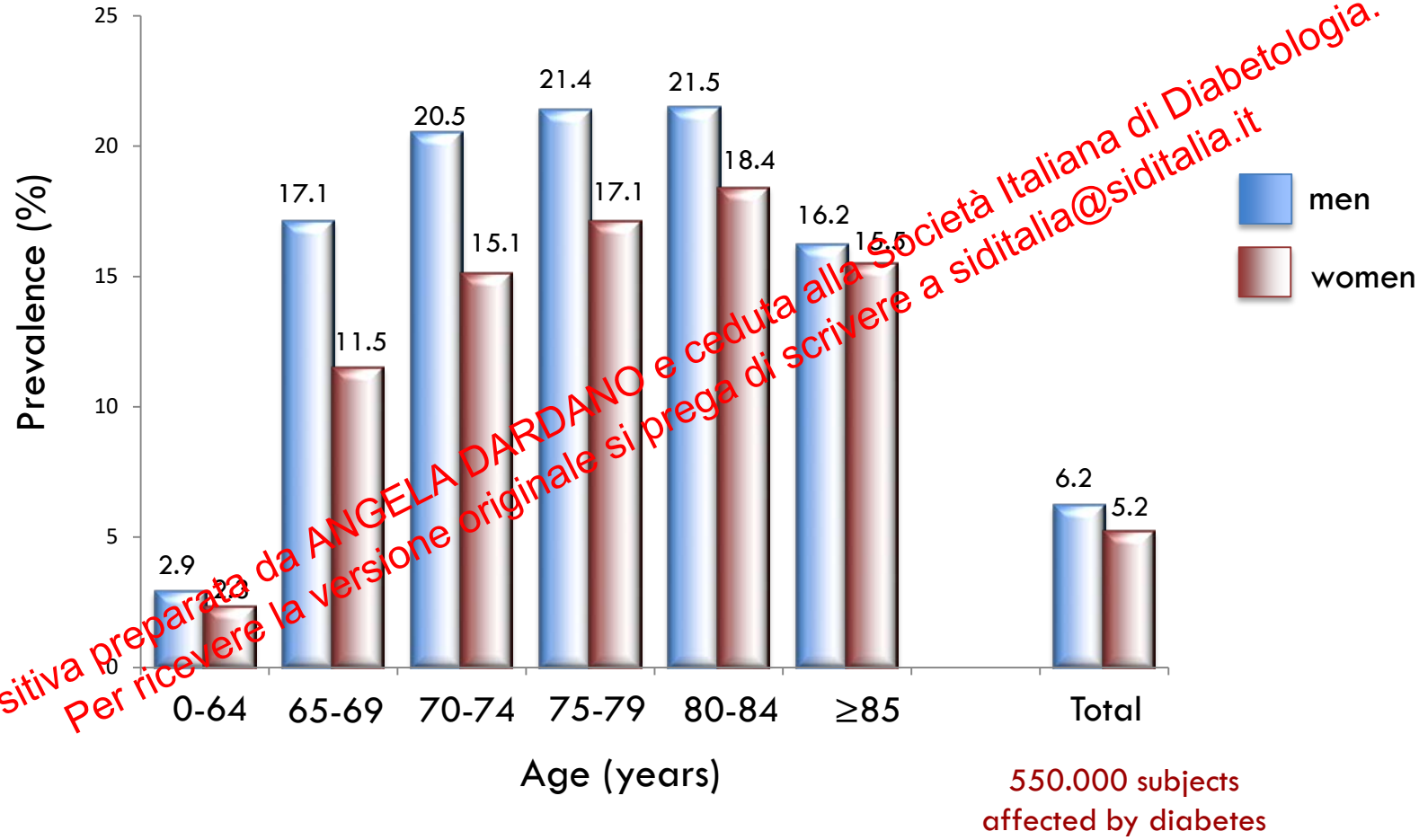
Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)



IDF. The global picture. IDF Diabetes Atlas 7th edition 2015. http://www.diabetesatlas.org

Epidemiology of diabetes mellitus in elderly subjects

Osservatorio ARNO Diabete Anziani



550.000 subjects
affected by diabetes

Modified by data edited by Cineca-SID

Epidemiology of diabetes mellitus in elderly subjects

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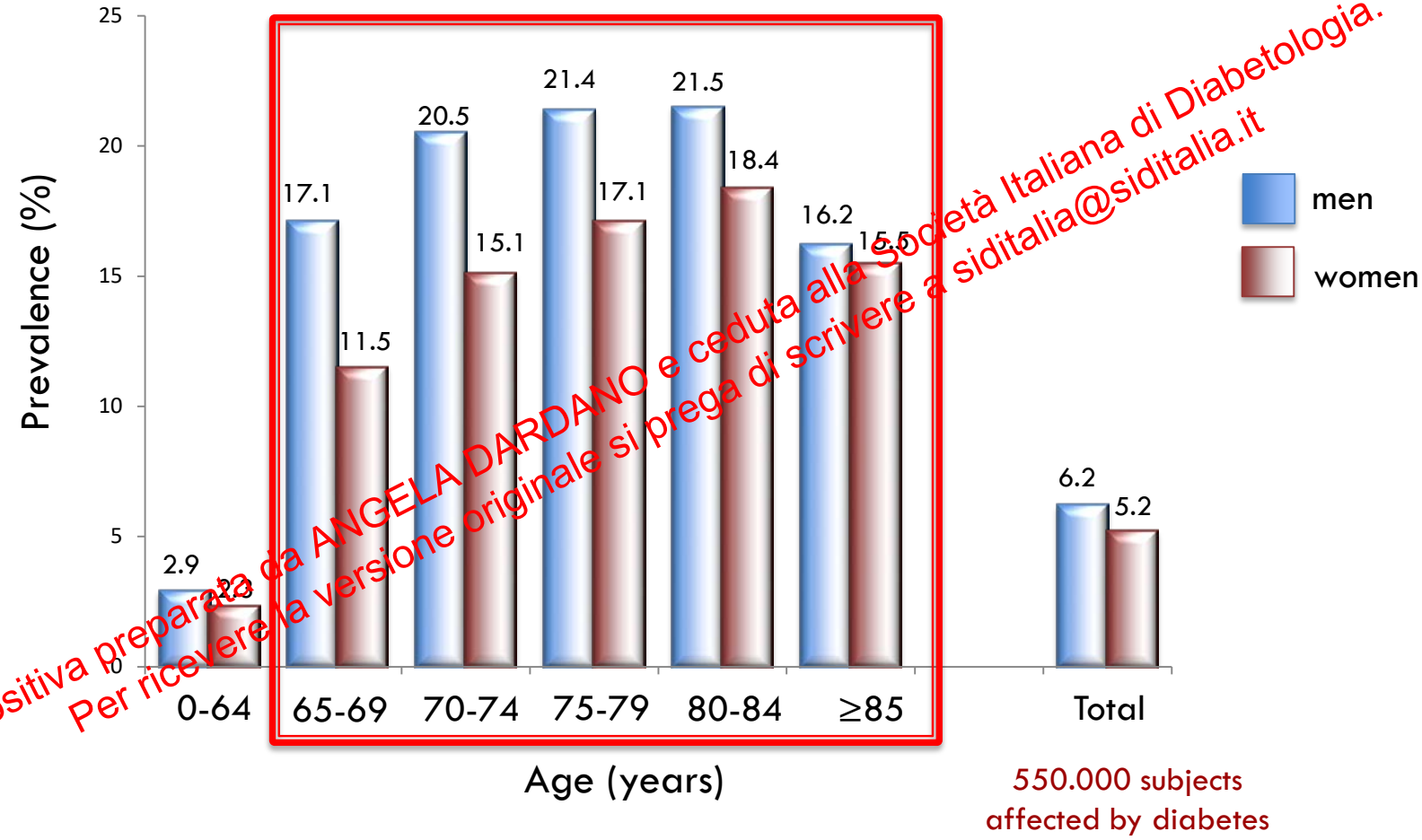

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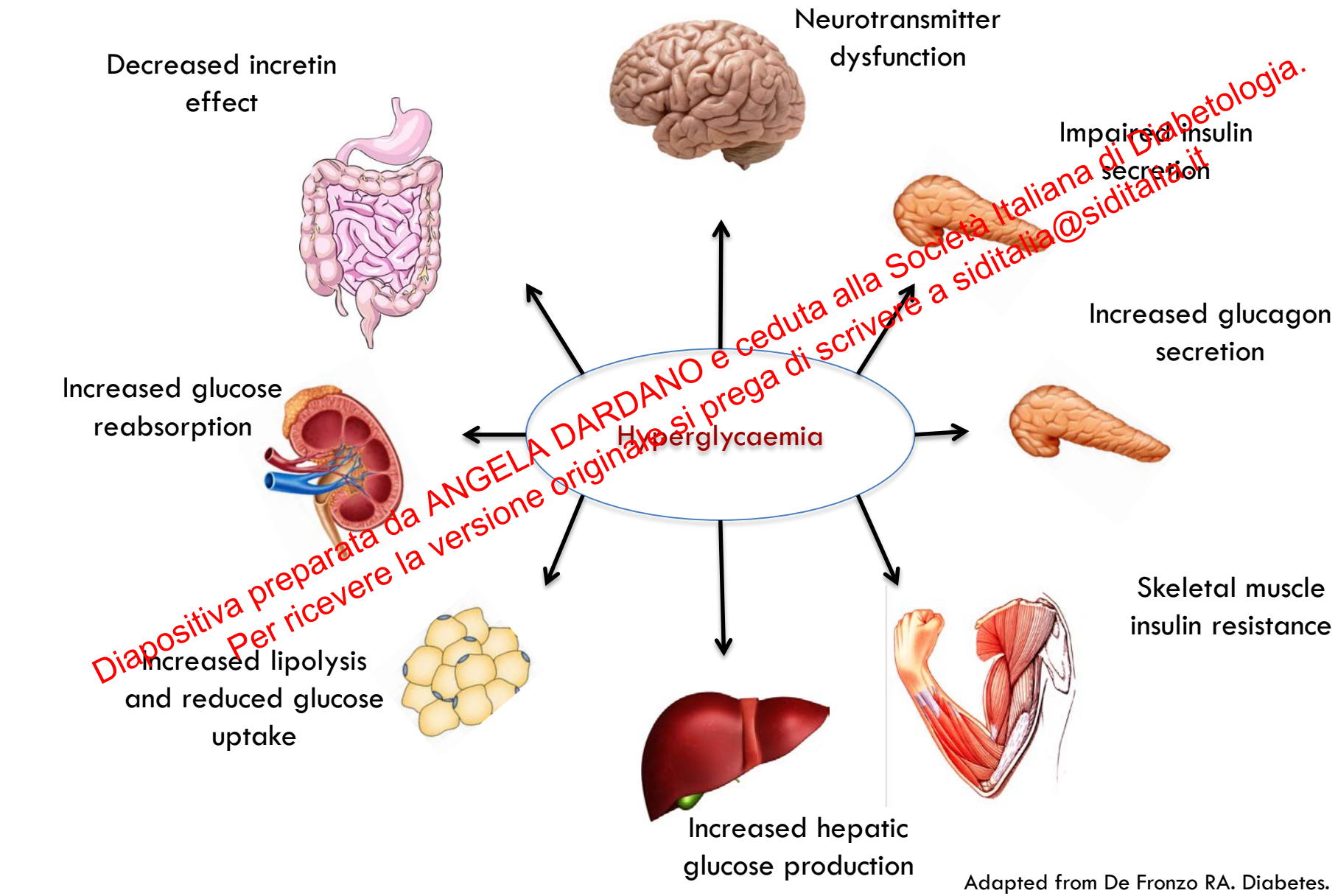
Pathogenesis of type 2 diabetes mellitus



Adapted from De Fronzo RA. Diabetes. 2009

AGING and pancreatic function

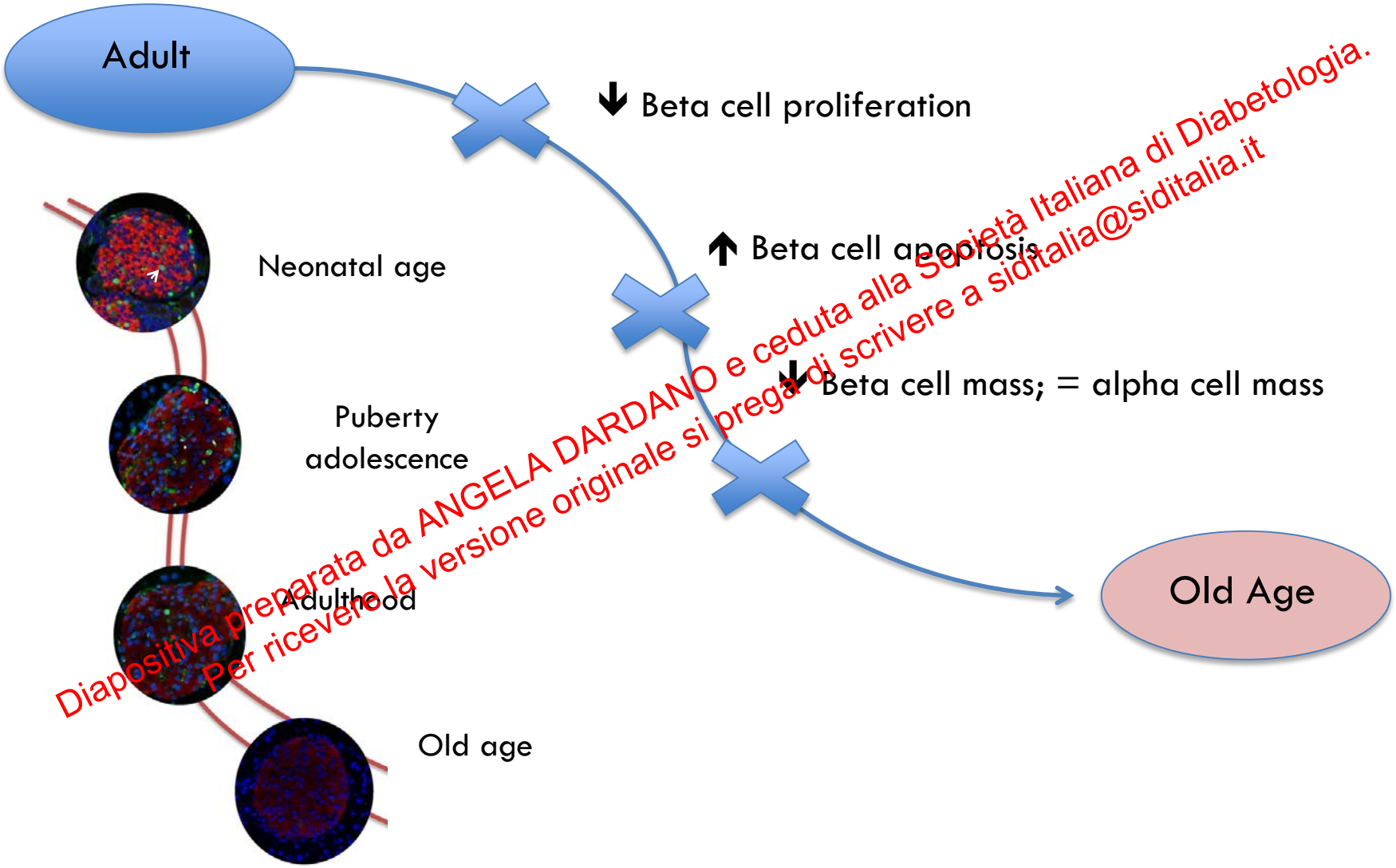
AGING and pancreatic function

Effect on glucose stimulated insulin secretion

1. glucose is transported into the *β* cells through the translocation of the glucose transporters (GLUTs), especially GLUT2;
2. generation of ATP through the oxidation of glucose;
3. elevation the ratio of ATP/ADP induces closure of cell-surface ATP-sensitive K^+ (K_{ATP}) channels, leading to cell membrane depolarization;
4. extracellular Ca^{2+} influx into the *β* cell;
5. a rise in cytosolic Ca^{2+} triggering the exocytosis of insulin granules

Gong Z et al. Int J Endocrinol. 2012

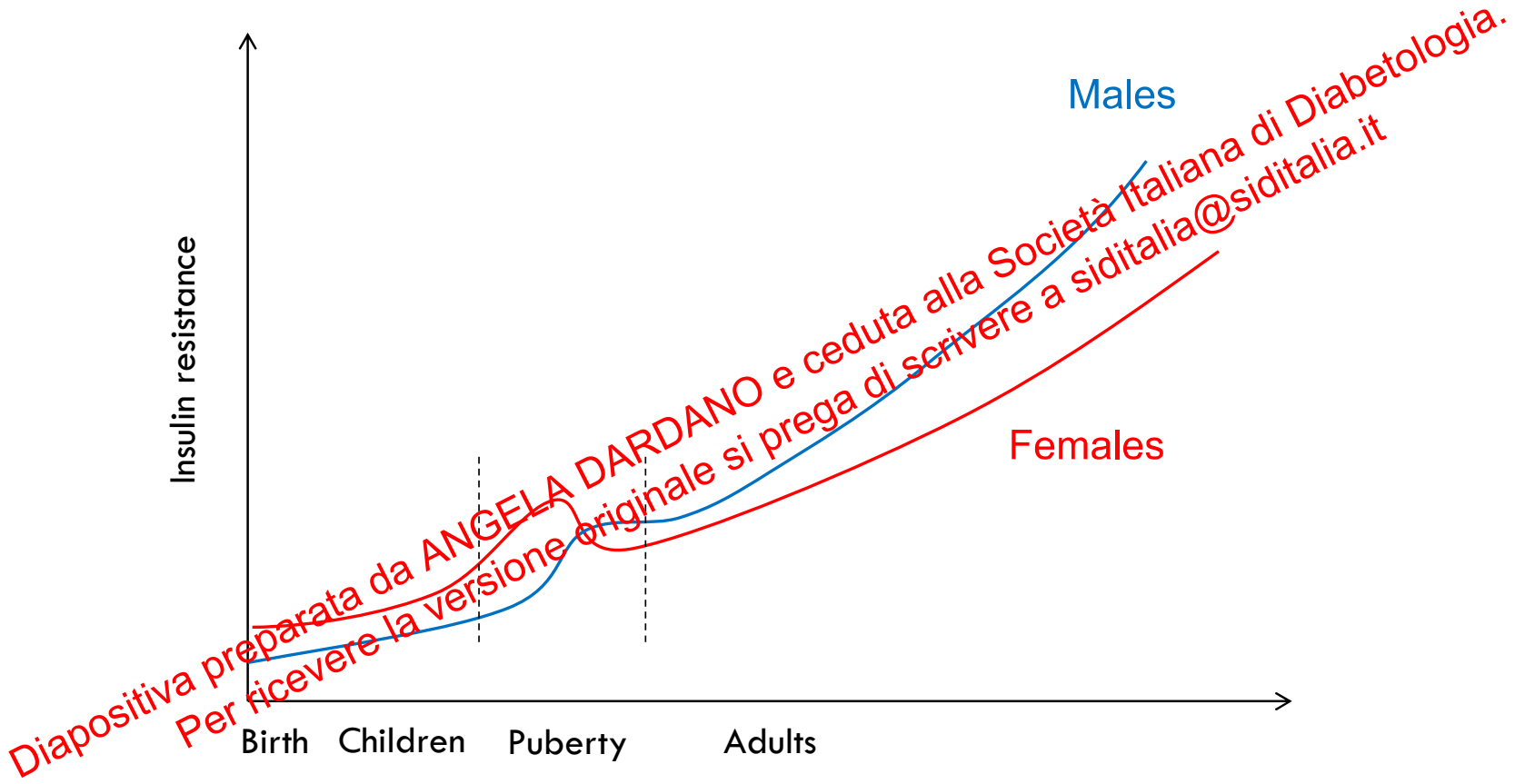
The regulation of plasticity of islet cell mass



Representative images of rodent islets at different ages.
Insulin (red), Ki67 (green), DAPI (blue) immunoreactivity

Modified from Mezza T et al. Diabetologia. 2014

Life course changes in insulin resistance



Sattar N. Best Pract Res Clin Endocrinol Metab. 2013

Relationships between adipose tissue and muscle in elderly: a mechanism leading to "sarcopenic obesity"

AGING

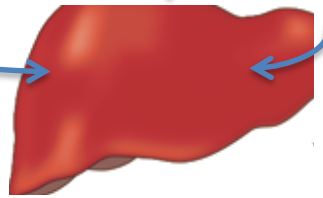
Weight gain

Pancreas

Muscle weakness
↓ Endurance capacity
↑ Fatigability
Muscle wasting

↑ Inflammation
↑ Fatty infiltration

↓ Adiponectin
↑ Leptin
↑ TNF alpha, IL6, MCP-1



Inflammation

↑ total/abdominal fat

↓ Physical activity

↓ Energy expenditure

↑ Insulin resistance

Macrophage recruitmen

Adapted from Zamboni M et al. Nutr Metab Cardiovasc Dis. 2008

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Definition of “elderly”


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Domanda 1(ct4)

Da che età si può dire che una persona è anziana?

1. Età ≥ 65 anni
2. Età ≥ 70 anni
3. Età ≥ 75 anni
4. Non esiste una soglia univoca

Risposte

Domanda 1(ct4)

Da che età si può dire che una persona è anziana?

1. Età ≥ 65 anni **(3 punti)**
2. Età ≥ 70 anni **(0 punti)**
3. Età ≥ 75 anni **(0 punti)**
4. Non esiste una soglia univoca **(6 punti)**

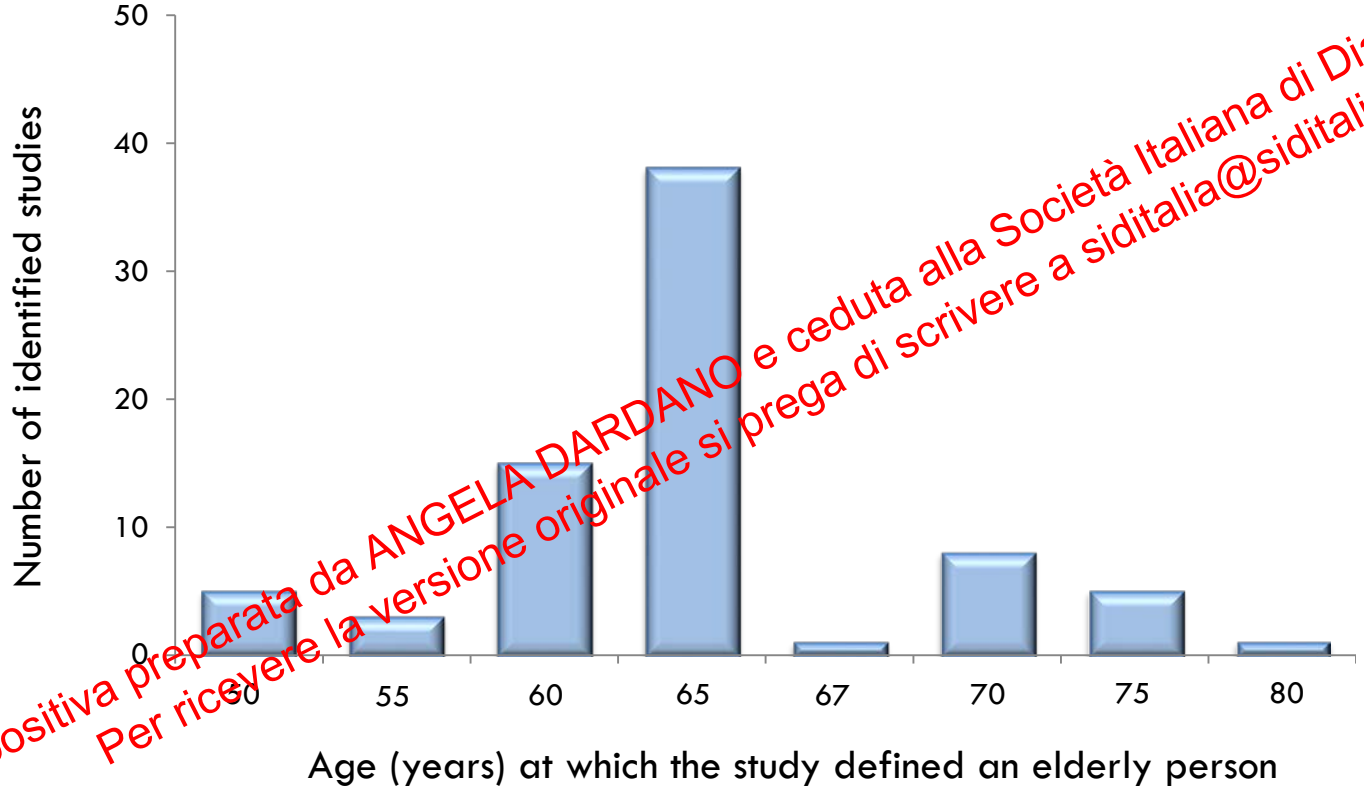
Definition of "elderly"

Conventionally, "elderly" has been defined as a chronological age of 65 years old

WHO. Definition of an older or elderly person. http://www.who.int/healthinfo/survey/ageingdefnolder/en/index.html .

Heterogeneity of the definition of elderly age

80 studies that included 271,470 patients
(PubMed, EMBASE and the Cochrane Library)



A range of 50–80 years across all studies reveals lack of uniformity in definitions of an elderly person

Sabharwal S et al. Springerplus. 2015

The heterogeneity in the clinical scenario of old patients

photographs from web

The heterogeneity in the clinical scenario of old patients

The institutionalized elderly patient

photographs from web

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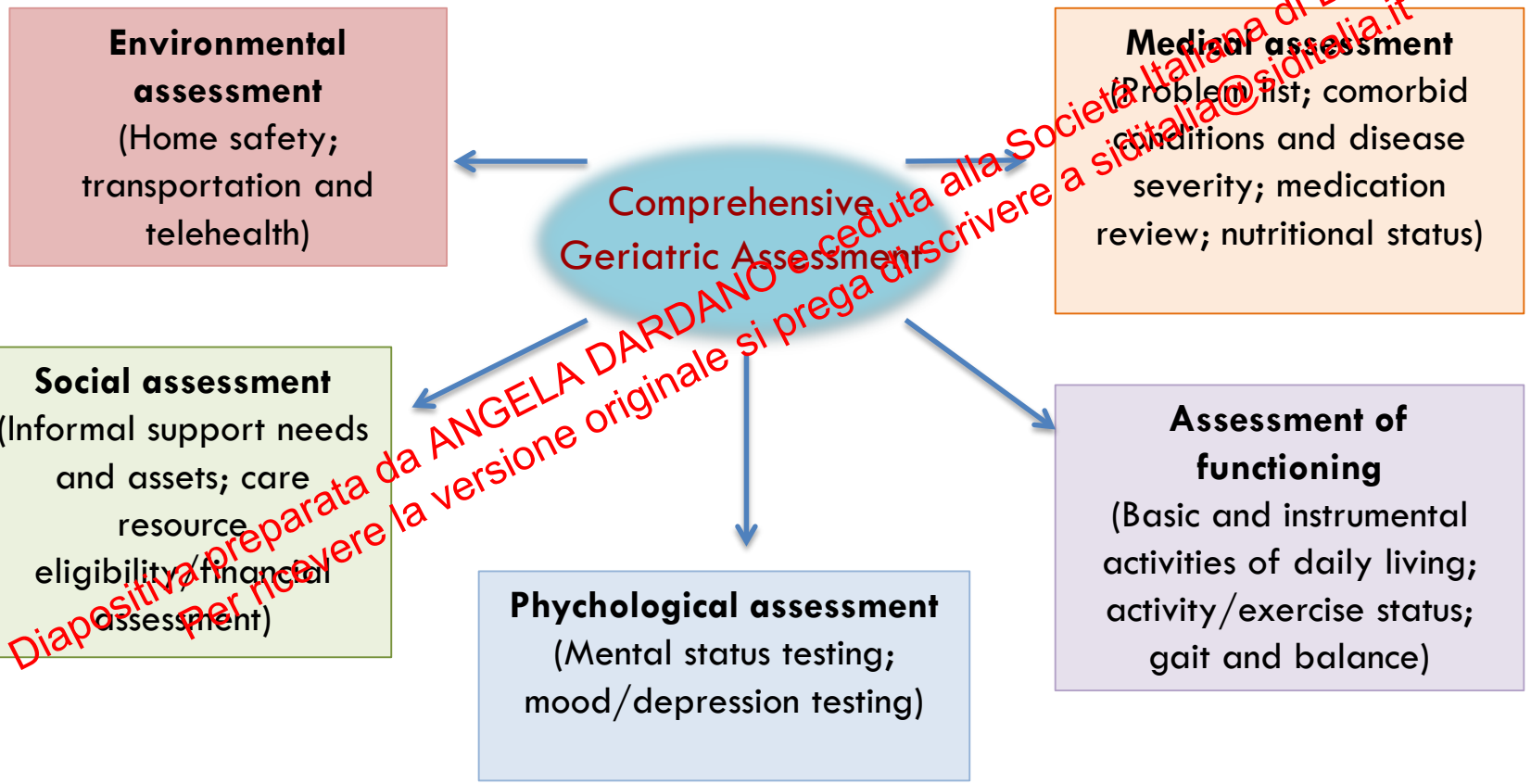
Comprehensive (multidimensional) Geriatric Assessment

"A multidimensional process designed to assess an elderly person's functional ability, physical health, cognitive and mental health, and socio-environmental situation"



Elsawy B eta al. Am Fam Physician. 2011

The dilemma of DM management in elderly patients

Rationale for treating elderly diabetic people

Cardiovascular morbility and mortality

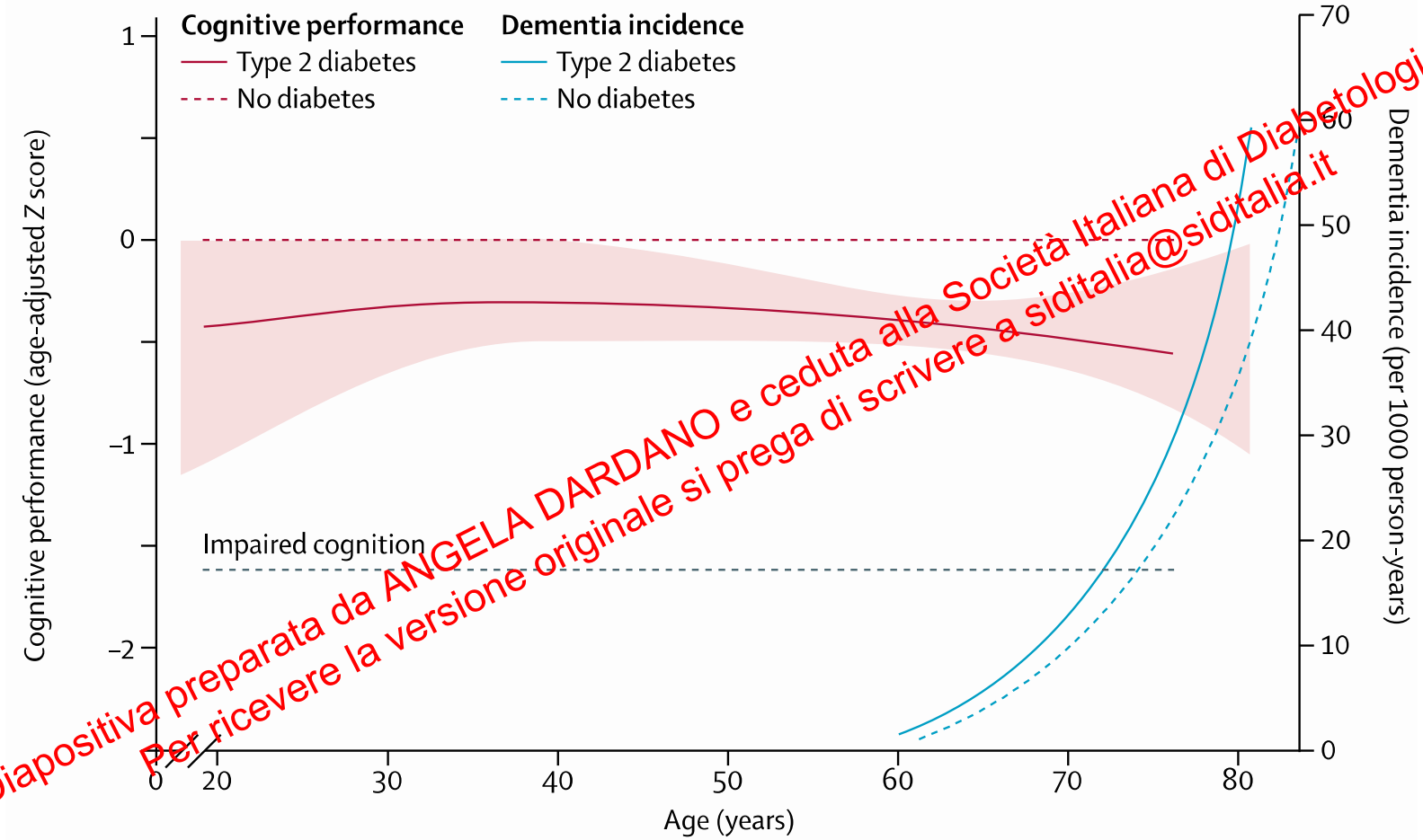
Functional disability

Geriatric syndromes (i.e. cognitive dysfunction)

Falls and fractures

Sinclair A et al. Lancet Diabetes Endocrinol. 2015; Koekkoek PS et al. Lancet Neurol. 2015; Araki A et al. Geriatr Gerontol Int. 2009; Volpato S et al. Curr Diabetes Rev. 2010; Schwartz AV. Bone. 2016

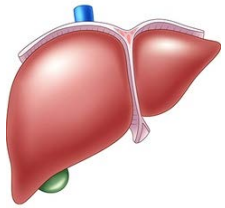
Cognitive decline in type 2 diabetes



Biessels GJ et al. Lancet Diabetes Endocrinol. 2014

Clinical pharmacology in the geriatric patient

Age related changes in pharmacokinetics and pharmacodynamics



- Drug absorption
- First-pass metabolism and bioavailability
- Drug distribution in the body
- Protein Binding
- Drug clearance
- Different concentrations of the drug at the receptor
- Variations in receptor number, receptor affinity, second messenger response, and cellular response
- Homeostatic regulation

Shi S et al. Current Drug Metabolism. 2011
Welker KL et al. Emerg Med Clin North Am. 2016

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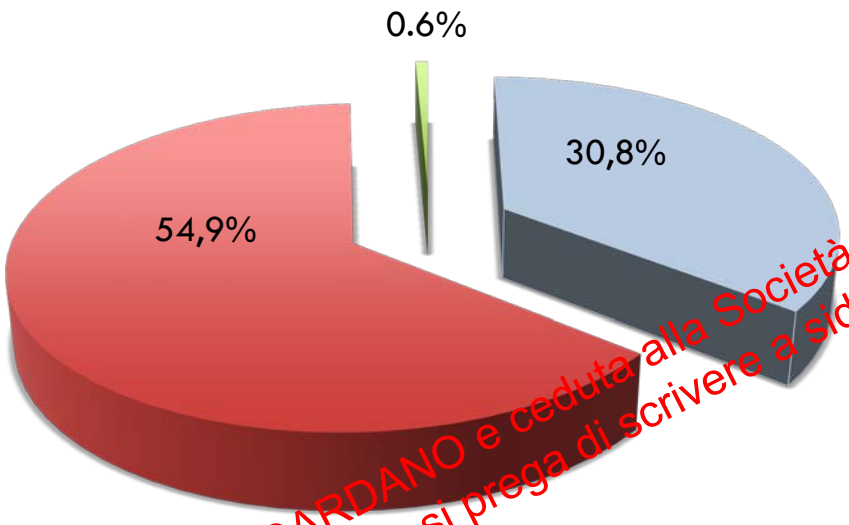
Review of the clinical trials in diabetes registered in ClinicalTrials.gov (2007-2010)

n=96,346 studies



Excludes ages > 65 yrs	30,8%
Excludes ages > 75 yrs	54.9%
Minimum age ≥ 65 yrs	0.6%
Minimum age ≥ 75 yrs	0.0

Lakey WC et al. Diabetologia, 2013

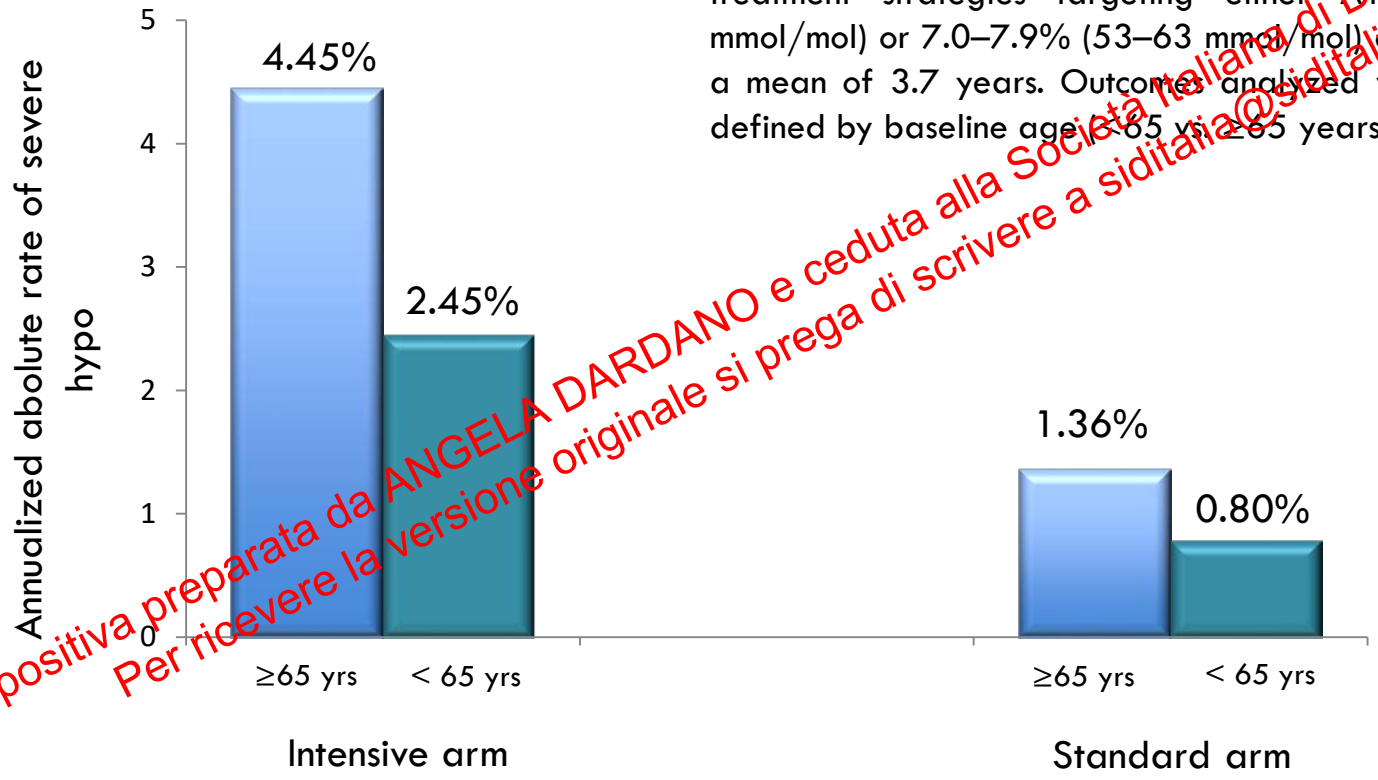
Intervention trials in T2DM patients – Age at entry

Trial	Age recruitment criterion (years)	Age at entry (years)
UKPDS[1]	25-65	54
ProACTIVE[2]	35-75	61.8
ADVANCE[3]	>55	66
ACCORD[4]	40-79	62.2
VADT[5]	45-79	60.4

1. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998
2. The prospective pioglitazone clinical trial in macrovascular events (PROactive): can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. Charbonnel B, et al. Diabetes Care. 2004
3. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. ADVANCE Collaborative Group. N Engl J Med. 2008
4. Effects of intensive glucose lowering in type 2 diabetes. Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med. 2008
5. Glucose control and vascular complications in veterans with type 2 diabetes. VADT Investigators. N Engl J Med. 2009

Hypoglycaemia risk in older versus younger adults in the ACCORD Trial

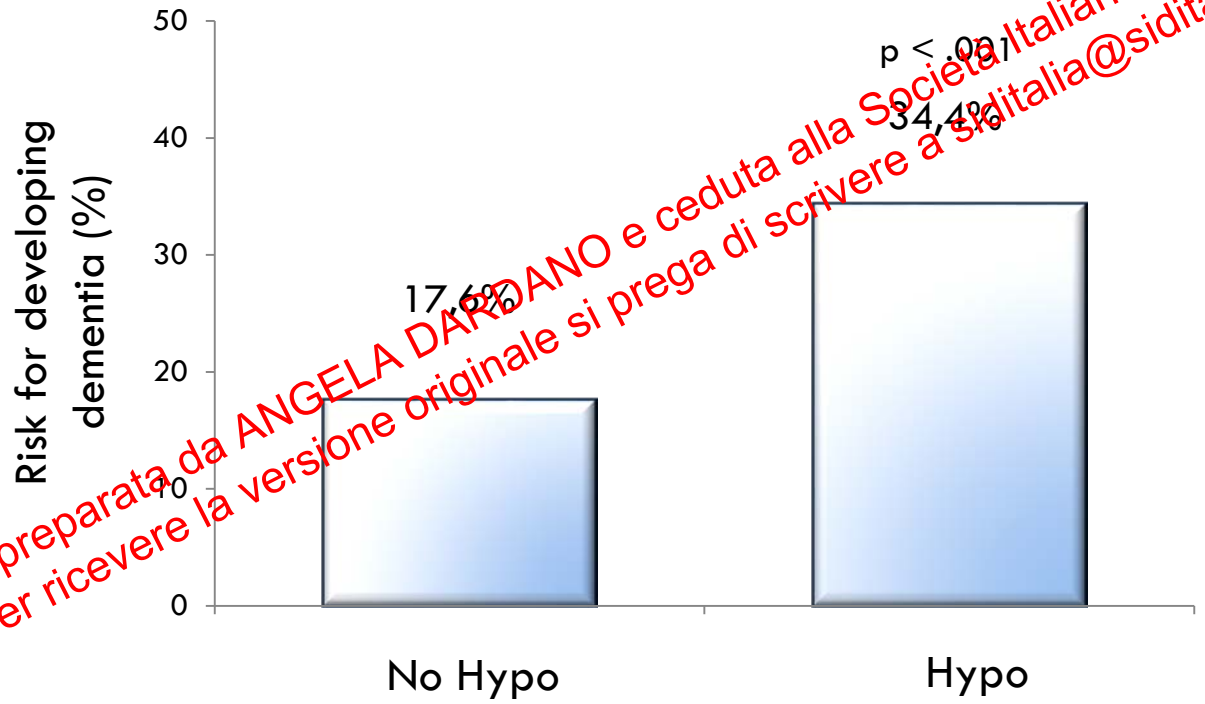
Participants with type 2 diabetes (n = 10,251) with a mean age of 62 years, a median duration of diabetes of 10 years, and a median A1C of 8.1% (65 mmol/mol) randomized to treatment strategies targeting either A1C <6.0% (42 mmol/mol) or 7.0–7.9% (53–63 mmol/mol) and followed for a mean of 3.7 years. Outcomes analyzed within subgroups defined by baseline age (<65 vs. ≥65 years)



Miller ME et al. Diabetes Care. 2014

Association between hypoglycemia and dementia in older adults with diabetes

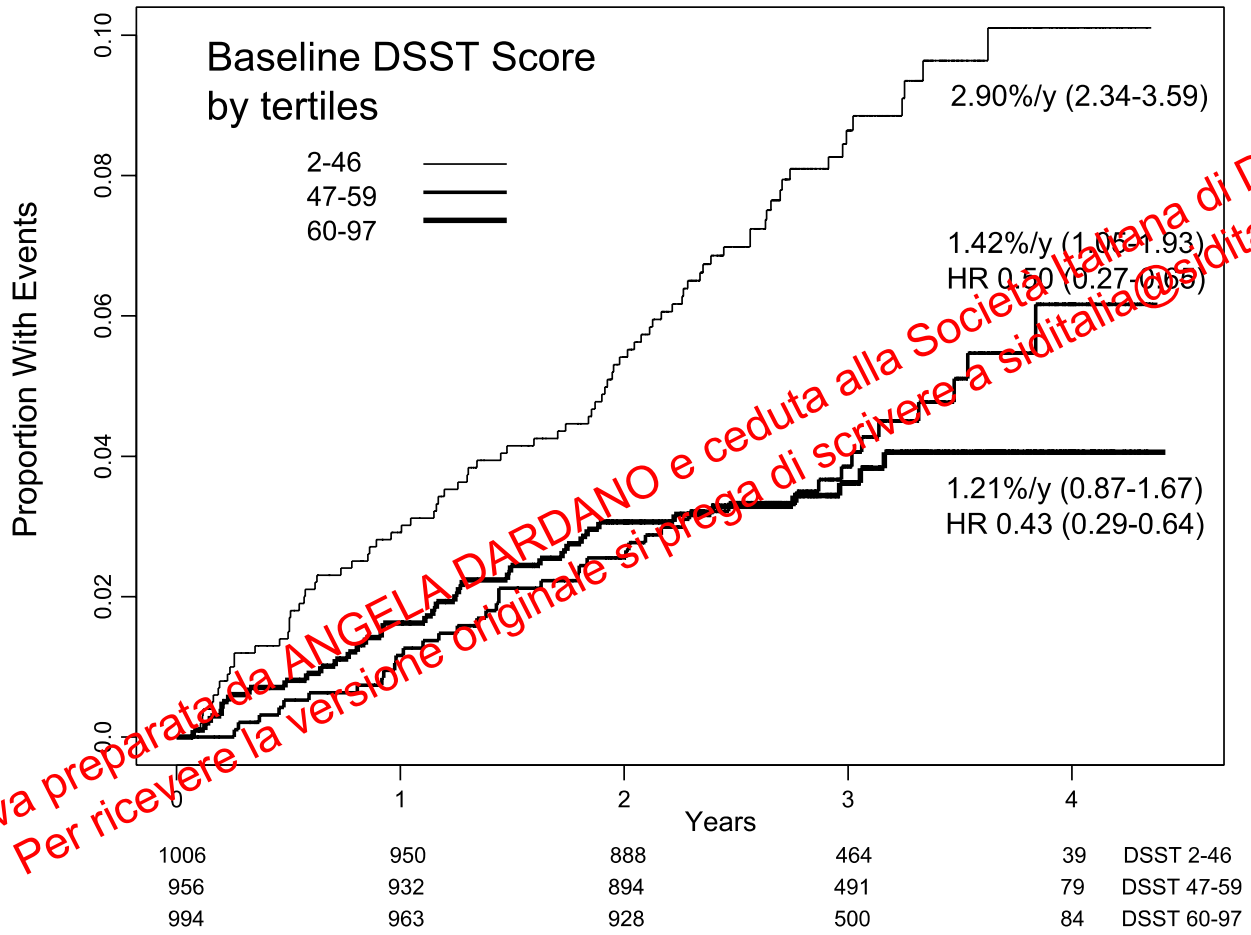
Study design: prospective population-based study; 783 older diabetic adults (mean age, 74.0 years), 12-year follow-up period



Yaffe K et al. JAMA Intern Med. 2013

Cognitive Impairment and risk of hypoglycaemia

Post hoc epidemiologic analysis of the ACCORD trial



Lower baseline Digit Symbol Substitution Test (DSST) score was associated with an increased risk for first episode of hypoglycemia requiring medical assistance

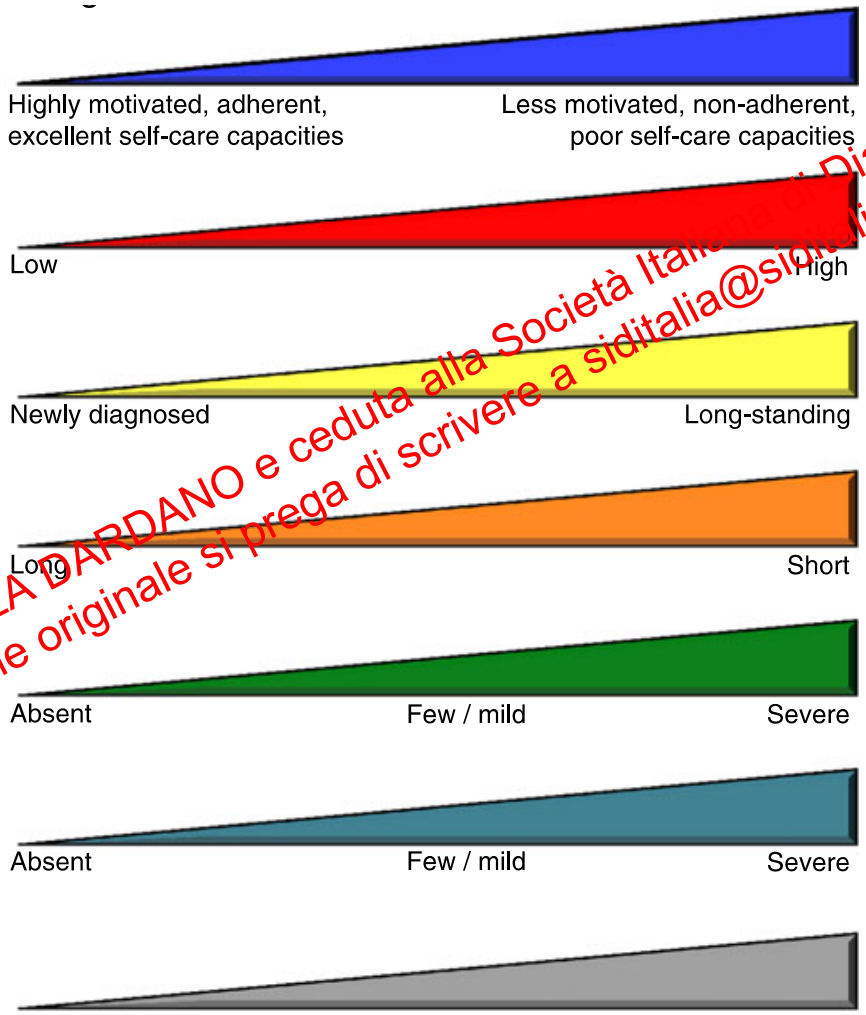
Punthakee Z et al. Diabetes Care. 2012

Glycaemic control and complications in older diabetic patients

The Diabetes and Aging Study

	Baseline HbA1c				
	<6%	6.0-6.9	7.0-7.9%	8.0-8.9%	≥ 9%
Mortality risk					
Age group					
60-69 yrs	1	0.92 (0.79-1.07)	0.83 (0.70-0.99)	0.91 (0.74-1.11)	1.17 (0.96-1.43)
70-79 yrs	1	0.83 (0.75-0.92)	0.85 (0.75-0.96)	0.86 (0.73-1.01)	1.11 (0.93-0.32)
> 80 yrs	1	0.83 (0.74-0.93)	0.83 (0.72-0.95)	1.05 (0.86-1.27)	1.20 (0.96-1.50)

Huang ES et al. Diabetes Care.2011



Ismail-Beigi F et al. Ann Intern Med. 2011; Inzucchi SE et al. Diabetologia. 2012

Functional categories of older people with diabetes

CATEGORY 1:
Functionally independent

→ People who are living independently, have no important impairments of activities of daily living (ADL), and who are receiving none or minimal caregiver support

CATEGORY 2:
Functionally dependent

→ People who, due to loss of function, have impairments of ADL such as bathing, dressing, or personal care
Subcategory A: Frailty
Subcategory B: Dementia

CATEGORY 3:
End of life care

→ Subjects characterized by a significant medical illness or malignancy with a life expectancy < 1 year

IDF Global Guideline for Managing Older People with Type 2 Diabetes. https://www.idf.org/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Domanda 2(ct4)

Nei soggetti anziani diabetici, il target di HbA1c è pari a:

1. 7-7.5% nei soggetti non fragili
2. Fino a 8.6% nei soggetti fragili
3. > 8.0%
4. < 7% indipendentemente dallo stato funzionale

Risposte

Domanda 2(ct4)

Nei soggetti anziani diabetici, il target di HbA1c è pari a:

1. 7-7.5% nei soggetti non fragili **(3 punti)**
2. Fino a 8.6% nei soggetti fragili **(6 punti)**
3. > 8.0% **(0 punti)**
4. < 7%, indipendentemente dallo stato funzionale **(0 punti)**

Glycemic target according to different categories

Guideline	Patient characteristic	HbA1c target mmol/mol	HbA1c target (%)
IDF	Functionally independent	53-59	7.0-7.5
	Functionally dependent	53-64	7.0-8.0
	Frail and/or dementia	Up to 70	Up to 8.6
	End of life	Avoid symptomatic hypo	
EDWPOP	Single system involvement	53-59	7.0-7.5
	Frail	60-70	7.6-8.6
IAGG, EDWPOP and International Task Force of Experts for DM position statement	Individual comorbidities and cognitive and functional status must be considered	53-59	7.0-7.5

IDF: International Diabetes Federation
EDWPOP: European Diabetes Working Party for Older People
IAGG: International Association of Gerontology and Geriatrics

Treatment goals according to ADA guidelines

Patient characteristics/health status	Rationale	Reasonable A1C goal	Fasting or preprandial glucose (mg/dl)	Bedtime glucose (mg/dl)
Healthy (few coexisting chronic illness, intact cognitive and functional status)	Longer remaining life expectancy	< 7.5% (58 mmol/mol)	90-130 mg/dl (5.0-7.2 mmol/L)	90-150 mg/dl (5.0-8.3 mmol/L)
Complex/intermediate (al least three coexisting chronic illnesses or 2 + instrumental ADL impairments or mild to moderate cognitive dysfunction)	Intermediate remaining life expectancy, high treatment burden, hypo vulnerability, fall risk	< 8.0% (64 mmol/mol)	90-150 mg/dl (5.0-8.3 mmol/L)	100-180 mg/dl (5.6-10.0 mmol/L)
Very complex/poor health (LTC or end - single - stage chronic illnesses or moderate to severe cognitive impairment or 2 + ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	< 8.5% (69 mmol/mol)	100-180 mg/dl (5.6-10.0 mmol/L)	110-200 mg/dl (6.1-11.1 mmol/L)

Modified from Standards of Medical Care in Diabetes-2017. Diabetes Care. 2017

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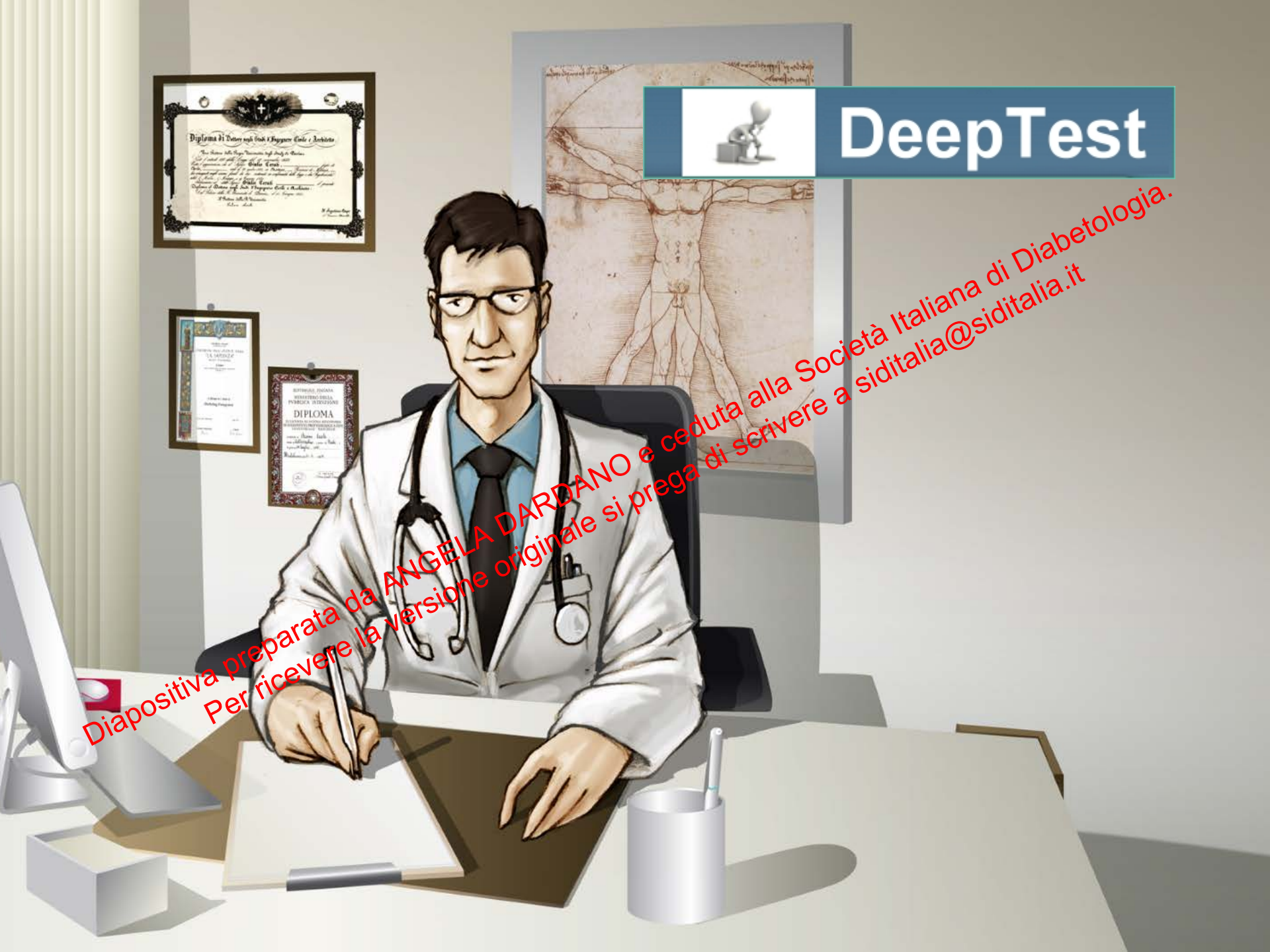
Treatment options in elderly diabetic patients

How the therapeutic strategy may be choosen, taking into account safety and patient's needs?


DeepTest
Diploma di Dottore negli Studi di Ingegneria Civile e Architetto
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Domanda 3(ct4)

PV, 72 anni, sesso maschile. Non fumatore. Ipercolesterolemia.
Diagnosi di DM tipo 2 nel Maggio 2016 (HbA1c 12.9%), per cui veniva avviata terapia insulinica basal bolus, con passaggio a terapia orale (pioglitazone, metformina, alogliptin) nel Novembre 2016 (HbA1c 8%).
Dicembre 2016: riscontro occasionale di onda T negativa in DI, aVL, V3-V6 -> malattia dei 3 vasi coronarici, per cui veniva sottoposto a PCI e DES.
Ottobre 2017: HbA1c 8.5%, glicemia a digiuno 168 mg/dl
Terapia domiciliare: pioglitazone (30 mg/die); metformina (1 g/die); alogliptin (12,5 mg/die). Opzioni terapeutiche:

1. Proseguire la terapia in atto
2. Associare a pioglitazone e metformina, inibitore SGLT2
3. Associare a pioglitazone e metformina, liraglutide
4. Aggiungere alla terapia in atto gliclazide

Risposte

Domanda 3(ct4)

PV, 72 anni, sesso maschile. Non fumatore. Ipercolesterolemia.
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Terapia domiciliare: pioglitazone (30 mg/die); metformina (1 g/die); alogliptin (12,5 mg/die). Opzioni terapeutiche:

1. Proseguire la terapia in atto **(1 punto)**
2. Associare a pioglitazone e metformina, inibitore SGLT2 **(4 punti)**
3. Associare a pioglitazone e metformina, liraglutide **(6 punti)**
4. Aggiungere alla terapia in atto gliclazide **(0 punti)**

Glucose-lowering algorithm for patients with type 2 diabetes

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

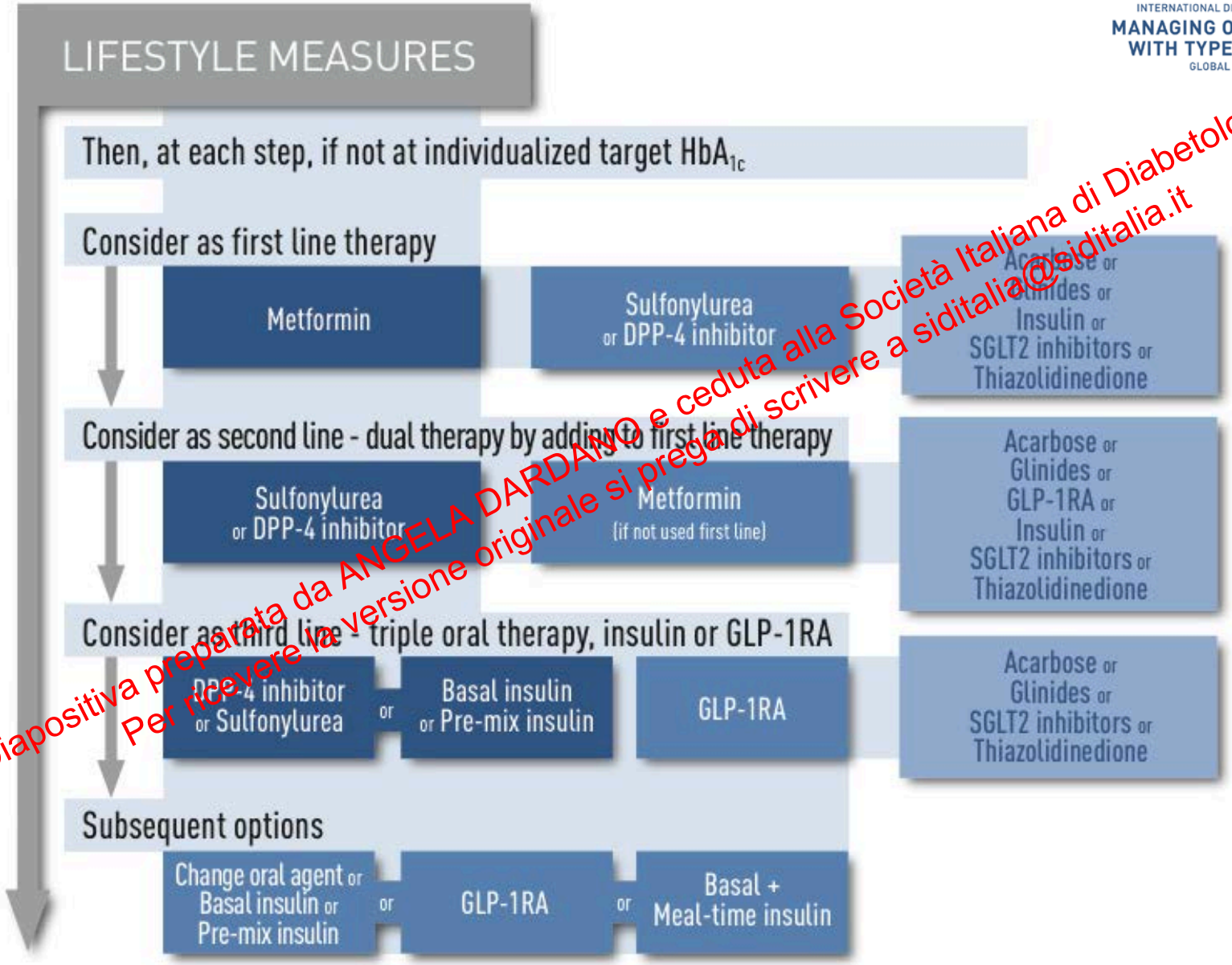
Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or GLP-1-RA	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§		or Insulin§		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e.,adding a fourth antihyperglycemic agent).

Combination injectable therapy

Modified from Standards of Medical Care in Diabetes – 2017

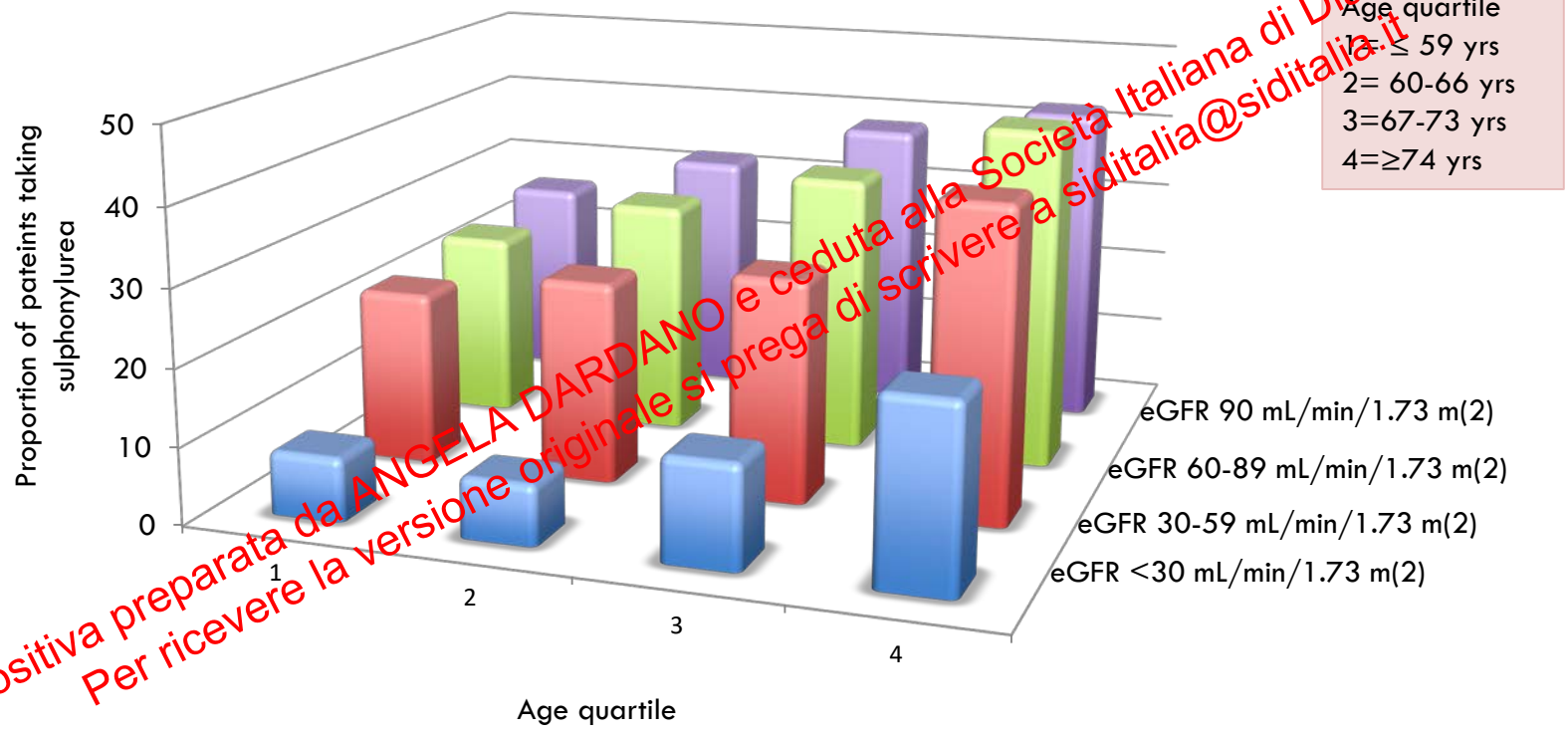
Treatment algorithm for older people with type 2 diabetes



IDF Global Guideline for Managing Older People with Type 2 Diabetes

Proportion of diabetic patients taking sulphonylurea according to age quartiles and eGFR classes: a real-life condition

15733 T2DM patients from the RIACE Italian Multicenter Study



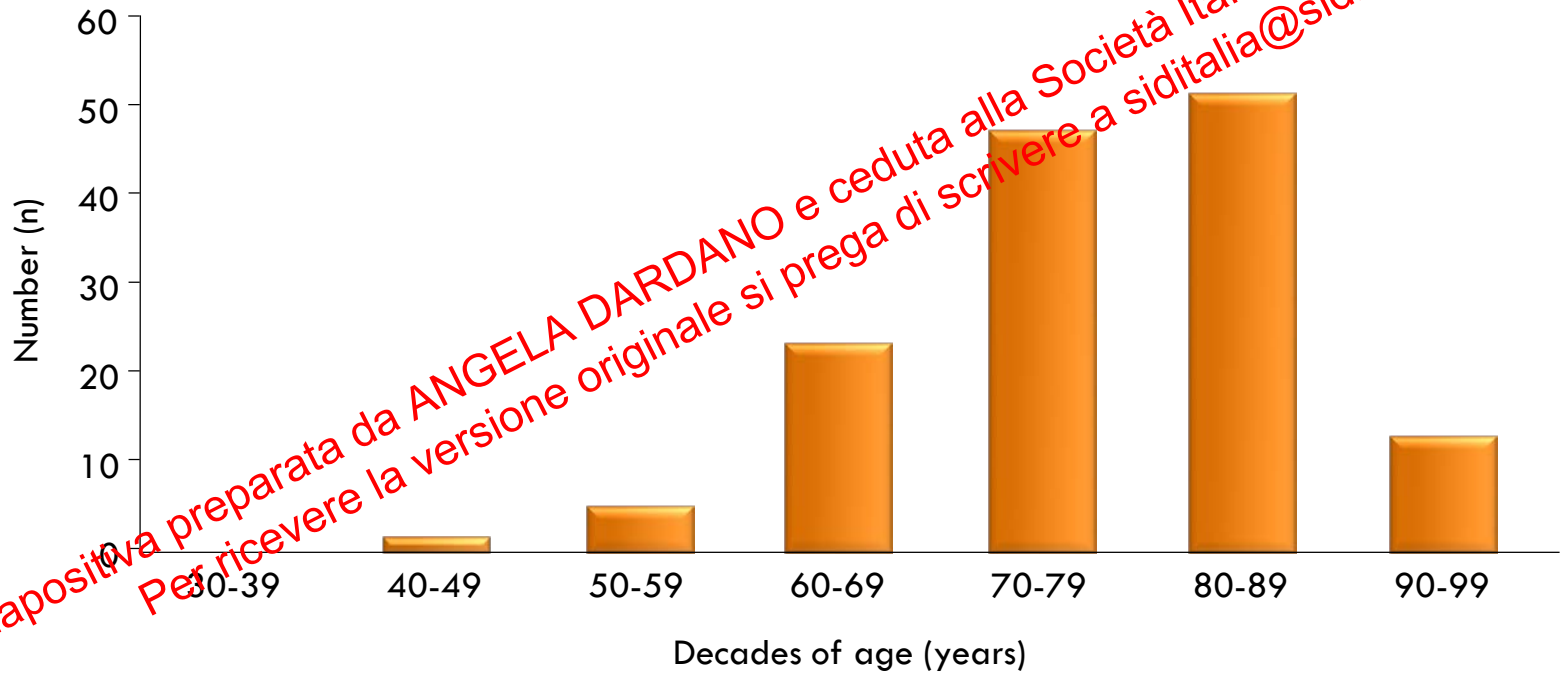
In real-life conditions, use of agents that are not recommended in elderly adults with diabetes mellitus with moderate to severe renal impairment is frequent

Modified from Solini A et al. J Am Geriatr Soc. 2013

Severe sulphonylurea-induced hypoglycaemia in older patients

10-year study period from 2000 to 2009, a total of 1419 cases of severe hypoglycemia registered among the 103,256 patients who attended the medical emergency department

Age distribution of 139 type 2 diabetic patients with severe sulphonylurea-induced hypoglycemia



Severe hypoglycemia defined as a symptomatic event requiring treatment with i.v. glucose and confirmed by a blood glucose measurement of < 50 mg/dl. Glimepiride (n = 98), glibenclamide (n = 40) or gliquidone (n = 1)

Holstein A et al. Expert Opin Drug Saf. 2010

RCTs with (new) oral agents in elderly diabetic patients

	Study design	Molecules	Age (years)
Bode BW et al. Am J Geriatr Pharmacother. 2011	Pooled analysis of six randomized, placebo-controlled, multinational trials	**Liraglutide**	≥65
Pencek R et al. Int J Clin Pract. 2012	Post hoc analysis from seven randomized, controlled phase 3 trials	**Exenatide once weekly**	≥ 65
Barnett AH et al. Lancet. 2013	Randomized, double-blind, parallel-group, multinational phase 3 study. ClinicalTrials.gov, number NCT01084005	**Linagliptin**	≥70
Schweizer A et al. Diabetes Ther. 2013	Sub-analysis of data from a prospective 24-week randomized placebo-controlled trial	**Vildagliptin**	≥75
Hanefeld M et al. Adv Ther. 2014	Meta-analysis from five of the GetGoal trials	**Lixisenatide**	≥65
Bron M et al. Diabetes Ther. 2014	Post hoc analysis of a global, multicenter, randomized, double-blind, active-controlled study	**Alogliptin**	65-90
Leiter LA et al. Diabetes Care. 2015	Double-blind randomized trial. SAVOR TIMI 53 trial	**Saxagliptin**	≥65; ≥75
Boustani MA et al. Diabetes Obes Metab. 2016	AWARD Clinical Trial Programme	**Dulaglutide**	≥65
Kohler S et al. Clin Ther. 2016	Pooled data from clinical trials	**Empagliflozin**	65-75; > 75
Fioretto P et al. Drugs Aging. 2016	Pooled analysis of nine double-blind phase III studies	**Dapagliflozin**	≥65; ≥75
Sinclair AJ et al. J Am Geriatr Soc. 2016	Pooled data from six randomized, double-blind, placebo-controlled studies	**Canagliflozin**	≥75
Bethel MA et al. Diabetes Care. 2017	Analysis of the baseline characteristics and clinical outcomes for TECOS participants	**Sitagliptin**	≥75

SID
fondata nel 1964
Società Italiana di Diabetologia

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

POSITION STATEMENT

Personalizzazione del trattamento dell'iperglicemia nell'anziano con diabete tipo 2

http://www.siditalia.it/news/1502-05-04-2017-position-statement-sid-sigg-personalizzazione-del-trattamento-dell-iperglicemia-nell-anziano-con-diabete-tipo-2

http://www.sigg.it/docs/Documento-ufficiale.pdf

Key principles underpinning the therapeutic choice

	Hypo	DKA	Renal/GU	Hearth	Cognitive function	Bone	Sarcopenia

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SU and GLN	Mild/moderate/severe	Neutral	More hypo risk	Uncertain risk of CV events	Possible risk related to hypo	Neutral	SU and GLN may induce atrophy

Agenda

1. Epidemiology of diabetes mellitus in the elderly
2. Pathogenesis of diabetes mellitus in the elderly
3. Setting the scene: who is the old patient?
4. Older patients: understanding needs
5. Goals of treatment
6. Treatment choices in the older patient with diabetes mellitus
7. Conclusions

Conclusions

- Type 2 diabetes mellitus is increasingly common in the elderly.
- Current recommendations emphasise that the optimisation of glycaemic control in the elderly must be tailored.
- The choice of anti-diabetes therapies should follow the aphorims **"START LOW, GO SLOW"**
- The **"ABC" of diabetes** may be translated in **"Always Best Care"**.

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"…Life may be compared to a piece of embroidery, of which, during the first half of his time, a man gets a sight of the right side, and during the second half, of the wrong. The wrong side is not so pretty as the right, but it is more instructive; it shows the way in which the threads have been worked together."

Arthur Schopenhauer

Thanks for your attention