Luchando contra la DM: perspectiva endocrinológica

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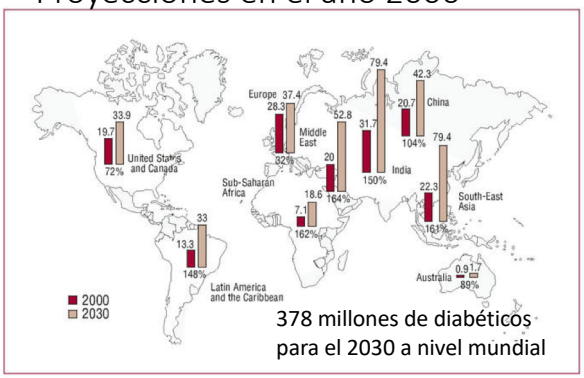
Conflictos de interés

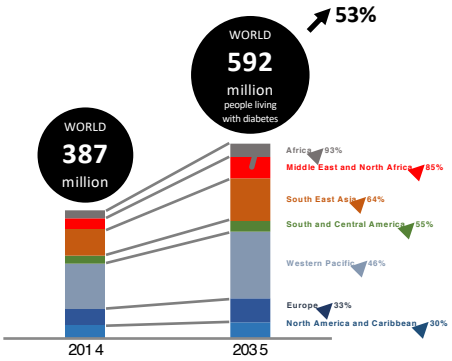
- Conferencista: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novartis Pharma, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Boehringer Ingelheim, Janssen
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer, Janssen
- Investigación clínica: Astra Zeneca, Novartis Oncology, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk

Introducción: epidemiología local

Proyecciones en el año 2000



378 millones de diabéticos para el 2030 a nivel mundial



Costos para América Latina y Caribe en 2015

- Costo indirecto $57.100.000.000
  - $27.500.000.000 por muerte prematura
  - $16.200.000.000 por discapacidad permanente
  - $13.300.000.000 por discapacidad temporal
- Costo directo $45.000.000.000 a $66.000.000.000
  - Tratamiento complicaciones: $26.000.000.000
  - Costo insulina: $6-11.000.000.000
  - Antidiabéticos orales: $4-6.000.000.000

Barcelo A. J Glob Health. 2017;7:201410

Costos LAC 2015

- Costo total: $102.000.000.000 a $123.000.000.000
- Similar al PIB para toda Guatemala!!!
- En promedio, costo por persona con DM por año es de $1088-1818
- Gasto por sistema nacional de salud $1061 por paciente

Barcelo A. J Glob Health. 2017;7:201410

Costa Rica

Población total: 4 808 000
Grupo de ingresos: Medianos altos

Mortalidad

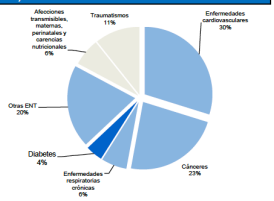
Número de muertes por diabetes

	hombres	*mujeres*
30-69 años	180	160
70 años o más	200	300

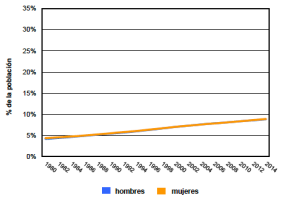
Número de muertes atribuibles a la hiperglucemia

	hombres	*mujeres*
30-69 años	330	240
70 años o más	370	480

Mortalidad proporcional (% del total de muertes, todas las edades)



Tendencias en la diabetes estandarizadas por edades



Prevalencia de la diabetes y de los factores de riesgo conexos

	hombres	mujeres	total
Diabetes	8.4%	8.7%	8.5%
Sobrepeso	58.0%	61.9%	59.9%
Obesidad	19.0%	29.2%	24.0%

http://www.who.int/diabetes/country-profiles/cri_es.pdf

Ticos pierden en promedio 13,2 años de vida por diabetes

María Isabel Solís Ramírez | Nov 12, 2014 | 06:32 PM | 2859 | CCSS

Lspan style="line-height: 1.3em;">La población costarricense pierde en forma prematura 13,2 años, en promedio, por la diabetes; una enfermedad que se caracteriza por altos niveles de azúcar en la sangre y que produce daños en diferentes órganos del cuerpo humano.

De acuerdo con la última encuesta de riesgo cardiovascular hecha por la CCSS, un 10.5% de la población mayor de 20 años tiene este padecimiento y según lo destacó el doctor Roy Wong, epidemiólogo que estuvo a cargo de la encuesta, lamentablemente la prevalencia de diabetes en Costa Rica es muy semejante a la que presentan países como Canadá y Estados Unidos y es superior a la que tienen las naciones centroamericanas.

http://www.who.int/diabetes/country-profiles/cri_es.pdf

Control glicémico y dyslipidemia en DM

Tabla 1. Características Basales de los Pacientes en DISCOVER-LA por País o Región

Characteristic	Central America* (n=2219) [mean ± SD**]	Mexico (n=458) [mean ± SD]	Colombia (n=200) [mean ± SD]	Argentina (n=302) [mean ± SD]	Brazil (n=444) [mean ± SD]
Males	39.3%	40.8%	51.5%	51.3%	46.8%
Age (months)	58.7 ± 12.8	56.8 ± 10.7	60.4 ± 10	59.9 ± 10.8	58.6 ± 11.5
Ethnicity					
Hispanic	88.5%	98.3%	66.8%	42.3%	6.1%
Caucasian	7.3%		8.0%	47%	67.3%
Black	0.5%		3.5%		11.9%
Mixed	3.7%		20.6%		12.6%
Tobacco use					
Smoker	1.4%	9.4%	7.1%	12.7%	8.6%
Ex-smoker	15.7%	22.3%	25.8%	24.7%	33.1%
BMI (kg/m²)					
<25	25 (19.6%)	86 (19.0%)	49 (25.0%)	28 (10.0%)	56 (13.2%)
25 to <30	61 (40.2%)	182 (40.2%)	82 (41.8%)	88 (31.4%)	170 (40.1%)
≥ 30	71 (40.1%)	185 (40.8%)	65 (33.2%)	164 (58.6%)	198 (46.7%)
Waist circumference (cm)	99.5 ± 16.6	97.6 ± 12.6	96.5 ± 11.4	107.1 ± 14.4	102.7 ± 12.4
High blood pressure (>130/90mmHg)	69 (38.6%)	118 (26.2%)	54 (27.3%)	114 (40.7%)	238 (56.5%)

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Tabla 2. Estudios de Laboratorio Basales de los Pacientes de DISCOVER-LA por País o Región

Characteristic	Central America* [mean ± SD**]	México [mean ± SD]	Colombia [mean ± SD]	Argentina [mean ± SD]	Brazil [mean ± SD]
Baseline HbA1c (%)	7.7 ± 1.8	8.9 ± 1.6	8.4 ± 2.1	8.8 ± 1.9	8.4 ± 1.9
<7	54 (32.7%)	14 (5.6%)	36 (20.2%)	33 (12.8%)	58 (14.4%)
7-10	95 (58.4%)	176 (70.7%)	110 (61.8%)	162 (63.0%)	279 (69.1%)
>10	14 (8.8%)	59 (23.7%)	32 (18.0%)	62 (24.1%)	67 (16.6%)
Total Cholesterol high(>180mg/dL)	50 (54.0%)	99 (50.5%)	72 (51.8%)	118 (57.3%)	139 (47.3%)
HDL low (<40M/50W)	54 (58.1%)	78 (72.9%)	82 (60.3%)	85 (49.1%)	156 (55.3%)
LDL high(>70 mg/dL)	78 (82.3%)	92 (84.4%)	70 (72.2%)	133 (89.9%)	211 (79.0%)
Triglycerides (mg/dL)	186.6 ± 131	209.8 ± 151.7	191.3 ± 136.3	180.4 ± 98.5	187.0 ± 127.1
Serum creatinine	0.9 ± 0.4	1.3 ± 2.0	1.2 ± 1.5	1.2 ± 1.4	1.0 ± 0.9

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Tabla 3. Condiciones Médicas Generales de los Pacientes en DISCOVER-LA por País o Región

Characteristic	Central America*	México	Colombia	Argentina	Brazil
Time since diagnosis (months) [mean ± SD**]	78.0 + 83.6	96.6 + 91.9	71.9 + 64	77.7 + 75.9	79.2 + 69.8
Years stayed on 1st line [mean ± SD]	6.0±6.4	7.2 ± 7.5	4.7 ± 4.6	5.4 ± 5.8	5.7 ± 4.9
Patient come to a diagnosis of diabetes					
Symptoms appeared	31.1%	64.8%	31%	21.2%	18.5%
Routine monitoring	60.3%	31.4%	60.5%	68.9%	76.6%
Referred by another physician	8.7%	3.7%	8.5%	9.9%	5.0%
Any macrovascular disease	9.6%	13.5%	17%	13.2%	15.3%
Hypertension	59.8%	46.3%	52%	57.3%	63.7%
Hyperlipidemia	38.8%	40.6%	48.5%	43%	55.9%

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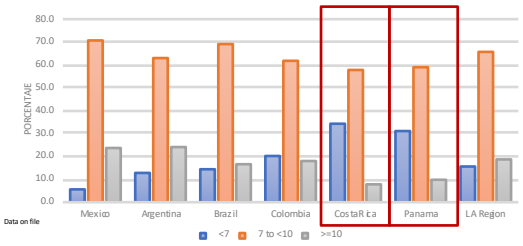
Promedio de HbA1c en pacientes de América Latina

La HbA1c basal media fue del 8,9 ± 1,6% y el 94,4% de los pacientes tenían valores ≥7%.



Data on file

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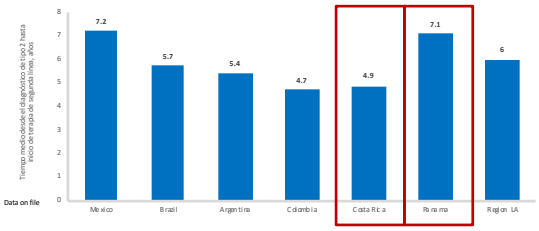
En México el tiempo desde el diagnóstico hasta el inicio de la terapia de segunda línea

La duración de la terapia de primera línea fue de 7,2 años y los fármacos utilizados fueron MET (83,1%) o SU (9,9%) solos.



Data on file

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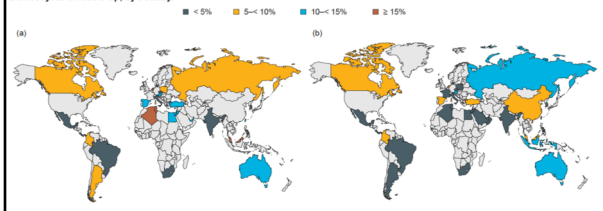
Tasa de eventos micro y macrovasculares al año

Figure 2. Proportion of patients for whom newly occurring (a) microvascular and (b) macrovascular complications were documented in the first year of follow-up, by country.



Kosiborod M. ADA 2018. Poster 1562

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Objetivos y tratamiento de dislipidemias

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Risk categories

Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE ≥10%.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10%.
Moderate-risk	SCORE is ≥1% and <5% at 10 years. Many middleaged subjects belong to this category.
Low-risk	SCORE <1%.

www.escardio.org/guidelines

European Heart Journal 2016 - doi:10.1093/eurheartj/ehv272

EAS

Intervention strategies

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	≥190 mg/dL ≥4.9 mmol/L
<1	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled
Class/Level	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle advice	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice, consider drug if uncontrolled
Class/Level	I/C	I/C	IIa/A	IIa/A	I/A
≥5 to <10, or high-risk	Lifestyle advice	Lifestyle advice, consider drug if uncontrolled	Lifestyle advice and drug treatment for most	Lifestyle advice and drug treatment	Lifestyle advice and drug treatment
Class/Level	IIa/A	IIa/A	IIa/A	I/A	I/A
≥10 or very high-risk	Lifestyle advice, consider drug*	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment	Lifestyle advice and concomitant drug treatment
Class/Level	IIa/A	IIa/A	I/A	IA	I/A

*In patients with myocardial infarction, statin therapy should be considered irrespective of total cholesterol levels.

www.escardio.org/guidelines

European Heart Journal 2016 - doi:10.1093/eurheartj/ehv272

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EUROPEAN SOCIETY OF CARDIOLOGY®

Guías National Lipid Association

Categoría riesgo	Criterio	Meta de tratamiento	Considerar tratamiento farmacológico
		Colesterol no HDL mg/dl *Colesterol LDL mg/dl*	
Bajo	- 0-1 factores de riesgo mayor cardiovascular - Considerar otros indicadores de riesgo, si son conocidos	<130 ***<100***	≥190 ***≥160***
Moderado	- 2 factores de riesgo mayor cardiovascular - Considerar cuantificación de riesgo (por calculadoras de riesgo) - Considerar otros indicadores de riesgo	<130 ***<100***	≥160 ***≥130***

Alto	- ≥3 factores de riesgo mayor cardiovascular
	- Diabetes mellitus (tipo 1 o 2)
	  - 0-1 factores de riesgo cardiovascular
	  - Sin lesión de órgano blanco
	- Enfermedad renal crónica estadio 3B o 4
	- LDL ≥190 mg/dl (hipercolesterolemia severa)
	- Cálculo de riesgo llegando al umbral de alto riesgo
		<130
		<100
			≥130
			≥100

Muy alto	- Enfermedad cardiovascular establecida
	- Diabetes mellitus (tipo 1 o 2)
	  - ≥2 factores de riesgo cardiovascular
	  - Lesión de órgano blanco
		<130
		<100
			≥100
			≥70

Para pacientes con enfermedad cardiovascular o diabetes mellitus, se debe considerar el uso de estatinas de intensidad moderada o alta independientemente de su perfil de lípidos

Jacobson TA. J Clin Lipidol. 2016;9(2):129

Guías Asociación Americana de Endocrinología Clínica (AACE)

Categoría de riesgoAE	Factores riesgo / riesgo a 10 años	Metas de tratamiento		
		LDL mg/dl	Colesterol no HDL mg/dl	Apo B mg/dl
Riesgo extremo	- Enfermedad cardiovascular establecida progresiva (angina inestable a pesar de LDL <70mg/dl) - Enfermedad cardiovascular establecida en pacientes con diabetes mellitus, enfermedad renal crónica estadio 3 ó 4, hipercolesterolemia familiar heterocigota - Historia de enfermedad cardiovascular prematura (<55 años en hombres y <65 años en mujeres)	<55	<80	<70
Muy alto riesgo	- Síndrome coronario agudo o enfermedad coronaria, carotídea, vascular periférico establecido u hospitalización reciente por ésta - Diabetes mellitus o enfermedad renal crónica estadio 3 ó 4 con 1 o más factores de riesgo - Hipercolestgerolemia familiar heterocigota	<70	<100	<80
Alto riesgo	- ≥2 factores de riesgo y riesgo a 10 años 10-20% - Diabetes mellitus o enfermedad crónica estadio 3 ó 4 sin otros factores de riesgo	<100	<130	<90
Riesgo moderado	≤2 factores de riesgo y riesgo a 10 años <10%	<100	<130	<90
Bajo riesgo	0 factores de riesgo	<130	<160	No recomienda

Jellinger PS. Endocr Pract. 2017;23(Supl 2):1

Qué tienen en común las guías?

	ACC/AHA	ESC	NLA	AACE
DM sin lesión de órgano blanco		alto riesgo (LDL 100-155 mg/dl), drogas para mayoría		LDL <100 mg/dl
DM con lesión de órgano blanco		Muy alto riesgo (LDL 70-100), drogas para mayoría		LDL <70 mg/dl
DM sin otros factores de riesgo	Si ASCVD <7.5%, estatinas de intensidad moderada		LDL <100 mg/dl Colesterol no HDL <130 mg/dl	
DM con más 2 factores de riesgo	Si ASCVD >7.5%, estatinas de alta intensidad		LDL <70 mg/dl, colesterol no HDL <100 mg/dl	

Objetivos y tratamiento de HTA en DM

Metas de PA en DM

Guideline/society	Target (mmHg)	First drug class recommendation
UK NICE [18][a]	130/80	ACEI/ARB
CHEP [21]	130/80	ACEI/ARB
WHO [22]	130/80	ACEI/ARB
IDF [23][b]	130/80	ACEI/ARB
JSH [24]	130/80	ACEI/ARB
IGH [25]	140/80	ACEI/ARB
ESC/ESH [19]	140/85	ACEI/ARB
ADA [4][c]	140/90	ACEI/ARB
JNC-8P [20]	140/90	ACEI/ARB
ASH/ISH [26, 27]	140/90	ACEI/ARB
AHA/ACC/ASH [26]	140/90	ACEI/ARB

Shaikh A. Diabetes Ther. 2017;8:891

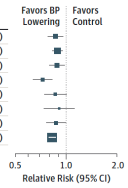
Metas en DM

Medical Society	BP Target
ADA 2018	< 140/90 mmHg
ESC/ESH Diabetes guideline 2013	< 140/85 mmHg
JNC 8 2014	< 140/90 mmHg
NICE (UK 2013)	< 140/80 mmHg, but if retinopathy, cerebrovascular disease, or microalbuminuria is present: < 130/80 mmHg

Metanálisis: reducción de PA en DM

Figure 2. Standardized Associations Between 10-mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes in Diabetic Patients

Outcome	No. of Studies	BP Lowering Events	BP Lowering Participants	Control Events	Control Participants	Relative Risk (95% CI)
Mortality	20	2334	27693	2319	25864	0.87 (0.78-0.96)
Cardiovascular disease	17	3230	25756	3280	24862	0.89 (0.83-0.95)
Coronary heart disease	17	1390	26150	1449	24761	0.88 (0.80-0.98)
Stroke	19	1350	27614	1475	26447	0.73 (0.64-0.83)
Heart failure	13	1235	21684	1348	20791	0.86 (0.74-1.00)
Renal failure	9	596	19835	560	18912	0.91 (0.74-1.12)
Retinopathy	7	844	9781	905	9566	0.87 (0.76-0.99)
Albuminuria	7	2799	13804	3163	12821	0.83 (0.79-0.87)



Emdin CA. JAMA. 2015;313:603

Reducción de eventos según PA inicial

Outcome	No. of Studies	Baseline SBP, Mean, mm Hg	BP Lowering, No. Events	BP Lowering, No. Participants	Control, No. Events	Control, No. Participants	Relative Risk (95% CI)	P for Interaction
Mortality, mm Hg								
≥140[16, 18, 19, 27-30, 35, 39-41, 51, 55, 56, 64, 65, 77-80]	13	149	1614	16418	1626	14580	0.73 (0.64-0.84)	
<140[17, 31, 36-38, 58-60, 80, 81]	7	137	720	1275	693	11284	1.07 (0.92-1.26)	P=.001
Overall							0.87 (0.78-0.96)	
Cardiovascular disease, mm Hg								
≥140[16, 18, 19, 27-30, 35, 39-41, 46, 47, 51-55]	11	148	1861	14976	1918	14068	0.74 (0.65-0.85)	
<140[17, 31, 36-38, 58-60, 80, 81]	6	137	1369	10780	1362	10794	0.96 (0.88-1.05)	P=.001
Overall							0.89 (0.83-0.95)	
Coronary heart disease, mm Hg								
≥140[16, 18, 27, 28, 30, 35, 39-41, 47, 51, 64, 65]	10	148	858	14875	931	13477	0.73 (0.61-0.87)	
<140[17, 31, 36-38, 43, 58-60, 80, 81]	7	137	532	11275	518	11284	0.97 (0.86-1.10)	P=.01
Overall							0.88 (0.80-0.98)	
Stroke, mm Hg								
≥140[16, 18, 30, 27, 28, 30, 35, 39-41, 46-47, 51, 55, 56, 63-65]	14	148	1129	19066	1245	17868	0.74 (0.64-0.86)	
<140[17, 36-38, 58-60, 80, 81]	5	137	221	8548	230	8579	0.69 (0.52-0.92)	P=.70
Overall							0.73 (0.64-0.83)	
Heart failure, mm Hg								
≥140[16, 18, 29, 30, 35, 39-41, 46, 47, 64, 65]	8	146	774	13592	814	12676	0.75 (0.59-0.94)	
<140[31, 42-45, 59-60, 80, 81]	5	137	461	8092	534	8115	0.97 (0.79-1.19)	P=.09
Overall							0.86 (0.74-1.00)	
Renal failure, mm Hg								
≥140[16, 18, 29, 30, 40, 41, 64, 65]	6	147	389	12475	346	11530	0.75 (0.52-1.08)	
<140[31, 58-60]	3	138	207	7360	214	7382	1.00 (0.77-1.29)	P=.21
Overall							0.91 (0.74-1.12)	
Retinopathy, mm Hg								
≥140[16, 19, 30, 64, 65, 77-80]	4	146	564	7946	586	7753	0.86 (0.70-1.04)	
<140[36-38, 59, 60, 80, 81]	3	137	280	1835	319	1813	0.88 (0.74-1.05)	P=.85
Overall							0.87 (0.76-0.99)	
Albuminuria, mm Hg								
≥140[16, 18-30, 40, 63]	4	146	1681	8447	1898	7647	0.71 (0.63-0.79)	
<140[17, 36-38, 59, 60]	3	137	1118	5357	1265	5174	0.86 (0.81-0.90)	P=.002
Overall							0.83 (0.79-0.87)	

Emdin CA. JAMA. 2015;313:603

Objetivos y tratamiento de control glicémico en DM

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

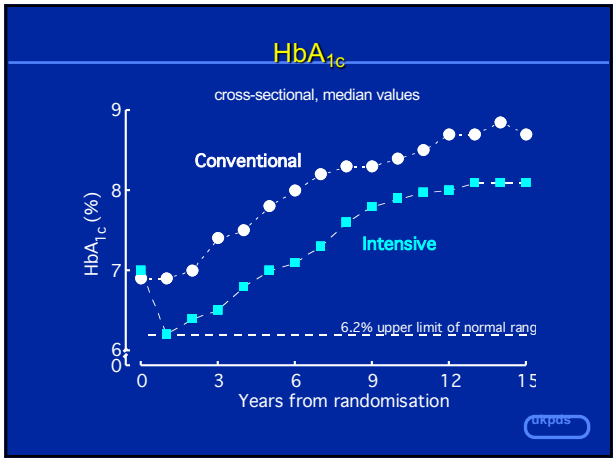
Study	Microvasc		CVD		Mortality	
UKPDS	↓	↓	↔	↓	↔	↓
DCCT / EDIC*	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Initial Trial

Long Term Follow-up

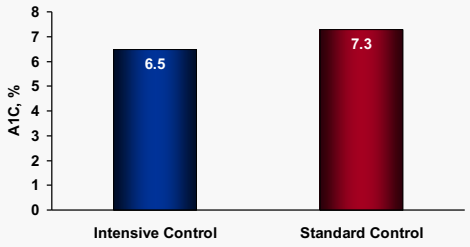
* in T1DM

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med.* 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329:977.
Nathan DM et al. *N Engl J Med.* 2005;353:2643. Gerstein HC et al. *N Engl J Med.* 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)



The ADVANCE Trial: Effect on A1C Level

After 5 years of follow-up, mean A1C was lower in the intensive-control group than in the standard-control group



The ADVANCE Collaborative Group. *N Engl J Med*. 2008;358(24):2560-2572.

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The ADVANCE Trial: Primary Endpoints

	Intensive Control n=5571	Standard Control n=5569	Relative Risk Reduction, % (95% CI)
Combined major macrovascular and microvascular events	1009 (18.1)	1116 (20.0)	10 (2 to 18)
Major macrovascular events	557 (10.0)	590 (10.6)	6 (-6 to 16)
Nonfatal myocardial infarction	153 (2.7)	156 (2.8)	2 (-23 to 22)
Nonfatal stroke	214 (3.8)	209 (3.8)	-2 (-24 to 15)
Death from cardiovascular events	253 (4.5)	289 (5.2)	12 (-4 to 26)
Major microvascular events	526 (9.4)	605 (10.9)	14 (3 to 23)
New or worsening nephropathy	230 (4.1)	292 (5.2)	21 (7 to 34)
New or worsening retinopathy	332 (6.0)	349 (6.3)	5 (-10 to 18)

Data are n (%).

The ADVANCE Collaborative Group. *N Engl J Med*. 2008;358(24):2560-2572.

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Impacto de agentes antidiabéticos

Reducción de eventos cardiovasculares/mortalidad	Neutros en eventos cardiovasculares
Empagliflozina	Insuling glargina
Canagliflozina	Insulina degludec
Liraglutide	Sitagliptina
Semaglutide	Saxagliptina (aumento de hospitalización por ICC?)
Pioglitazona	Alogliptina (aumento de hospitalización por ICC?)
Exenatide semanal	Lixisenatide

Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

A1C is less than 9%, **consider Monotherapy.**

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 Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table 8.1)

A1C at target after 3 months of monotherapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Dual Therapy

Dual Therapy Lifestyle Management + Metformin + Additional Agent

ASCVD?

Yes: - Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p. S75 and **Table 8.1**)

No: - Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)

A1C at target after 3 months of dual therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Triple Therapy

Triple Therapy Lifestyle Management + Metformin + Two Additional Agents

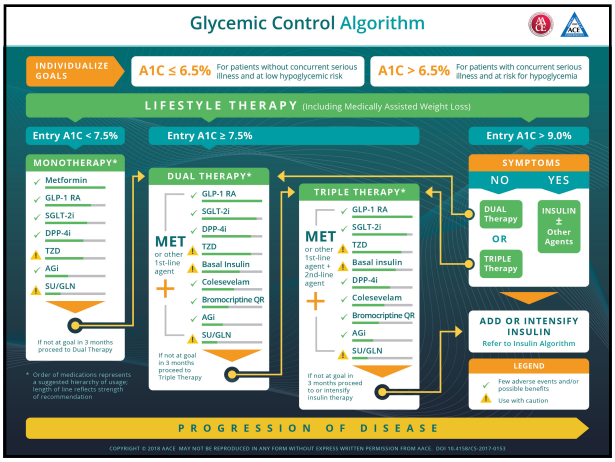
Add third agent based on drug-specific effects and patient factors# (See Table 8.1)

A1C at target after 3 months of triple therapy?

Yes: - Monitor A1C every 3–6 months

No: - Assess medication-taking behavior
- Consider Combination Injectable Therapy (See Figure 8.2)

Combination Injectable Therapy (See Figure 8.2)



Preguntas…

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Puede descargar la presentación en:

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