Controverse:

Merita controlul intensiv al glicemiei?

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Antia BS, Pansanit A, Ekpa OD, Ekpe UJ, Mahidol C, Kittakoop P.

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Madi HA, Riches K, Warburton P, O'Regan DJ, Turner NA, Porter KE.

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1: The medicine wheel nutrition intervention: a diabetes education study with the cheyenne river sioux tribe.
Kattelmann KK, Conti K, Ren C.
J Am Diet Assoc. 2009 Sep;109(9):1532-9.
PMID: 19699832 [PubMed - in process]
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Vriesendorp TM, Roos YB, Kruyt ND, Biessels GJ, Kappelle LJ, Vermeulen M, Holleman F, DeVries JH, Ho
J Neurol Neurosurg Psychiatry. 2009 Sep;80(9):1040-3.
PMID: 19684236 [PubMed - indexed for MEDLINE]
Related Articles
3: Liver safety in patients with type 2 diabetes treated with pioglitazone: results from a 3-year, randomized, c study in the US.
Tolman KG, Freston JW, Kupfer S, Perez A.
Drug Saf. 2009;32(9):787-800. doi: 10.2165/11316510-000000000-00000.

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1: The effects of isolated telephone interventions on glycemic control in type 2 diabetes: a literature review.
Graziano JA, Gross CR.
ANS Adv Nurs Sci. 2009 Jul-Sep;32(3):E28-41.
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Yoo[illegible] [illegible]avaghan [illegible]elle [illegible] Roach P.
Clin Ther. 2[illegible] Jul;31(7):[illegible]1-2[illegible]
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3: Optimal insulin regimens in type 2 diabetes mellitus: systematic review and meta-analyses.
Lasserson DS, Glasziou P, Perera R, Holman RR, Farmer AJ.
Diabetologia. 2009 Oct;52(10):1990-2000. Epub 2009 Jul 31.
PMID: 19644668 [PubMed - in process]
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5 RCT !!

rosiglitazona

†

Table 3. Lifetime Risks for End-Stage Renal Disease*

Hemoglobin A_{1c} Level	Lifetime Risk for End-Stage Renal Disease†			
	Age at Onset of Diabetes			
	45 y	55 y	65 y	75 y
	%			
7	**2.0** (0.9–5.7)	**0.9** (0.4–2.7)	**0.3** (0.1–1.0)	**0.1** (0.0–0.2)
8	**2.7** (1.1–7.5)	**1.3** (0.5–3.6)	**0.5** (0.2–1.4)	**0.1** (0.0–0.3)
9	**3.5** (1.3–9.7)	**1.6** (0.6–4.8)	**0.6** (0.2–1.8)	**0.1** (0.0–0.4)
10	**4.3** (1.5–11.8)	**2.1** (0.7–6.0)	**0.8** (0.2–2.3)	**0.2** (0.1–0.6)
11	**5.0** (1.7–13.8)	**2.5** (0.8–7.1)	**0.9** (0.3–2.9)	**0.2** (0.1–0.7)

* For patients who develop end-stage renal disease, the average amount of time spent in this disease state was 5.2 years for those who were 45 years of age at diabetes onset, 4.6 years for those who were 55 years of age at onset, 4.0 years for those who were 65 years of age at onset, and 2.7 years for those who were 75 years of age at onset.

† Base-case results are given in boldface; one-way sensitivity analyses for the range of estimates for the transition probability with the greatest effect (transition from proteinuria to end-stage renal disease) are given in parentheses.

Vijan S. Ann Int Med, 1997

Table 2. Lifetime Risk for Blindness Due to Diabetic Retinopathy*

Hemoglobin A_{1c} Level	Lifetime Risk for Blindness†			
	Age at Onset of Diabetes			
	45 y	55 y	65 y	75 y
	%			
7	**0.3** (0.2–0.5)	**0.1** (0.1–0.2)	**<0.1** (0.0–0.1)	**<0.1** (0.0–0.1)
8	**1.1** (0.6–1.7)	**0.5** (0.3–0.7)	**0.2** (0.1–0.3)	**<0.1** (0.0–0.1)
9	**2.6** (1.5–4.0)	**1.2** (0.7–1.9)	**0.5** (0.3–0.7)	**0.1** (0.1–0.2)
10	**5.0** (3.0–7.6)	**2.5** (1.5–3.9)	**1.0** (0.6–1.6)	**0.3** (0.1–0.4)
11	**7.9** (4.7–11.9)	**4.4** (2.5–6.6)	**1.9** (1.1–2.9)	**0.5** (0.3–0.8)

* For patients who become blind, the average amount of time spent blind was 11.0 years for those who were 45 years of age at diabetes onset, 8.3 years for those who were 55 years of age at onset, 5.2 years for those who were 65 years of age at onset, and 3.2 years for those who were 75 years of age at onset.

† Base-case results are given in boldface; one-way sensitivity analyses for the range of estimates for the transition probability with the greatest effect (transition from retinopathy to blindness) are given in parentheses.

Vijan S. Ann Int Med, 1997

Table 5. Benefits of an Intervention That Decreases Hemoglobin A_{1c} Levels by 2 Percentage Points, Stratified by Age at Onset*

Hemoglobin A_{1c} Level Used as Criterion for Inclusion in the Intervention	Marginal Duration of Treatment To Prevent 1 Year of Blindness†			
	Age at Onset of Diabetes			
	40–49 y	50–59 y	60–69 y	70–79 y
%	← patient-years →			
≥12	28	40	61	230
≥11	50	113	136	816
≥10	108	171	390	1012
≥9	223	418	1135	5062

* Analyses were based on the patient population characteristics of patients with type 2 diabetes at a large staff-model health maintenance organization in whom diabetes was diagnosed in the past 5 years.

† Marginal effects were calculated from the incremental benefit and incremental increase in treatment compared with the previous treatment strategy.

Vijan S. Ann Int Med, 1997

Table 6. Three-Way Sensitivity Analyses: Reduction in Risk for Microvascular Complications*

Change in Hemoglobin A_{1c} Level	Absolute Reduction in Risk for Blindness with 1-Percentage Point Reduction in Hemoglobin A_{1c} Level			
	Age at Onset of Diabetes			
	45 y	55 y	65 y	75 y
	← % →			
8 to 7	**0.8** (0.3–1.4)	**0.4** (0.2–0.6)	**0.2** (0.1–0.2)	**<0.1** (0.0–0.1)
9 to 8	**1.5** (0.6–3.3)	**0.7** (0.3–1.7)	**0.3** (0.1–0.7)	**0.1** (0.0–0.1)
10 to 9	**2.4** (1.0–4.9)	**1.3** (0.4–3.0)	**0.5** (0.2–1.4)	**0.2** (0.1–0.5)
11 to 10	**2.9** (1.2–4.3)	**1.9** (0.7–3.3)	**0.9** (0.2–2.1)	**0.2** (0.1–0.8)

* Reduction in base-case rate is given in boldface; ranges of three-way sensitivity analysis are given in parentheses. Sensitivity analyses were conducted with simultaneous variation in the rates of transition from well to incidence of retinopathy, incidence of retinopathy to progression of retinopathy, and progression of retinopathy to blindness. When the best (base-case) estimates are used, for a patient who is 45 years of age at diabetes onset, a reduction in mean hemoglobin A_{1c} level from 8% to 7% results in an 8 in 1000 reduction in lifetime risk for blindness. However, the risk reduction could range from 3 in 1000 to 14 in 1000; the variation is due to the range of estimates found in the literature.

Vijan S. Ann Int Med, 1997

BMJ

Seeing what you want to see in randomised controlled trials: versions and perversions of UKPDS data

James McCormack and Trisha Greenhalgh

BMJ 2000;320;1720-1723

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Table 1 Effect of 10 years' treatment with chlorpropamide, glibenclamide, or insulin on patients with newly diagnosed type 2 diabetes

	Any diabetes related end points* (%)	Microvascular disease (%)	Individual macrovascular disease end points†	Median haemoglobin A_{1c} (%)
Dietary advice plus chlorpropamide, glibenclamide, or insulin	35.3	8.2	No significant difference between the groups for any of the individual end points‡	Chlorpropamide 6.7; glibenclamide 7.2; insulin 7.1
Dietary advice only	38.5	10.6		7.9
Relative risk reduction	8.2	22.6		Significantly lower for all drugs compared with dietary advice
Absolute risk reduction	3.2§	2.4		
No needed to treat for 10 years to prevent one event	31	42		

*Sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous haemorrhage, retinal photocoagulation, blindness in one eye, cataract extraction.
†Deaths related to diabetes, all cause mortality, myocardial infarction, stroke, blindness, renal failure, or neurological events.
‡P value for myocardial infarctions was 0.052 (dietary advice plus drug treatment 14.2% *v* dietary advice 16.3%). However, because the study was continued after the initial results showed no differences, a breakpoint for significance of 0.05 is debatable.
§2.7% of this 3.2% was due to a significant reduction in retinal photocoagulation.

Hb A1c – FR sau marker surogat?

- **Relatie cauzala: ↓ Hb A1c → ↓ efectului (complicatii)**
- **↓ Hb A1c= 1% → NU au scazut complicatiile macrovasculare (UKPDS 33, clorpropamid, glibenclamid, insulina)**
- **↓ Hb A1c= 0,6% → NUMAI metforminul a scazut complicatiile macrovasculare (UKPDS 34) (RAR=5-10% decese, IM, AVC)**

5 RCT

- UKPDS (x2) 1998/2008
- ProACTIVE 2005
- ADVANCE
- ACCORD
- VADT

} 2008

- Ray K et al. *Lancet 2009*
- Kelly T. *Ann Int Med 2009*

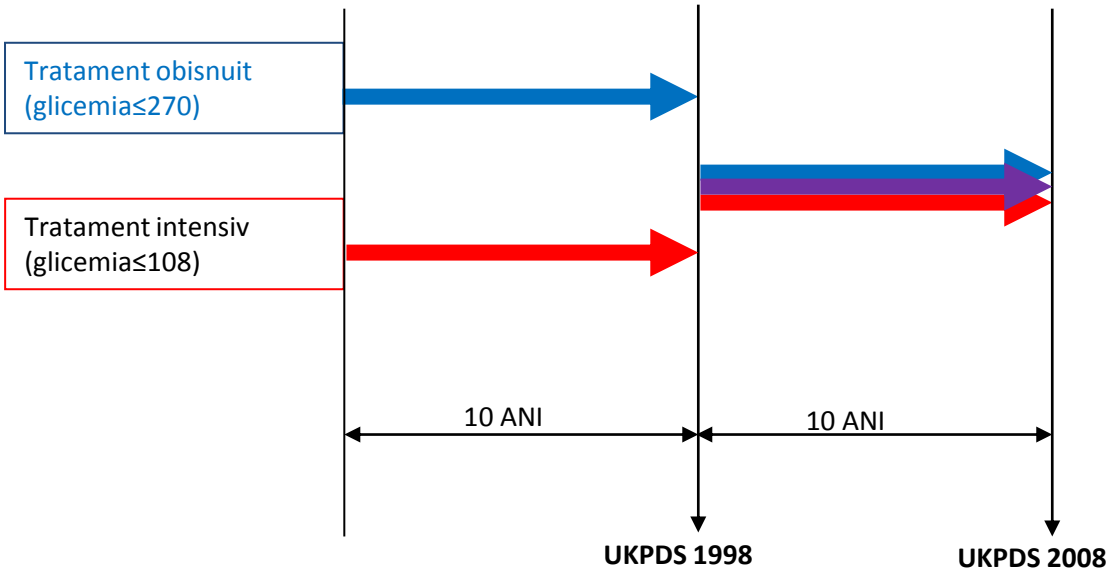
- **Ray K et al. *Lancet 2009***
  - **Scaderea medie HbA_{1c} = 0,9%**
  - **RRR=17% IM nonfatal**

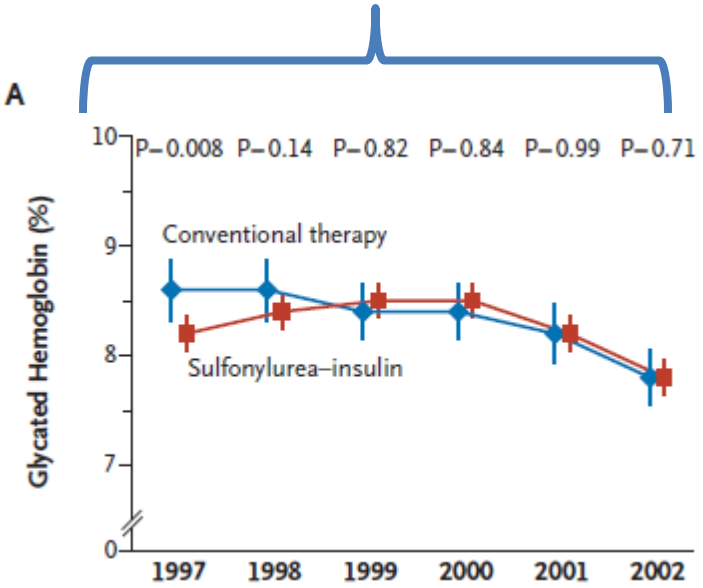
    (RAR=0,23%, NNT=435/ 1 an)
  - **RRR=15% evenimente coronariene**
  - **0% AVC, mortalitate totala**
- **Kelly T. *Annals of Int Med 2009***
  - **RAR evenimente coronariene: 1,5% / 5 ani**

    (NNT= 67/5ani, 333/1 an)
    - **(RRR=10%)**
  - **CAR hipoglicemie severa: 3,9%**

    (NNH = 25/ 5ani, 125/1 an)
  - **0% deces CV, mortalitate totala, AVC**

UKPDS – “Dupa 20 de ani”





Holman RR et al. N Engl J Med 2008

UKPDS – “Dupa 20 de ani”

Efect	RAR (‰)	NNT (10 ani)	NNT(1an)
Deces dat. diabet	2,5	400	4000
Deces	3,5	290	2900
IM	2,8	360	3600
Complic microvasculare	3,2	310	3100
Deces dat. diabet	4,7	210	2100
Deces	7,2	140	1400
IM	6,3	160	1600
Complic microvasculare	1	1000	10000

Grupul sulfoniluree-insulina
Grupul metformin

Holman RR et al. N Engl J Med 2008

Diferentele intre studii

- UKPDS: diabet la debut / 8-12 ani
- UKPDS: 53 ani / 63
- UKPDS: tinta HbA1c = 7%
  / 6-6,5% (real: 6,4, ACCORD)
- UKPDS: bazal HbA1c = 7,1%
  / 9,4 (VADT), 8,3 (ACCORD)

- UKPDS: durata studiu 10 ani / 5 ani

Diferentele intre studii (risc bazal)

	UKPDS	ProACTIVE	ADVANCE	VADT	ACCORD
Decese totale	19,5	25,6	19,1	18,9	11,3
IM nonfatal	9,1	19	5,6	15,5	13,1
Boala coronariana	16,7	26,7	12,1	17,9	13,8

‰ persoane-ani

Comparatie tratamente (NNT/1 an)

	Control glicemic	Control HTA	Statine
Decese	290*	361*	81† / 220
IM	360*	361*	63† / 125‡/149¥

*UKPDS

† 4S

‡ HPS

¥CARDS

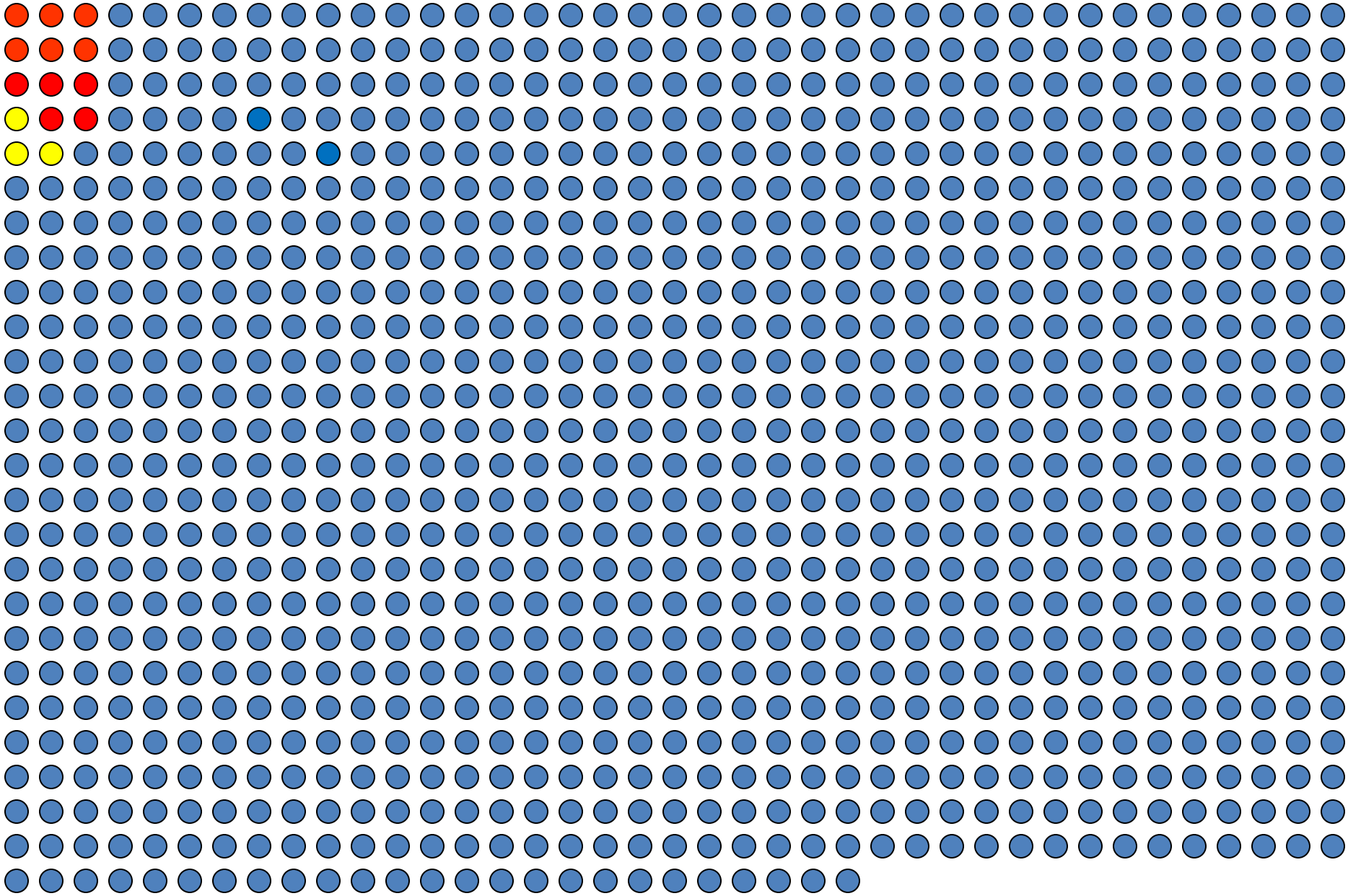
Concluzii

- **Cost-eficienta creste cu nivelul HbA1c si scade cu varsta (si durata diabetului?)**
- **Este important tratamentul la debutul bolii (UKPDS)**
- **Efectele sunt foarte mici in raport cu efortul**
- **Nu scade mortalitatea (nici CV, nici totala)**
- **Creste controlul intensiv mortalitatea (ACCORD)?**
- **Are metforminul un efect mult mai important decat restul antidiabeticelor, la obezi (UKPDS)?**
- **Cel mai bine este sa nu faci diabet!!**

Concluzii

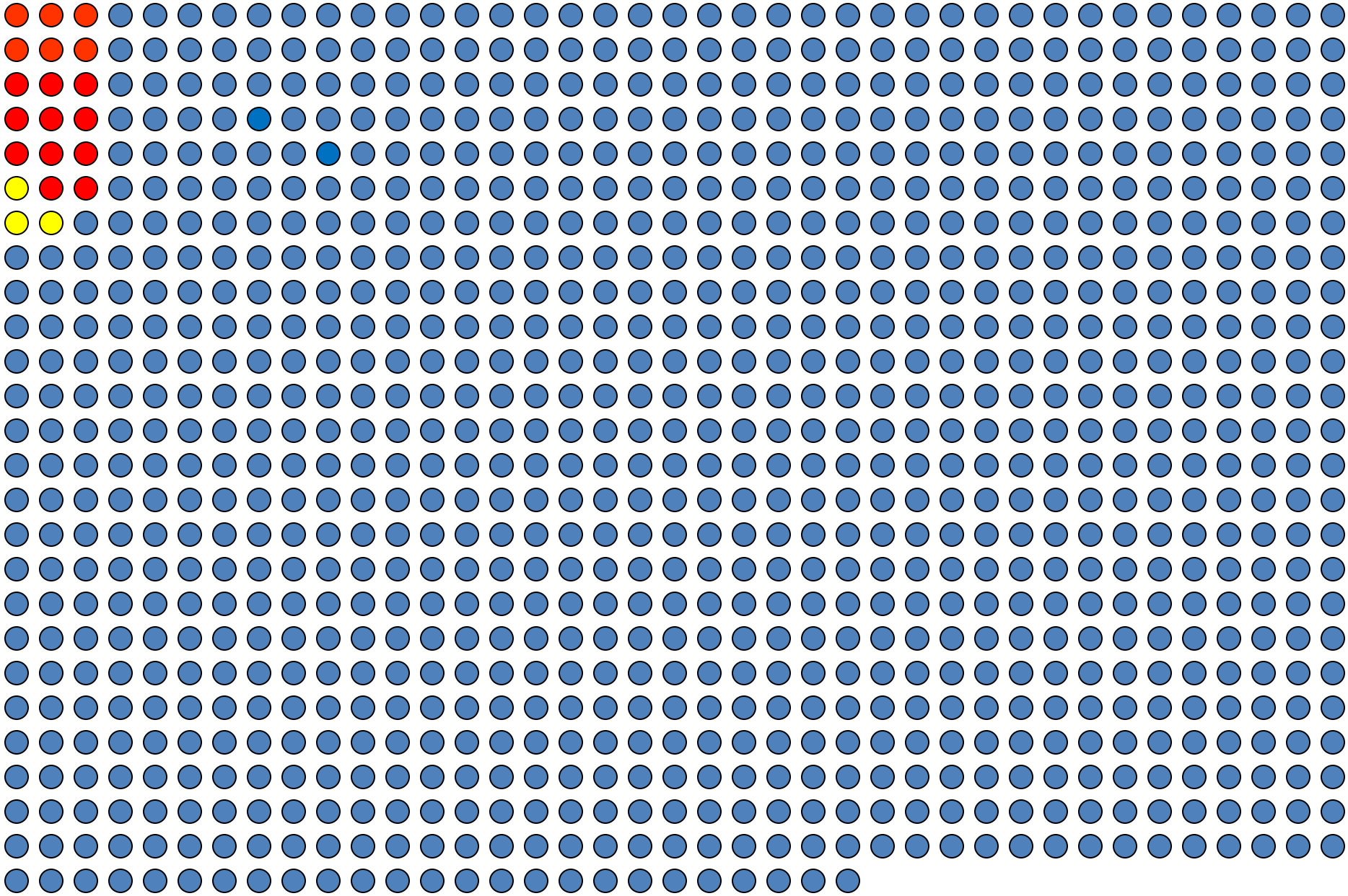
- **Unele ghiduri de diabet recomanda valori scazute ale HbA1c (6,5-7%) pt DZ de tip 2 in scopul evitarii sau intarzierii complicatiilor.**
- Analiza marilor RCT recente sugereaza ca **mentinerea stricta a glicemiei incarca pacientul cu programe terapeutice complexe, hipoglicemie, crestere ponderala si costuri si ofera in schimb beneficii incerte.**
- **Clinicienii trebuie sa aiba ca prioritati sprijinul pacientilor pentru o stare generala buna si un stil sanatos de viata, si reducerea riscului cardiovascular.**
- **Tinta pentru HbA1c trebuie individualizata astfel incat eforturile necesare pentru a o atinge sa reflecte contextul clinic personal, ca si valorile si preferintele in cunostinta de cauza ale pacientului.**

V Montori. Evid Base Med 2008/ Ann Int Med 2009



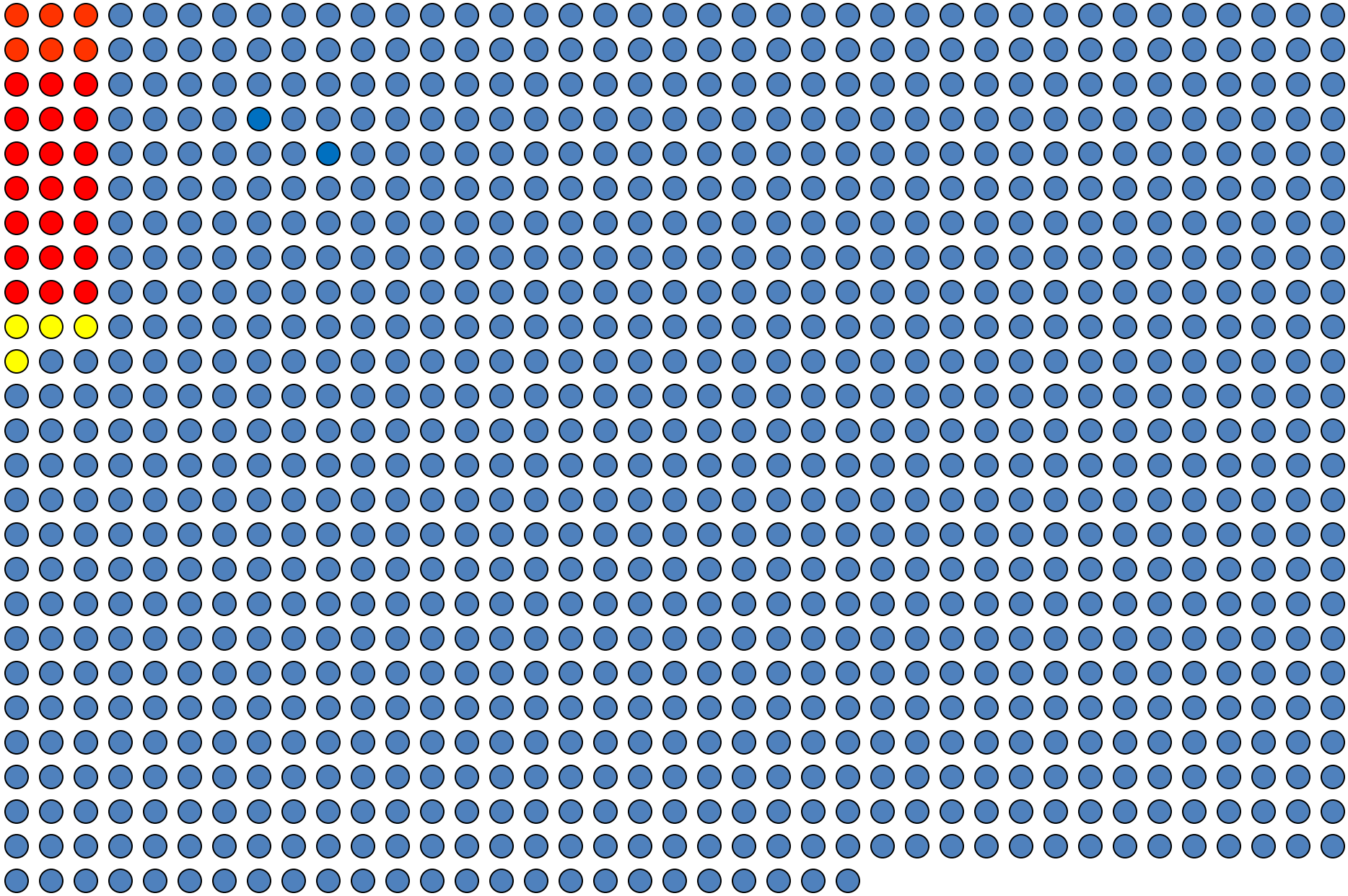
Complicatii microvasculare - 10 ani!!!

Holman RR et al. N Engl J Med 2008



IM - 10 ani!!!

Holman RR et al. N Engl J Med 2008



Mortalitate totala - 10 ani!!!

Holman RR et al. N Engl J Med 2008

- **33.070 pts. (*Ray K et al. Lancet 2009*)**
- **27.802 pts. (*Kelly T. Ann Int Med 2009*)**

Exista sau nu efecte importante???

- **160 pts.**

Steno (*Gœde P. NEJM, 2008*)