La personalizzazione della terapia farmacologica nel diabete tipo 2: l'algoritmo terapeutico per l'anziano fragile

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Riassunto

Il Gruppo di Studio "Diabete nell'anziano" ha ritenuto opportuno proporre un percorso terapeutico personalizzato dedicato al paziente anziano fragile e/o con importanti comorbilità in considerazione delle peculiari caratteristiche di questa tipologia di pazienti nei quali gli obiettivi prioritari dovrebbero essere l'assenza di sintomi, la migliore qualità di vita possibile, evitare l'ipoglicemia e la prevenzione delle complicanze acute e croniche. Una emoglobina glicata compresa fra 7,6% e 8,5% (60 ÷ 69 mmol/mol) rappresenta un target metabolico sufficiente a garantire questi obiettivi. L'Algoritmo riflette le opinioni degli Autori, supportate quando possibile dalle evidenze della Letteratura.

Le scelte farmacologiche hanno privilegiato i farmaci che non provocano ipoglicemia (Metformina, DPP4-i e Acarbosio) ed anche nella scelta delle insuline si è data priorità all'utilizzo degli analoghi dell'insulina che sembrano essere più vantaggiosi rispetto all'insulina umana per il minor rischio ipoglicemico e per la maggior maneggevolezza.

Summary

The Study Group "Diabetes in the Elderly" suggests a personalized therapeutic algorytm dedicated to frail diabetic patient, in consideration of particular features of this kind of patient. The best quality of life, control of hyperglycemia and its symptoms, good health status, and prevention of micro and macrovascular complications avoiding hypoglycaemia are the general aims of the treatment. A target of glycated hemoglobin included between 7,6% e 8,5% (60÷69 mmol/mol) seems to be a sufficient metabolic target to warrant these goals. Metformin, DPP4 inhibitors and Acarbose are the drugs to prefer in order to their feature to avoid hypoglycemia. When oral agents fail to lower glucose levels adequately, Insulin Analogues rather human insulin represent a good choice for their easy handling and minor risk of hypoglycemia.

Presentazione dell'algoritmo

Nel 2011 l'AMD, consapevole della necessità che la terapia farmacologica del diabete mellito tipo 2 dovesse essere personalizzata quanto più possibile sulle caratteristiche del paziente, elaborava dei "percorsi di intervento farmacologico" (i cosiddetti Algoritmi) che si prefiggevano di aiutare tutti i Medici a definire, sul singolo paziente, gli obiettivi metabolici e le strategie terapeutiche più appropriate per raggiungerli.

Nascevano così 5 algoritmi dedicati a 5 tipologie di pazienti di frequente incontro nella pratica clinica quotidiana (Paziente non in terapia antidiabetica e con iperglicemia severa; paziente normopeso/sovrappeso con iperglicemia lieve moderata; paziente obeso con iperglicemia lieve moderata; paziente con presenza di rischio professionale correlato a possibili ipoglicemie e iperglicemia lieve/moderata; paziente con insufficienza renale cronica e iperglicemia lieve/moderata)[1].

In questa personalizzazione del trattamento, il paziente anziano, definito come paziente > 70 anni, riceveva una caratterizzazione limitatamente alla definizione degli obiettivi metabolici da raggiungere, a seconda della presenza o meno di complicanze micro/macrovascolari.

Il Gruppo di Studio AMD "Diabete nell'Anziano" ha ritenuto opportuno proporre un ulteriore percorso personalizzato dedicato al paziente anziano fragile e/o con importanti comorbilità sulla base di alcune riflessioni:

- Il progressivo aumento della prevalenza del diabete mellito tipo 2 da una parte e l'aumentata aspettativa di vita dall'altra fanno presumere che nelle prossime decadi i soggetti anziani rappresenteranno la maggior parte dei pazienti diabetici. Già adesso quasi il 60% dei pazienti che affluiscono ai Centri Specialistici Italiani ha più di 65 anni.
- Gli "Anziani con diabete mellito" sono, peraltro, un gruppo molto eterogeneo, comprendendo i soggetti con malattia neodiagnosticata in età senile, quelli con malattia di lunga durata; in buono stato di salute oppure affetti da malattie croniche, disabilità più o meno invalidanti che possono determinare diverse aspettative di vita.
- Nei pazienti anziani è abbastanza frequente la c.d. "Sindrome clinica da fragilità". Per quanto non esi-

Paziente con diabete di tipo 2, anziano fragile con iperglicemia lieve/moderata (HbA1c < 9%)

Obiettivi Terapeutici	Primo gradino terapeutico	Criteri di fragilità
HbA1c: 7,6 ÷ 8,5% (60 ÷ 69 mmol/mol) Glicemia digiuno: 136 – 162 mg/dl	Intervento su stile di vita (educazione, terapia medica nutrizionale e se possibile attività fisica) 3 mesi di intervento	– Ospite di Casa di Riposo / RSA – Decadimento cognitivo – Importante impedimento funzionale arti inferiori – Allettamento – Storia di comorbilità invalidanti
Obiettivi Terapeutici NON raggiunti		
Non usare o particolare cautela – VFG < 45 ml/min (NO assolutamente < 30 ml/min) – Scompenso cardiaco in compenso labile – Disturbi gastrointestinali – Insufficienza respiratoria – Anoressia o malnutrizione proteico calorica	Metformina	Opzioni alternative – DPP-4i – SU a basso rischio ipo – Acarbosio
Obiettivi Terapeutici NON raggiunti		
	Metformina + DPP4i	Opzioni alternative – Met + SU a basso rischio ipo – Met + Acarbosio
Obiettivi Terapeutici NON raggiunti		
	Metformina + DPP4i + Insulina basale	Opzioni alternative – Met + SU basso rischio ipo + Insulina basale – Met + Acarbosio + Insulina basale
Obiettivi Terapeutici NON raggiunti		
	Metformina + Insulina • Basal-Plus • Premixed b.i.d • Basal-Bolus	

NOTE ESPLICATIVE

- Gli obiettivi terapeutici sono da perseguire "in sicurezza" evitando l'ipoglicemia.
- La connotazione dell'iperglicemia all'automonitoraggio (a digiuno o post-prandiale) perde gran parte del suo significato negli step terapeutici in questa tipologia di pazienti.
- La valutazione del VFG (MDRD o CKD-EPI) va effettuata alla diagnosi, ad ogni variazione terapeutica e periodicamente, al fine di scegliere oculatamente farmaci e dosaggi.
- Per Sulfoniluree a basso rischio di ipoglicemia si intendono, in ordine di preferenza, Gliclazide, Glipizide e Glimepiride. La Glibenclamide è controindicata nel pz anziano fragile e/o con comorbilità.
- il Pioglitazone trova una difficile collocazione in questi pazienti per il rischio di ritenzione idrica e scompenso cardiaco, di osteoporosi e per la non infrequente coesistenza di maculopatia
- La Repaglinide non è raccomandata (secondo la stessa scheda tecnica) per i pazienti > 75 anni
- Gli Agonisti/Analoghi del GLP1 non hanno, al momento, indicazione per i pazienti > 75 anni e non sono sicuramente adatti per il paziente fragile di età < 75 anni
- Le opzioni alternative sono da considerare anche in funzione del MMG, il quale in Italia non può prescrivere i DPP4i

sta una definizione universalmente accettata, la fragilità implica concettualmente una riduzione delle riserve biologiche (ridotta riserva omeostatica) e funzionali con conseguente ridotta capacità di risposta ad uno stimolo stressante. Da un punto di vista operativo quando parliamo di "anziano fragile" possiamo pensare ad un soggetto di età avanzata affetto da pluripatologie, frequentemente disabile nel quale sono spesso presenti problematiche socio-familiari, economiche, ambientali ed in cui un fattore scatenante (anche iatrogeno) aumenta la probabilità di morbilità acuta, ospedalizzazione, comparsa di sindromi geriatriche, morte.

– Secondo l'Associazione Medica Americana quasi la metà degli ultraottantenni è portatore di fragilità e la pressochè totalità degli ospiti delle RSA/Case di

Riposo sarebbe fragile. Giova ricordare che in una recente indagine svolta in Friuli quasi il 20% degli anziani ospiti di queste Strutture era diabetico.

– Non esistono in letteratura trials di intervento che abbiano testato gli effetti del controllo glicemico a questa età ed in questa tipologia di pazienti.
– Nei pazienti anziani fragili o con importanti comorbilità gli obiettivi della terapia sono perciò diversi rispetto ad altre fasce di età e devono coniugarsi con l'aspettativa di vita, il contesto socio-economico e culturale, la necessità di non appesantire una già corposa politerapia. Sinteticamente gli obiettivi terapeutici nell'anziano con diabete devono mirare a: controllare l'iperglicemia per mantenere il paziente asintomatico quanto più a lungo; garantire la migliore qualità di vita possibile; prevenire le complicanze acute e croniche; evitare l'ipoglicemia. Una emoglobina glicata compresa fra 7,6% e 8,5% (60 ÷ 69 mmol/mol) rappresenta un target metabolico sufficiente a garantire questi obiettivi.

Sulla base di queste considerazioni il nostro Gruppo di Studio ha elaborato un percorso terapeutico per raggiungere obiettivi metabolici commisurati alle caratteristiche di questa tipologia di pazienti.

Si sottolinea che l'algoritmo riflette le opinioni degli Autori (basate sulla esperienza clinica e sul buon senso) supportate, quando possibile, dalle evidenze della letteratura. Come tale, è classificabile con un livello di prova VI secondo quanto previsto dal Piano Nazionale delle Linee-Guida[2].

L'obiettivo è quello di fornire delle indicazioni di intervento per conseguire gli obiettivi sopradescritti in un regime di sicurezza (quanto più possibile) avendo bene in mente che l'ipoglicemia in questi pazienti può essere responsabile di eventi particolarmente pericolosi. Le scelte hanno privilegiato i farmaci che non provocano ipoglicemia ed in questa ottica Metformina, DPP4-i e Acarbosio rappresentano le opzioni migliori. Quando si renda necessario l'uso dell'insulina, gli Analoghi dell'insulina sembrano essere più vantaggiosi rispetto all'insulina umana per il minor rischio ipoglicemico e per la maggior maneggevolezza.

BIBLIOGRAFIA

1. Ceriello A, Gallo M, Armentano V, Perriello G, Gentile S, De Micheli A; Associazione Medici Diabetologi. Personalizing treatment in type 2 diabetes: a self-monitoring of blood glucose inclusive innovative approach. Diabetes Technol Ther. 2012 Apr;14(4):373-8. doi: 10.1089/dia.2011.0233. Epub 2012 Jan 4.
2. Programma nazionale per le linee guida (PNLG). Manuale Metodologico. Come produrre, diffondere e aggiornare raccomandazioni per la pratica clinica. Zadig, Milano. http://www.pnlg.it, 2004.
3. Brown AF, Mangione CM, Saliba D, Sarkisian C a. Guidelines for improving the care of the older person with diabetes mellitus. JAGS; 51(5 Suppl Guidelines):S265–80, 2003.
4. AMD. Le Monografie degli Annali AMD 2011: Focus su: Anziani con Diabete. 2012.
5. European Diabetes Working Party for Older People. Clinical Guidelines for Type 2 Diabetes Mellitus in Older People: 1–124, 2004.
6. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet; 352:854–865, 1998.
7. Turner R, Holman R, Cull C, et Al, Group UPDS (UKPDS). Intensive blood-glucose control with sulphonilureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UPDS 33). Lancet; 352:837–853, 1998.
8. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes : UKPDS 39. BMJ; 317:713–720, 1998.
9. ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet; 370:829–840, 2007.
10. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet; 364:685–696, 2004.
11. Heart Protection Study Collaborative Group. MRC / BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes : a randomised placebo-controlled trial. Lancet; 361:2005–2016, 2003.
12. Nikitin Y, Anderson C, Ph D, et al. Treatment of Hypertension in Patients 80 Years of Age or Older Hyvet Study. N Engl J Med; 358, 2008.
13. Shepherd J, Blauw G, Murphy M, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet; 360:1623–1630, 2002.
14. Afilalo J, Duque G, Steele R, et al. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. J Am Coll Cardiol; 51(1):37–45, 2008.
15. Doubova S, Morales H, Arreola L, Ortega M. Potential drug-drug and drug-disease interactions in prescriptions for ambulatory patients over 50 years of age in family medicine clinics in Mexico City. BMC Health Services Research; 7(1):147, 2007.
16. Rizvi AA. Management of Diabetes in Older Adults : The American Journal of the Medical Sciences. Am J Med Sci; 333(1):35–47, 2007.
17. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med; 365(21):2002–12, 2011.
18. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach: Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care; 35(6):1364–1379, 2012.
19. Lee S, Eng C. Goals of glycemic control in frail older patients with diabetes. JAMA; 305(13):1350–1351, 2011.
20. Yau CK, Eng C, Cenzer IS, et al. Glycosylated hemoglobin and functional decline in community-dwelling nursing home-eligible elderly adults with diabetes mellitus. J Am Geriatr Soc; 60(7):1215–21, 2012.
21. Sinclair A, Morley JE, Rodriguez-Mañas L, et al. Diabetes Mellitus in Older People: Position Statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. JAMDA; 13(6):497–502, 2012.
22. Sinclair A, Paolisso G, Castro M, et al. European Diabetes

Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. Diabetes & Metabolism; 37(3):S27–S38, 2011.
23. Kirpichnikov D, McFarlane S, Sowers J. Annals of Internal Medicine | Metformin: An Update. Annals of Internal Medicine; 137:25–33, 2002.
24. Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. Journal of Clinical Investigation; 108(8):1167–1174, 2001.
25. Mather KJ, Verma S, Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. J Am Coll Cardiol; 37(5):1344–1350, 2001.
26. Standeven KF, Ariëns RAS, Whitaker P, et al. The Effect of Dimethylbiguanide on Thrombin Activity, FXIII Activation, Fibrin Polymerization, and Fibrin Clot Formation. Diabetes; 51(1):189–197, 2002.
27. Chu NV, Kong APS, Kim DD, et al. Differential Effects of Metformin and Troglitazone on Cardiovascular Risk Factors in Patients With Type 2 Diabetes. Diabetes Care; 25(3):542–549, 2002.
28. DeFronzo RA, Goodman AM. Efficacy of Metformin in Patients with Non-Insulin-Dependent Diabetes Mellitus. N Engl J Med; 333(9):541–549, 1995.
29. Lee CG, Boyko EJ, Barrett-Connor E, et al. Insulin Sensitizers May Attenuate Lean Mass Loss in Older Men With Diabetes. Diabetes Care; 34(11):2381–2386, 2011.
30. AIFA. Metformina - Raccomandazioni sull'utilizzo nella gestione del diabete mellito di tipo 2. 2011. http://www.agenziafarmaco.gov.it/it/content/raccomandazioni-sull%E2%80%99utilizzo-dei-medicinali-base-di-metformina-nella-gestione-del-diabete-m
31. Roussel R, Travert F, Pasquet B, et al. Metformin Use and Mortality Among Patients With Diabetes and Atherothrombosis. Arch Intern Med; 170(21):1892–1899, 2010.
32. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane database of systematic reviews (Online); 4(4), 2010.
33. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Metformin, Sulfonylureas, or Other Antidiabetes Drugs and the Risk of Lactic Acidosis or Hypoglycemia. Diabetes Care; 31(11):2086–2091, 2008.
34. Eurich DT, Majumdar SR, McAlister FA, Tsuyuki RT, Johnson JA. Improved Clinical Outcomes Associated With Metformin in Patients With Diabetes and Heart Failure. Diabetes Care; 28(10):2345–2351, 2005.
35. Shah D, Fonarow G, Horwich T. Metformin Therapy and Outcomes in Patients With Advanced Systolic Heart Failure and Diabetes. Journal of Cardiac Failure; 16(3):200–206, 2010.
36. Aguilar D, Chan W, Bozkurt B, Ramasubbu K, Deswal A. Metformin Use and Mortality in Ambulatory Patients With Diabetes and Heart Failure / Clinical Perspective. Circulation: Heart Failure; 4(1):53–58, 2011.
37. Lipska KJ, Bailey CJ, Inzucchi SE. Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency. Diabetes Care; 34(6):1431–1437, 2011.
38. NICE. Tipe 2 Diabetes: The Management of Type 2 Diabetes: NICE Clinical Guidelines 87. http://guidance.nice.org.uk/CG66, 2009.
39. De Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ; 340(may19 4):c2181–c2181, 2010.
40. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. Diabetes Research and Clinical Practice; (July 7, published on line), 2012.
41. Holst JJ. Glucagon-Like Peptide-1: from extract to agent. The Claude Bernard Lecture, 2005. Diabetologia; 2:253–260, 2006.
42. Gutzwiller J-P, Tschopp S, Bock A, et al. Glucagon-Like Peptide 1 Induces Natriuresis in Healthy Subjects and in Insulin-Resistant Obese Men. Journal of Clinical Endocrinology & Metabolism; 89(6):3055–3061, 2004.
43. Nyström T, Gutniak MK, Zhang Q, et al. Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. American Journal of Physiology - Endocrinology And Metabolism; 287(6):E1209–15, 2004.
44. Bose AK, Mocanu MM, Carr RD, et al. Glucagon-like Peptide 1 Can Directly Protect the Heart Against Ischemia/Reperfusion Injury. Diabetes; 54(January):146–151, 2005.
45. Kavianipour M, Ehlers MR, Malmberg K, et Al. Glucagon-like peptide-1 (7-36) amide prevents the accumulation of pyrauvate and lactate in the ischemic and non ischemic porcine myocardium. Peptides; 24:569–578, 2003.
46. Sokos GG, Nikolaidis LA, Mankad S, Elahi D, Shannon RP. Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. Journal of Cardiac Failure; 12(9):694–699, 2006.
47. Nikolaidis LA, Mankad S, Sokos GG, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation; 109(8):962–5, 2004.
48. Nikolaidis LA, Elahi D, Hentosz T, et al. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing-induced dilated cardiomyopathy. Circulation; 110(8):955–61, 2004.
49. Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in Type 2 (non-insulin-dependent) diabetes. Diabetologia; 29(1):46–52, 1986.
50. Toft-Nielsen M-B, Damholt MB, Madsbad S, et al. Determinants of the Impaired Secretion of Glucagon-Like Peptide-1 in Type 2 Diabetic Patients. Journal of Clinical Endocrinology & Metabolism; 86(8):3717–3723, 2001.
51. Basu R, Breda E, Oberg AL, et al. Mechanisms of the Age-Associated Deterioration in Glucose Tolerance. Diabetes; 52(7):1738–1748, 2003.
52. Korosi J, McIntosh CHS, Pederson RA, et al. Effect of Aging and Diabetes on the Enteroinsular Axis. j Gerontol A Biol Sci; 56(9):M575–M579, 2001.
53. Fineman MS, Bicsak TA, Shen LZ, et al. Effect on Glycemic Control of Exenatide (Synthetic Exendin-4) Additive to Existing Metformin and/or Sulfonylurea Treatment in Patients With Type 2 Diabetes. Diabetes Care; 26(8):2370–2377, 2003.
54. DeFronzo RA, Ratner RE, Han J, et al. Effects of Exenatide (Exendin-4) on Glycemic Control and Weight Over 30 Weeks in Metformin-Treated Patients With Type 2 Diabetes. Diabetes Care; 28(5):1092–1100, 2005.
55. Ratner RE, Maggs D, Nielsen LL, et al. Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. Diabetes, Obesity and Metabolism; 8(4):419–428, 2006.
56. Buse JB, Henry RR, Han J, et al. Effects of Exenatide (Exendin-4) on Glycemic Control Over 30 Weeks in Sulfonylurea-Treated Patients With Type 2 Diabetes. Diabetes Care; 27(11):2628–2635, 2004.
57. Zinman B, Hoogwerf BJ, Durán García S, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Annals of Internal Medicine; 146(7):477–85, 2007.
58. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of Exe-

natide (Exendin-4) on Glycemic Control Over 30 Weeks in Patients With Type 2 Diabetes Treated With Metformin and a Sulfonylurea. Diabetes Care; 28(5):1083–1091, 2005.
59. Riddle MC, Henry RR, Poon TH, et al. Exenatide elicits sustained glycaemic control and progressive reduction of body weight in patients with type 2 diabetes inadequately controlled by sulphonylureas with or without metformin. Diabetes Metab. Res. Rev; 22(6):483–491, 2006.
60. Heine RJ, Van Gaal L, D J, et Al. Exenatide versus Insulin Glargine in Patients with Suboptimally Controlled Type 2 DiabetesA Randomized Trial. Annals of Internal Medicine; 143(8):559–569, 2005.
61. Nauck MA, Duran S, Kim D, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia; 50(2):259–267, 2007.
62. Marre M, Shaw J, Brändle M, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabetic Medicine; 26(3):268–78, 2009.
63. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet; 373(9662):473–81, 2009.
64. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care; 32(1):84–90, 2009.
65. Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care; 32(7):1224–30, 2009.
66. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia; 52(10):2046–55, 2009.
67. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet; 374(9683):39–47, 2009.
68. Shyangdan DS, Royle P, Clar C, et al. Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane database of systematic reviews (Online)2011;(10).
69. Bennett WL, Maruthur NM, Singh S, et al. Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An Update Including New Drugs and 2-Drug Combinations. Annals of Internal Medicine; 154(9):602–613, 2011.
70. Esposito K, Chiodini P, Bellastella G, Maiorino MI, Giugliano D. Proportion of patients at HbA1c target 7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients. Diabetes, Obesity and Metabolism; 228–233, 2012.
71. Best JH, Hoogwerf BJ, Herman WH, et al. Risk of Cardiovascular Disease Events in Patients with Type 2 Diabetes Prescribed the GLP-1 Receptor Agonist Exenatide Twice Daily or Other Glucose-Lowering Therapies: A Retrospective Analysis of the LifeLink™ Database. Diabetes Care. 2011.
72. Monami M, Cremasco F, Lamanna C, et al. Glucagon-Like Peptide-1 Receptor Agonists and Cardiovascular Events: A Meta-Analysis of Randomized Clinical Trials. Experimental Diabetes Research; 2011:1–10, 2011.
73. Stevens J, Cai J, Pamuk ER, et al. The Effect of Age on the Association between Body-Mass Index and Mortality. N Engl J Med; 338(1):1–7, 1998.
74. Flicker L, McCaul KA, Hankey GJ, et al. Body Mass Index and Survival in Men and Women Aged 70 to 75. Journal of the American Geriatrics Society; 58(2):234–241, 2010.
75. Baetta R, Corsini A. Pharmacology of Dipeptidyl Peptidase-4 Inhibitors. Drugs; 71(11):1441–1467, 2011.
76. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ; 344, 2012.
77. Esposito K, Cozzolino D, Bellastella G, et al. Dipeptidyl peptidase-4 inhibitors and HbA1c target of <7% in type 2 diabetes: meta-analysis of randomized controlled trials. Diabetes, Obesity and Metabolism; 13(7):594–603, 2011.
78. Yeom J-A, Kim ES, Park H-S, et al. Both sitagliptin analogue & pioglitazone preserve the β-cell proportion in the islets with different mechanism in non-obese and obese diabetic mice. BMB Reports; 44(11):713–718, 2011.
79. Monami M, Cremasco F, Lamanna C, Marchionni N, Mannucci E. Predictors of response to dipeptidyl peptidase-4 inhibitors: evidence from randomized clinical trials. Diabetes Metab. Res. Rev.; 27(4):362–372, 2011.
80. Schweizer A, Dejager S, Foley JE, Shao Q, Kothny W. Clinical experience with vildagliptin in the management of type 2 diabetes in a patient population ≥75 years: a pooled analysis from a database of clinical trials. Diabetes, Obesity and Metabolism; 13(1):55–64, 2011.
81. Barzilai N, Guo H, Mahoney EM, et al. Efficacy and tolerability of sitagliptin monotherapy in elderly patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin; 27(5):1049–1058, 2011.
82. Doucet J, Chacra A, Maheux P, et al. Efficacy and safety of saxagliptin in older patients with type 2 diabetes mellitus. Curr Med Res Opin; 27(4):863–869, 2011.
83. Chan JCN, Scott R, Arjona Ferreira JC, et al. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. Diabetes, Obesity and Metabolism; 10(7):545–555, 2008.
84. Nowicki M, Rychlik I, Haller H, et al. Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment. Diabetes, Obesity and Metabolism; 13(6):523–532, 2011.
85. Lukashevich V, Schweizer A, Shao Q, Groop P-H, Kothny W. Safety and efficacy of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment: a prospective 24-week randomized placebo-controlled trial. Diabetes, Obesity and Metabolism; 13(10):947–954, 2011.
86. Graefe-Mody U, Friedrich C, Port A, et al. Effect of renal impairment on the pharmacokinetics of the dipeptidyl peptidase-4 inhibitor linagliptin*. Diabetes, Obesity and Metabolism; 13(10):939–946, 2011.
87. Ito M, Abe M, Okada K, et al. The dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin improves glycemic control in type 2 diabetic patients undergoing hemodialysis. Endocrine Journal; 58(11):979–987, 2011.
88. Monami M, Lamanna C, Desideri CM, Mannucci E. DPP-4 Inhibitors and Lipids: Systematic Review and Meta-Analysis. Advances in Therapy; 29(1):14–25, 2011.
89. Patil HR, Al Badarin FJ, Shami HAA, et al. Meta-Analysis of Effect of Dipeptidyl Peptidase-4 Inhibitors on Cardiovascular Risk in Type 2 Diabetes Mellitus. The American Journal of Cardiology, 2012.
90. Monami M, Dicembrini I, Antenore A, Mannucci E. Dipeptidyl Peptidase-4 Inhibitors and Bone Fractures. Diabetes Care; 34(11):2474–2476, 2011.
91. Monami M, Dicembrini I, Martelli D, Mannucci E. Safety

of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. Curr Med Res Opin; 27(S3):57–64, 2011.
92. Yki-Järvinen H. Drug Therapy - Thiazolidinediones. N Engl J Med; 351:1106–1118, 2004.
93. Nissen SE, Wolski K. Rosiglitazone Revisited: An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality. Arch Intern Med; 170(14):1191–1201, 2010.
94. Schernthaner G, Ritz E, Schernthaner G-H. Strict glycaemic control in diabetic patients with CKD or ESRD: beneficial or deadly? Nephrology Dialysis Transplantation; 25(7):2044–2047, 2010.
95. Nissen SE, Nicholls SJ, Wolski K, et al. Comparison of Pioglitazone vs Glimepiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes: The PERISCOPE Randomized Controlled Trial. JAMA; 299(13):1561–1573, 2008.
96. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet; 366(9493):1279–1289, 2005.
97. Erdmann E, Dormandy JA, Charbonnel B, et al. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. Journal of the American College of Cardiology; 49(17):1772–1780, 2007.
98. Wilcox R, Bousser M-GG, Betteridge JJ, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke; a journal of cerebral circulation; 38(3):865–873, 2007.
99. Singh S, Loke YK, Furberg CD. Thiazolidinediones and Heart Failure. Diabetes Care; 30(8):2148–2153, 2007.
100. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ; 180(1):32–9, 2009.
101. Lewis J, Ferrara A, Peng T, et Al. Risk of bladder cancer among diabetic patints treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care; 34(916-922), 2011.
102. Warren G. Association Between Thiazolidinedione Treatment and Risk of Macular Edema Among Patients With Type 2 Diabetes. Arch Intern Med; Published ahead of print, 2012.
103. Hanefeld M, Cagatay M, Petrowitsch T, et al. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. European Heart Journal; 25(1):10–16, 2004.
104. Fa VDL, Plbj L, Rp A, Eh VDL, Gehm R. Alpha-glucosidase inhibitors for type 2 diabetes mellitus (Review). Cochrane database of systematic reviews (Online). 2009;(1).
105. Maedler K, Carr RD, Bosco D, et al. Sulfonylurea induced beta-cell apoptosis in cultured human islets. The Journal of clinical endocrinology and metabolism; 90(1):501–6, 2005.
106. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med; 355(23):2427–2443, 2006.
107. Gangji AS, Cukierman T, Gerstein HC, Goldsmith CH, Clase CM. A Systematic Review and Meta-Analysis of Hypoglycemia and Cardiovascular Events. Diabetes Care; 30(2):389–394, 2007.
108. Tayek J. SUR receptor activity vs. incidence of hypoglycaemia and cardiovascular mortality with sulphonylurea therapy for diabetics. Diabetes, Obesity and Metabolism; 10(11):1128–1129, 2008.
109. AMD, SID. Standard Italiani per la cura del Diabete Mellito 2009-2010. 2009.
110. Scognamiglio R, Avogaro A, Vigili de Kreutzenberg S, et al. Effects of Treatment With Sulfonylurea Drugs or Insulin on Ischemia-Induced Myocardial Dysfunction in Type 2 Diabetes. Diabetes; 51(3):808–812, 2002.
111. Monami M, Luzzi C, Lamanna C, et al. Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. Diabetes/Metabolism Research and Reviews; 22(6):477–482, 2006.
112. Monami M, Marchionni N, Masotti G, Mannucci E. Effect of combined secretagogue/biguanide treatment on mortality in type 2 diabetic patients with and without ischemic heart disease. International journal of cardiology; 126(2):247–51, 2008.
113. Pantalone KM, Kattan MW, Yu C, et al. The risk of overall mortality in patients with Type 2 diabetes receiving different combinations of sulfonylureas and metformin: a retrospective analysis. Diabetic Medicine; 29(8):1029–1035, 2012.
114. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med; 358(24):2560–2572, 2008.
115. Hueb W, Uchida AH, Gersh BJ, et al. Effect of a hypoglycemic agent on ischemic preconditioning in patients with type 2 diabetes and stable angina pectoris. Coronary artery disease; 18(1):55–9, 2007.
116. Mannucci E, Cremasco F, Romoli E, Rossi A. The use of insulin in elderly patients with type 2 diabetes mellitus. Expert opinion on pharmacotherapy; 12(18):2865–81, 2011.
117. Ligthelm RJ, Kaiser M, Vora J, Yale J-F. Insulin use in elderly adults: risk of hypoglycemia and strategies for care. Journal of the American Geriatrics Society; 60(8):1564–70, 2012.
118. Holman R, Thorne K, Farmer A, et al. Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. N Engl J Med; 361:1736–1747, 2007.
119. Bretzel RG, Nuber U, Landgraf W, et al. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. The Lancet; 371(9618):1073–1084, 2008.
120. Janka HU, Plewe G, Riddle MC, et al. Comparison of Basal Insulin Added to Oral Agents Versus Twice-Daily Premixed Insulin as Initial Insulin Therapy for Type 2 Diabetes. Diabetes Care; 28(2):254–259, 2005.
121. Raskin P, Allen E, Hollander P, et al. Initiating Insulin Therapy in Type 2 Diabetes. Diabetes Care; 28(2):260–265, 2005.
122. Ligthelm RJ. Self-titration of biphasic insulin aspart 30/70 improves glycaemic control and allows easy intensification in a Dutch clinical practice. Primary care diabetes; 3(2):97–102, 2009.
123. Raccah D, Bretzel RG, Owens D, Riddle M. When basal insulin therapy in type 2 diabetes mellitus is not enough—what next? Diabetes Metab. Res. Rev; 23(4):257–264, 2007.
124. Owens DR. Stepwise intensification of insulin therapy in Type 2 diabetes management—exploring the concept of the basal-plus approach in clinical practice. Diabetic Medicine. 2012 (september published on line).
125. Velussi M. Lispro insulin treatment in comparison with regular human insulin in type 2 diabetic patients living in nursing homes. Diabetes, nutrition & metabolism; 15(2):96–100, 2002.
126. Hewitt J, Smeeth L, Chaturvedi N, Bulpitt CJ, Fletcher AE. Self management and patient understanding of diabetes in the older person. Diabetic Medicine; 28(1):117–122, 2011.