# Seguridad cardiovascular de insulinas

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## Conflictos de interés

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

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## Agenda

- Asociación fisiopatológica de insulinas y eventos cardiovasculares
- Estudios epidemiológicos
- Insulinas humanas
- Análogos de insulina
- Dosis dependiente?

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**EFECTOS DE INSULINA: PROATEROSCLERÓTICAS O ANTIATEROSCLERÓTICAS?**

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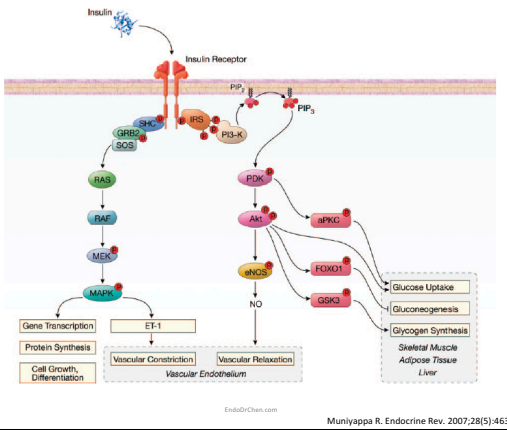


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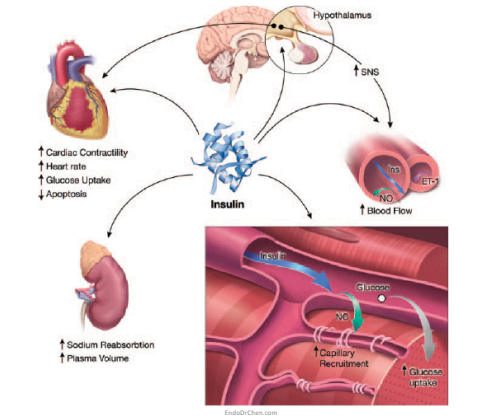
Muniyappa R. Endocrine Rev. 2007;28(5):463

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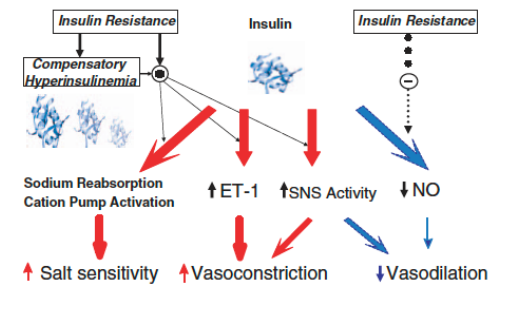
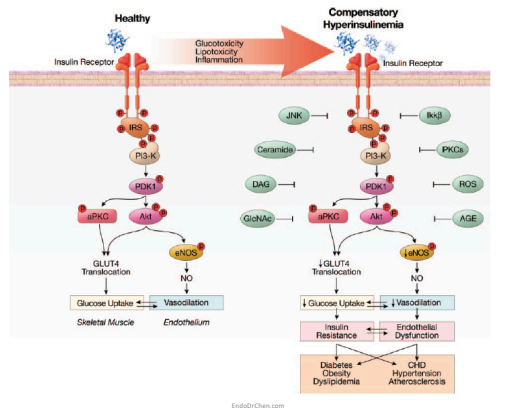
Muniyappa R. Endocrine Rev. 2007;28(5):463

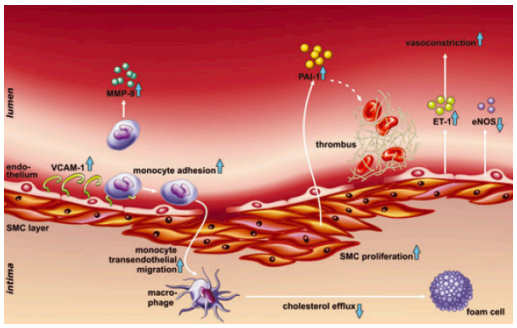



Muniyappa R. Endocrine Rev. 2007;28(5):463




Muniyappa R. Endocrine Rev. 2007;28(5):463

## Efectos aterogénicos de insulina




Rensing KL. Diab Obes Metab. 2011;13:1073

## Consideraciones

- La asociación de insulina con eventos cardiovasculares se ha basado en la medición de niveles endógenos de insulina, no en uso farmacológico
  - Son un reflejo del estado de resistencia a la insulina del paciente
  - Gradiente porta/sistémico es diferente, sólo medimos circulación sistémica
- Diseño de estudios antiguos
  - Muchos pacientes que inician con insulina tienen mayor tiempo de evolución de DM y mayor cantidad de comorbilidades
- Nuevos requerimientos de seguridad cardiovascular

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**EVIDENCIA CON INSULINAS HUMANAS**

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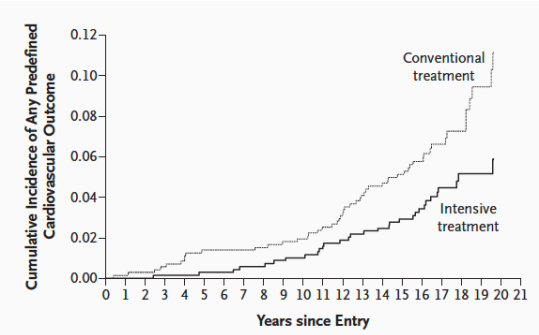
## EDIC: cardiovascular

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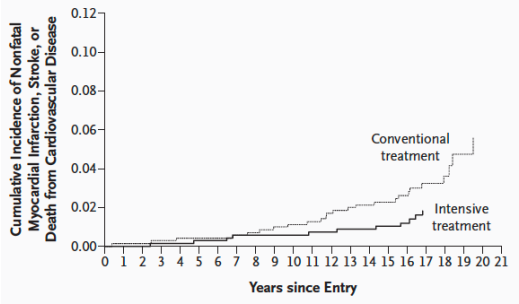
DCCT/EDIC Study Research Group. N Engl J Med. 2005;353:2643

## EDIC cardiovascular

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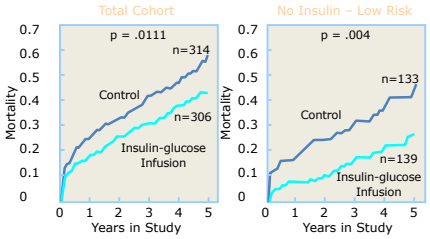
DCCT/EDIC Study Research Group. N Engl J Med. 2005;353:2643

Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI): *Benefit of Tight Glycemic Control in No Insulin – Low Risk Cohort*

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Malmberg K, et al. *BMJ.* 1997;314:1512-1515.

## DIGAMI-2: mortalidad total

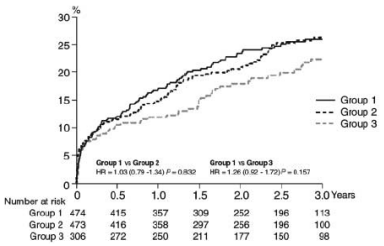


**Figure 2** Mortality in groups 1, 2, and 3 (intention to treat analysis).

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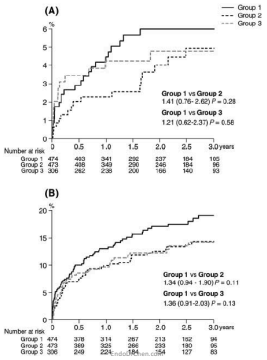
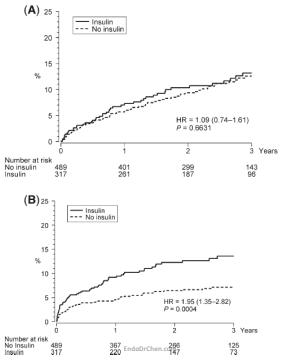
Malmberg K. Eur Heart J. 2005;26:650

## DIGAMI2: ictus e IAM



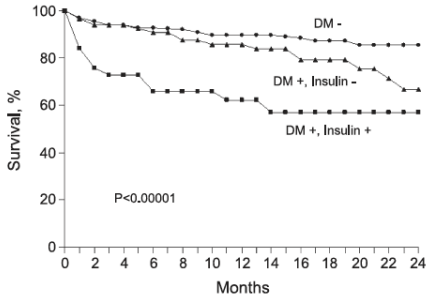

Malmberg K. Eur Heart J. 2005;26:650

## DIGAMI2: análisis post hoc




Melbin LG. Eur Heart J. 2008;29:166

## ICC y mortalidad




Smooke S. Am Heart j. 2005;149:168

| N | Total cohort (554) | Nondiabetic patients (422) | Non-insulin-treated diabetic patients (89) | Insulin-treated diabetic patients (43) | P |
|---|---|---|---|---|---|
| Age (y) | 52.0 ± 13.1 | 51.0 ± 13.3 | 55.6 ± 12.0 | 54.0 ± 10.4 | .006 |
| Males (%) | 75.6 | 75.6 | 77.5 | 72.1 | .466 |
| NYHA III-IV (%) | 76.8 | 75.9 | 79.1 | 81.5 | .754 |
| EF (%) | 24.6 ± 7.4 | 24.6 ± 7.5 | 24.4 ± 6.5 | 24.8 ± 8.1 | .945 |
| LVEDD (mm) | 67.1 ± 10.4 | 67.2 ± 10.4 | 68.2 ± 10.0 | 62.7 ± 11.1 | .80 |
| Severe mitral regurgitation (%) | 15.0 | 13.7 | 24.2 | 13.0 | .140 |
| CAD (%) | 45.1 | 40.6 | 55.1 | 69.0 | .0001 |
| Smoking (%) past or present | 73.1 | 73.8 | 74.6 | 60.0 | .392 |
| Hypertension (%) | 53.5 | 46.2 | 66.7 | 72.2 | .001 |
| Duration of diabetes (y) | NA | NA | 5.7 ± 5.7 | 10.7 ± 10.1 | .0001 |
| BMI | 27.5 ± 6.2 | 26.9 ± 6.2 | 29.8 ± 6.0 | 28.8 ± 5.4 | .002 |
| Peak $VO_2$ (mL/kg per min) | 13.8 ± 4.9 | 14.2 ± 5.0 | 12.8 ± 3.6 | 11.6 ± 5.3 | .037 |
| Systolic blood pressure (mm Hg) | 113.4 ± 22.6 | 110.4 ± 20.1 | 119.4 ± 23.1 | 124.3 ± 33.1 | .001 |
| Cardiac index (L/min per $m^2$) | 3.43 ± 1.27 | 3.43 ± 1.30 | 3.52 ± 1.25 | 3.23 ± 1.11 | .667 |
| PCW (mm Hg) | 21.4 ± 8.8 | 20.8 ± 8.9 | 22.4 ± 8.3 | 24.0 ± 8.2 | .131 |
| Serum sodium (mmol/L) | 136.2 ± 4.7 | 136.4 ± 4.7 | 136.2 ± 4.8 | 134.6 ± 4.5 | .105 |
| Serum BUN (mg/dL) | 27.5 ± 18.5 | 25.2 ± 17.0 | 32.2 ± 19.5 | 38.9 ± 23.9 | .0001 |
| Serum creatinine (mg/dL) | 1.54 ± 1.66 | 1.54 ± 1.82 | 1.38 ± 0.63 | 1.92 ± 1.49 | .265 |
| Serum Hb (g/dL) | 13.2 ± 1.9 | 13.4 ± 1.8 | 13.0 ± 2.1 | 12.2 ± 1.8 | .004 |
| Total cholesterol (mg/dL) | 170.3 ± 56.8 | 169.3 ± 50.5 | 174.1 ± 69.8 | 172.5 ± 84.0 | .810 |
| HbA1c (%) | NA | NA | 7.85 ± 2.06 | 6.93 ± 1.33 | .136 |
| ACE inhibitor or ARB (%) | 89.2 | 90.0 | 91.0 | 76.7 | .023 |
| β-Blocker (%) | 73.8 | 74.6 | 75.3 | 62.8 | .230 |
| Statin (%) | 44.6 | 39.1 | 64.0 | 58.1 | .0001 |

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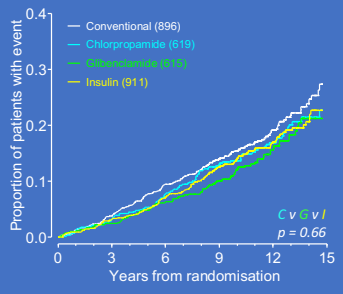
Smooke S. Am Heart J. 2005;149:168

## UKPDS: Myocardial Infarction




**EVIDENCIA CON INSULINAS ANÁLOGOS**

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## ORIGIN Research Questions

*In **high risk** people with IFG, IGT or early diabetes,*

*a) does insulin replacement therapy targeting fasting normoglycemia (≤ 5.3 mM or 95 mg/dl) with insulin glargine, reduce CV outcomes more than standard approaches to dysglycemia?*

*b) does adding omega 3 FA reduce CV death?*

## Participants (Key Inclusion Criteria)

- **Age ≥ 50 yrs**
  ***AND***
- **Dysglycemia**
  ***AND***
  - *EITHER* IFG or IGT or new type 2 DM by OGTT
    [i.e. FPG ≥ 110 (6.1); or 2 Hr PG ≥ 140 (7.8)]
  - *OR* prior type 2 DM @ stable dose ≥ 10 wks & …
    - on no OADs … + HbA1c < 9.0%
    - < half-max 1 OAD + HbA1c < 8.5%
    - ≥ half-max 1 OAD + HbA1c < 8.0%
- **High CV Risk**
  - *EITHER* Prior MI, stroke, revasc, angina + doc. ischemia
  - *OR* MA, proteinuria, LVH, 50% art. stenosis, ABI < 0.9

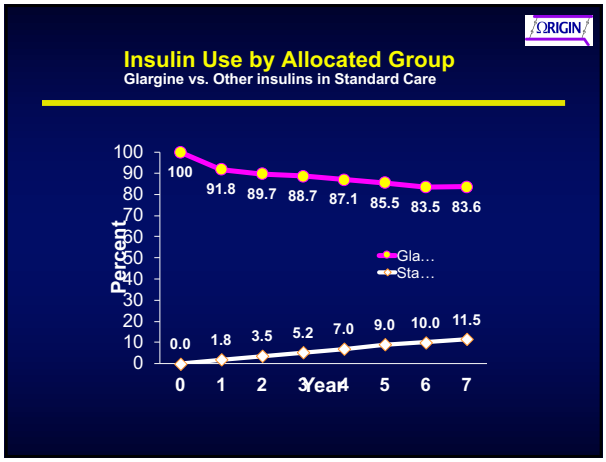
## Major Outcomes: Glargine Trial

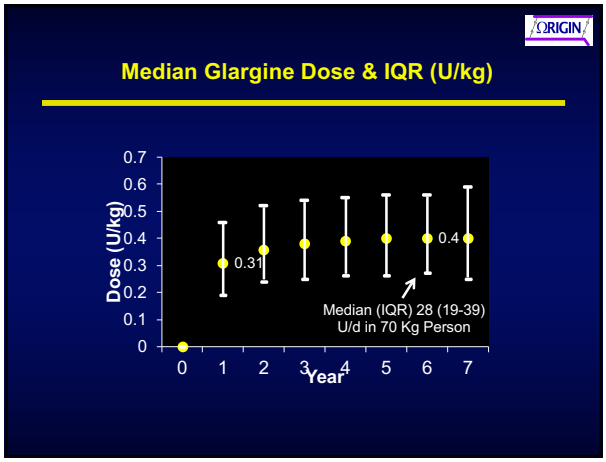
***Primary***

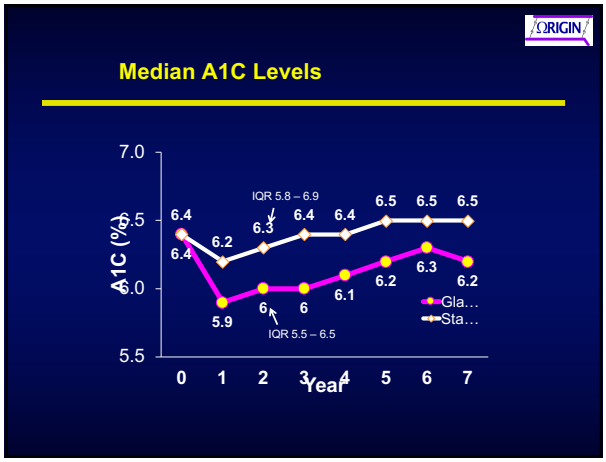
- CV death OR MI OR stroke
- CV death OR MI OR stroke OR revasc OR CHF hosp'n

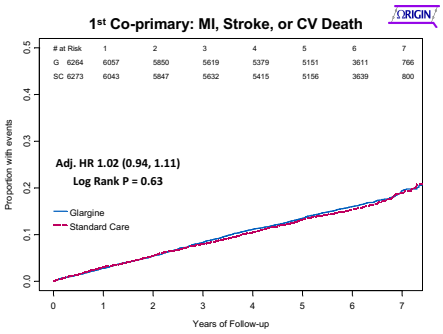
***Secondary***

- Microvascular composite
  (i.e. doubling of serum Cr, progression of albuminuria category, dialysis/renal transplant, laser Rx/vitrectomy for retinopathy)
- New type 2 diabetes (in those without baseline diabetes)
- All cause death


ORIGIN
Insulin Use by Allocated Group
Glargine vs. Other insulins in Standard Care
Percent
100
91.8
89.7
88.7
87.1
85.5
83.5
83.6
0.0
1.8
3.5
5.2
7.0
9.0
10.0
11.5
Gla…
Sta…
Year
0 1 2 3 4 5 6 7


ORIGIN
Median Glargine Dose & IQR (U/kg)
Dose (U/kg)
0.31
0.4
Median (IQR) 28 (19-39)
U/d in 70 Kg Person
Year
0 1 2 3 4 5 6 7


ORIGIN
Median A1C Levels
A1C (%)
IQR 5.8 – 6.9
IQR 5.5 – 6.5
6.4
6.2
6.3
6.4
6.4
6.5
6.5
6.5
6.4
5.9
6
6
6.1
6.2
6.3
6.2
Gla…
Sta…
Year
0 1 2 3 4 5 6 7


1st Co-primary: MI, Stroke, or CV Death
ORIGIN
# at Risk 1 2 3 4 5 6 7
G 6264 6057 5850 5619 5379 5151 3611 766
SC 6273 6043 5847 5632 5415 5156 3639 800
Adj. HR 1.02 (0.94, 1.11)
Log Rank P = 0.63
Glargine
Standard Care
Proportion with events
0.0 0.1 0.2 0.3 0.4 0.5
0 1 2 3 4 5 6 7
Years of Follow-up
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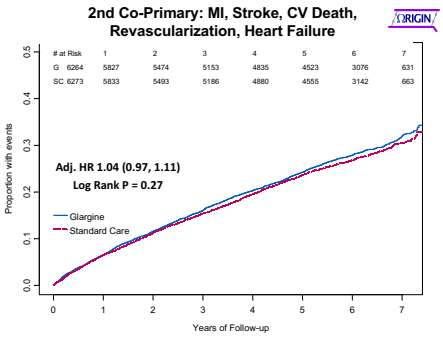
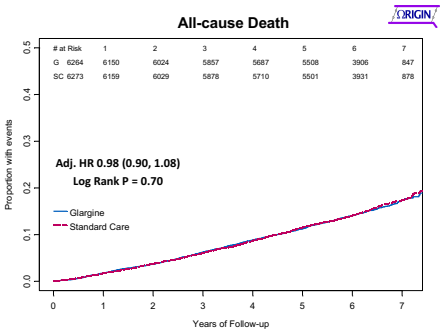

2nd Co-Primary: MI, Stroke, CV Death, Revascularization, Heart Failure
ORIGIN
# at Risk 1 2 3 4 5 6 7
G 6264 5827 5474 5153 4835 4523 3076 631
SC 6273 5833 5493 5186 4880 4555 3142 663
Adj. HR 1.04 (0.97, 1.11)
Log Rank P = 0.27
Glargine
Standard Care
Proportion with events
0.0 0.1 0.2 0.3 0.4 0.5
0 1 2 3 4 5 6 7
Years of Follow-up
EndoDrChen.com


All-cause Death
ORIGIN
# at Risk 1 2 3 4 5 6 7
G 6264 6150 6024 5857 5687 5508 3906 847
SC 6273 6159 6029 5878 5710 5501 3931 878
Adj. HR 0.98 (0.90, 1.08)
Log Rank P = 0.70
Glargine
Standard Care
Proportion with events
0.0 0.1 0.2 0.3 0.4 0.5
0 1 2 3 4 5 6 7
Years of Follow-up
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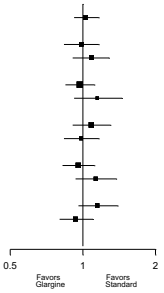
## 1st Co-Primary - Subgroups

ORIGIN

| | HR (95% CI) | P Interaction |
|---|---|---|
| Overall | 1.02 (0.94 -1.11) | |
| Placebo Allocation | 0.99 (0.88 -1.12) | |
| Omega 3 Allocation | 1.06 (0.94 -1.19) | 0.47 |
| Male | 0.98 (0.89 -1.09) | |
| Female | 1.11 (0.94 -1.31) | 0.22 |
| Age < 65 yrs | 1.06 (0.93 -1.21) | |
| Age >= 65 yrs | 0.99 (0.88 -1.11) | 0.43 |
| BMI <= 30 | 0.97 (0.87 -1.09) | |
| BMI > 30 | 1.09 (0.95 -1.26) | 0.18 |
| A1C<6.4% (Median) | 1.11 (0.97 -1.27) | |
| A1C>=6.4% (Median) | 0.95 (0.85 -1.07) | 0.09 |

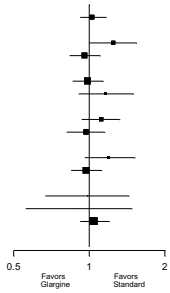



**MI, Stroke, CV Death**

## 1st Co-Primary - Subgroups

ORIGIN

| | HR (95% CI) | P Interaction |
|---|---|---|
| Overall | 1.02 (0.94 -1.11) | |
| No Prior CV Event | 1.17 (1.00 -1.37) | |
| Prior CV Event | 0.97 (0.87 -1.07) | 0.05 |
| No Metformin | 0.99 (0.90 -1.10) | |
| Metformin | 1.12 (0.94 -1.34) | 0.23 |
| No Statin Use | 1.08 (0.95 -1.22) | |
| Statin Use | 0.98 (0.86 -1.10) | 0.25 |
| No ACE-I/ARB | 1.14 (0.97 -1.35) | |
| ACE-I/ARB | 0.98 (0.89 -1.09) | 0.13 |
| IFG/IGT | 0.99 (0.75 -1.30) | |
| New DM | 0.93 (0.65 -1.32) | |
| Prior DM | 1.03 (0.94 -1.14) | 0.82 |

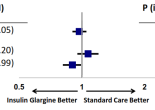



**MI, Stroke, CV Death**

### Microvascular outcome decreased with insulin glargine if baseline HbA1c was ≥6.4% but not <6.4%

- Allocation to insulin glargine reduced the incidence of the microvascular outcome in participants with baseline HbA1c ≥6.4% but not in those with lower baseline HbA1c

| | HR (95%CI) | P (interaction) |
|---|---|---|
| **Overall** | 0.97 (0.90, 1.05) | |
| **HbA1c < 6.4%** | 1.07 (0.95, 1.20) | **0.03** |
| **HbA1c ≥ 6.4%** | 0.90 (0.81, 0.99) | |



## Numerically larger HbA1c difference with insulin glargine vs standard care in those with baseline HbA1c ≥6.4%

- In participants with baseline HbA1c ≥6.4%, the median HbA1c difference was 0.33% with insulin glargine vs standard care (P<0.00001)
- In participants with baseline HbA1c <6.4%, the median HbA1c difference was 0.22% with insulin glargine vs standard care (P<0.00001)

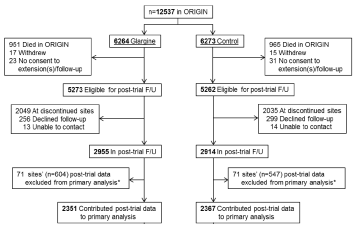
| | HR for microvascular outcome (95% CI) | Median (IQR) HbA1c difference post-randomisation, % | | Median HbA1c difference between groups, % |
|---|---|---|---|---|
| | | Insulin glargine | Standard care | |
| **HbA1c <6.4%** | 1.07 (0.95 to 1.20) | +0.06 (-0.21; +0.40) | +0.27 (-0.02; +0.64) | -0.22; P<0.0001 |
| **HbA1c ≥6.4%** | **0.90 (0.81 to 0.99)** | -0.65 (-0.16; -0.91) | -0.33 (-0.83; +0.13) | **-0.33; P<0.0001** |



## ORIGINALE Trial
**Objective**

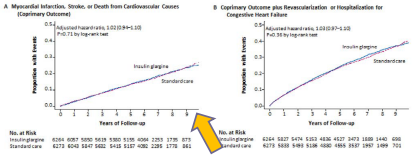
**Determine the effects of a median 6.2 years' exposure to insulin glargine versus standard care or omega-3 fatty acids versus placebo on CV and other outcomes during an additional median follow-up of 2.7 years**

## ORIGINALE Trial
**Results (1) – Glargine: Participant flow**

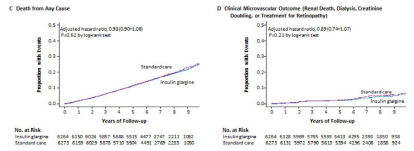



*Sites retaining <80% of surviving randomized participants in either the glargine or standard care groups for post-trial follow-up

## ORIGINALE Trial
**Results (4) – Glargine: Outcome events over time**




## ORIGINALE Trial
**Results (5) – Glargine: Outcome events over time**




## ORIGINALE Trial
**Results (8) – Glargine: New diabetes**

- No difference in the number of newly diagnosed diabetes between groups
- More newly diagnosed + possible diabetes in the standard care group

| | Insulin Glargine N (%) | Standard Care N (%) | Odds Ratio (95% CI) | P |
|---|---|---|---|---|
| Definite Diabetes | 278 (37.7) | 300 (41.7) | 0.85 (0.69-1.04) | 0.12 |
| Definite & Possible Diabetes | 304 (41.2) | 343 (47.7) | 0.77 (0.63-0.95) | 0.014 |

**Definite diabetes:** A1c ≥6.5% (48 mmol/mol) or the new use of any glucose-lowering drugs

**Possible diabetes**: Diagnosed or treated by a nonstudy physician during the trial without documented confirmation

## ORIGINALE Trial

**Results (9) – Glargine: Hypoglycemia**

- Proportion of participants experiencing at least one hypoglycemic event during the whole study period was higher in the glargine group than in the standard care group:
  - **Severe hypoglycemia** (5.8% vs. 1.9%; P <0.001)
  - **Non-severe hypoglycemia** (57.6% vs. 26.0%; P <0.001)

U.S. Food and Drug Administration
Protecting and Promoting Public Health
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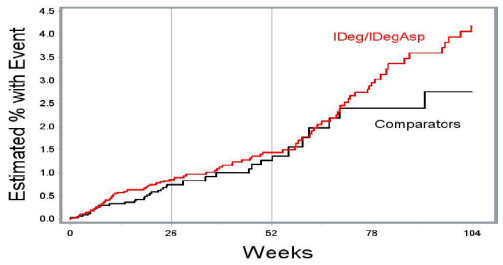
## K-M Plot of MACE+




| N at risk: | 5768 | 5056 | 2491 | 1378 | 811 |
|---|---|---|---|---|---|
| | 3446 | 3038 | 1107 | 458 | 265 |

Updated DB, Censor: 7 days



U.S. Food and Drug Administration
Protecting and Promoting Public Health
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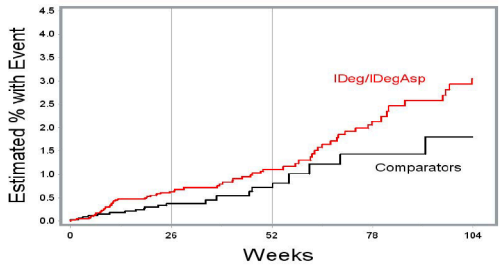
## K-M Plot of MACE




| N at risk: | 5768 | 5065 | 2500 | 1392 | 821 |
|---|---|---|---|---|---|
| | 3446 | 3048 | 1109 | 460 | 265 |

Updated DB, Censor: 7 days

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## Primary Analysis Result

| | IDeg/IDegAsp (*N* = 5794) | Comparator (*N* = 3461) |
|---|---|---|
| **MACE+** | | |
| Events | 95 | 37 |
| HR (95% CI) | **1.30 (0.88, 1.93)** | |
| **MACE** | | |
| Events | 70 | 21 |
| HR (95% CI) | **1.67 (1.01, 2.75)** | |

Cox model stratified by trial

Updated DB, Censor: 7 days



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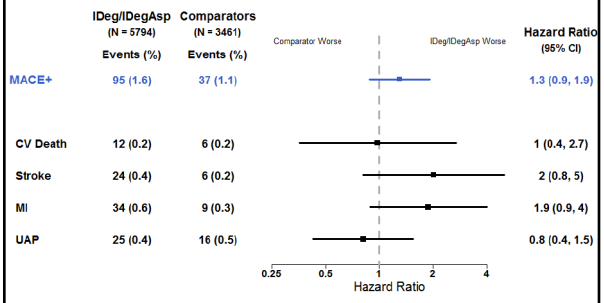
## MACE+ Components




Updated DB, Censor: 7 days



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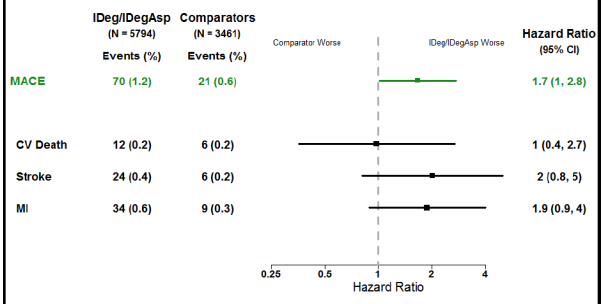
## MACE Components




Updated DB, Censor: 7 days

## Type 1 Diabetes (4 trials)

| | MACE+ | | MACE | |
|---|---|---|---|---|
| | IDeg/IDegAsp | Comparator | IDeg/IDegAsp | Comparator |
| N | 1469 | 656 | 1469 | 656 |
| Events (%) | 10 (0.7%) | 4 (0.6%) | 7 (0.5%) | 2 (0.3%) |
| HR (95% CI) | **0.96 (0.30, 3.09)** | | **1.30 (0.27, 6.29)** | |

Cox model stratified by trial

Updated DB, Censor: 7 days



## Type 2 Diabetes (13 trials)

| | MACE+ | | MACE | |
|---|---|---|---|---|
| | IDeg/IDegAsp | Comparator | IDeg/IDegAsp | Comparator |
| N | 4325 | 2805 | 4325 | 2805 |
| Events (%) | 85 (2.0%) | 33 (1.2%) | 63 (1.5%) | 19 (0.7%) |
| HR (95% CI) | **1.35 (0.89, 2.04)** | | **1.71 (1.01, 2.90)** | |

Cox model stratified by trial

Updated DB, Censor: 7 days



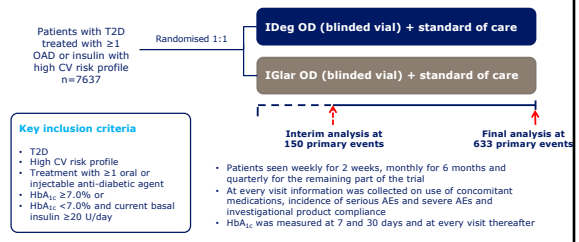
## IGlar-controlled (12 trials)

| | MACE+ | | MACE | |
|---|---|---|---|---|
| | IDeg/IDegAsp | IGlar | IDeg/IDegAsp | IGlar |
| N | 4397 | 2540 | 4397 | 2540 |
| Events (%) | 87 (2.0%) | 27 (1.1%) | 62 (1.4%) | 16 (0.6%) |
| HR (95% CI) | **1.54 (0.99, 2.40)** | | **1.82 (1.03, 3.19)** | |

Cox model stratified by trial

Updated DB, Censor: 7 days

## Trial design




**Key inclusion criteria**

- T2D
- High CV risk profile
- Treatment with ≥1 oral or injectable anti-diabetic agent
- $HbA_{1c}$ ≥7.0% or
- $HbA_{1c}$ <7.0% and current basal insulin ≥20 U/day

- Patients seen weekly for 2 weeks, monthly for 6 months and quarterly for the remaining part of the trial
- At every visit information was collected on use of concomitant medications, incidence of serious AEs and severe AEs and investigational product compliance
- $HbA_{1c}$ was measured at 7 and 30 days and at every visit thereafter

AEs, adverse events; OAD, oral anti-diabetic drug; OD, once daily; T2D, type 2 diabetes

Marso *et al. Am Heart J.* 2016; doi:10.1016/j.ahj.2016.06.004

## Endpoints

**Primary endpoint:**

- Time from randomisation to the first occurrence of a 3-component MACE
  - CV death, nonfatal myocardial infarction or nonfatal stroke

**Secondary endpoints:**

- Severe hypoglycaemia according to ADA criteria†
- Time from randomisation to all-cause death
- Frequency of serious AEs
- Frequency of AEs leading to discontinuation of the investigational product

ADA, American Diabetes Association
† An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions

Marso *et al. Am Heart J.* 2016; doi:10.1016/j.ahj.2016.06.004

## DEVOTE inclusion and exclusion criteria (1)

| Inclusion criteria | Exclusion criteria |
|---|---|
| Type 2 diabetes | An acute coronary or cerebrovascular event in the previous 60 days |
| $HbA_{1c}$ ≥7.0 % or $HbA_{1c}$ <7.0 % and current insulin treatment corresponding to ≥20 U/day of basal insulin | Planned coronary, carotid or peripheral artery revascularisation |
| Age ≥50 years at screening and at least one of the following conditions: | Chronic heart failure NYHA class IV |
| • Prior myocardial infarction | Current haemodialysis or peritoneal dialysis or eGFR <30 mL/min/1.73 $m^2$ per CKD-Epi |
| • Prior stroke or prior TIA | End-stage liver disease, defined as the presence of acute or chronic liver disease and recent history of one or more of the following: ascites, encephalopathy, variceal bleeding, bilirubin ≥2.0 mg/dL, albumin level ≤3.5 g/dL, prothrombin time ≥4 seconds prolonged, international normalised ratio ≥1.7 or prior liver transplant |
| • Prior coronary, carotid or peripheral arterial revascularisation | Known or suspected hypersensitivity to trial products or related products |

**Table 1.** DEVOTE inclusion and exclusion criteria.
CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; TIA, transient ischemic attack

Marso *et al. Am Heart J.* 2016; doi:10.1016/j.ahj.2016.06.004

## DEVOTE inclusion and exclusion criteria (2)

| Inclusion criteria | Exclusion criteria |
|---|---|
| • >50% stenosis on angiography or other imaging of coronary, carotid or lower-extremity artery | Female of child-bearing potential who is pregnant, breast-feeding or intends to become pregnant, or is not using adequate contraceptive methods as required by local law or practice |
| • History of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging, or unstable angina pectoris with ECG changes | Expected simultaneous participation in any other clinical trial of an investigational medicinal product. Participation in a clinical trial with stent(s) is allowed |
| • Asymptomatic cardiac ischaemia documented by positive nuclear imaging test or exercise test or dobutamine stress echo | Receipt of any investigational medicinal product within 30 days before randomisation. **Brazil:** Receipt of any investigational medicinal product within 1 year before randomisation unless there is a direct benefit to the patient at the investigator's discretion |
| • Chronic heart failure NYHA class II-III | Current or past (within the last 5 years) malignant neoplasms (except basal cell and squamous cell skin carcinoma) |
| • Chronic kidney disease corresponding to glomerular filtration rate 30–59 mL/min/1.73m² per CKD-Epi | Any condition that, in the investigator's opinion, would make the patient unable to adhere to the initial trial visit schedule and procedures |

**Table 1.** DEVOTE inclusion and exclusion criteria
ECG, electrocardiogram

Marso *et al. Am Heart J.* 2016; doi:10.1016/j.ahj.2016.06.004

## DEVOTE inclusion and exclusion criteria (3)

| Inclusion criteria | Exclusion criteria |
|---|---|
| Age ≥60 years at screening and at least one of the following risk factors: | |
| • Microalbuminuria or proteinuria | |
| • Hypertension and left ventricular hypertrophy by ECG or imaging | |
| • Left ventricular systolic and diastolic dysfunction by imaging | |
| • Ankle/brachial index <0.9 | |

**Table 1.** DEVOTE inclusion and exclusion criteria

Marso *et al. Am Heart J.* 2016; doi:10.1016/j.ahj.2016.06.004

## Degludec

- FDA aprobó la comercialización de degludec basado en un análisis interino de DEVOTE
- Resultados finales para 2018

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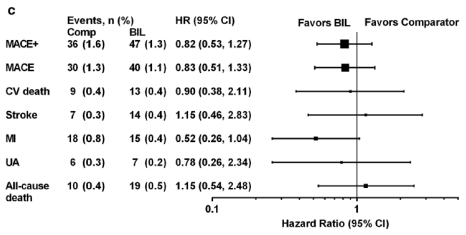
Marso SP. Am Heart J. 2016;179:175

## Peglispro: eventos CV en DM-1 + DM-2

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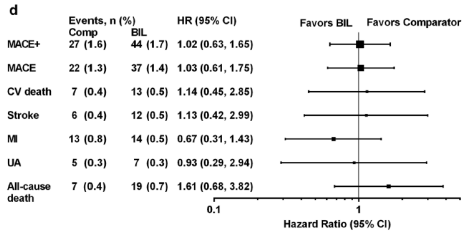
Hoogwerf BJ. Cardiovasc Diabetol. 2016;15:78

## Peglispro: eventos CV en DM-2

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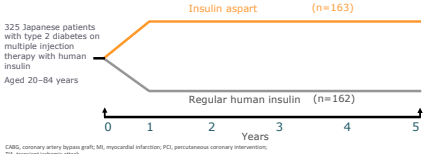
Hoogwerf BJ. Cardiovasc Diabetol. 2016;15:78

## The effect of insulin aspart on cardiovascular disease

- Aim: to investigate the morbidity and mortality by cardiovascular disease in patients with type 2 diabetes treated either with insulin aspart or regular human insulin
- A prospective, randomized, open-label, blinded endpoint trial
- Intermediate/long-acting insulin was added when necessary. The primary endpoint was composite cardiovascular events (MI, angina, PCI/CABG, TIA/cerebral infarction)




CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack

Nishimura *et al. Diabetologia* 2008;51(Suppl. 1):S543 (Poster 1349)

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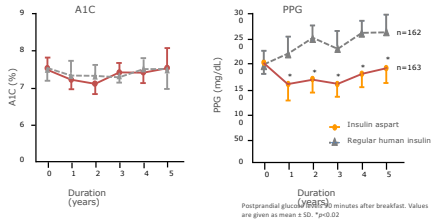
## A1C and postprandial glucose control




Postprandial glucose 90 minutes after breakfast. Values are given as mean ± SD. *p<0.02

Nishimura *et al. Diabetologia* 2008;51(Suppl. 1):S543 (Poster 1349)

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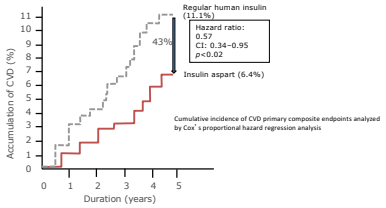
## Long-term use of insulin aspart and effect on cardiovascular disease (CVD)




Cumulative incidence of CVD primary composite endpoints analyzed by Cox's proportional hazard regression analysis

Nishimura *et al. Diabetologia* 2008;51(Suppl. 1):S543 (Poster 1349)

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## Lower incidence of recorded cardiovascular outcomes in patients with type 2 diabetes using insulin aspart vs. those on human regular insulin: observational evidence from general practices

W. Rathmann[1] & K. Kostev[2]

[1] *German Diabetes Center, Institute of Biometrics and Epidemiology, Düsseldorf, Germany*
[2] *Department LifeLink Epidemiology, IMS HEALTH, Frankfurt, Germany*

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Rathman W. Diab Obes Metab. 2013;15:358

## Metodología

- Análisis de bases de datos en atención primaria de Alemania
- Sólo pacientes que han usado insulina aspart o insulina simple, no permitía combinaciones
- Pacientes a quienes se les prescribió por primera vez la insulina

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Rathman W. Diab Obes Metab. 2013;15:358

| Variables | Insulin aspart | Regular insulin |
|---|---|---|
| *N* | 3154 | 3154 |
| Age (years) | 60.0 (10.2) | 60.0 (10.2) |
| Diabetes treatment period (practice) (years) | 2.2 (2.5) | 2.2 (2.5) |
| Males (%) | 57.4 | 57.4 |
| Private health insurance (%) | 5.8 | 5.8 |
| Diabetologist treatment (%) | 42.1* | 32.6* |
| Region (West Germany) (%) | 73.1* | 78.6* |
| Urban residency†(%) | 26.6 | 26.2 |
| Antidiabetic treatment‡(%) | | |
| Biguanides | 26.2 | 26.1 |
| Sulphonylureas | 13.5* | 19.7* |
| Acarbose | 4.1* | 6.0* |
| NPH insulin | 47.6* | 67.9* |
| Long-acting analogues | 50.7* | 27.6* |
| Co-medication‡(%) | | |
| Antihypertensives | 59.4 | 62.5 |
| Lipid-lowering drugs | 32.0 | 28.6 |
| Antithrombotic agents | 20.9 | 23.4 |

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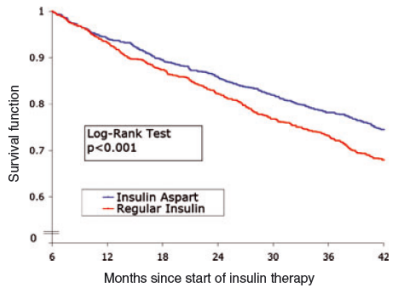
Rathman W. Diab Obes Metab. 2013;15:358

## Eventos cardiovasculares

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Rathman W. Diab Obes Metab. 2013;15:358

## Glulisina vs insulina regular

| Variables | Insulin glulisine | Regular insulin |
|---|---|---|
| n | 952 | 11,157 |
| Age (y) | 60.7 (11.2)* | 64.7 (10.9)* |
| Observational period prior to the index date (y) | 2.6 (3.7)* | 1.6 (3.0)* |
| Males (%) | 54.3 | 52.4 |
| Diabetologist treatment (%) | 43.0 | 44.5 |
| Private health insurance (%) | 9.8* | 3.5* |
| Region (West Germany) (%) | 71.5* | 68.2* |
| Urban residency[a] (%) | 26.5 | 25.6 |
| Antidiabetic treatment[b] (%): | | |
| Any oral antidiabetics | 41.3* | 33.1* |
| Sulfonylureas | 18.3 | 16.4 |
| Biguanides | 34.0* | 27.2* |
| Acarbose | 7.4* | 4.2* |
| NPH insulin | 25.6* | 64.6* |
| Long-acting insulin analogs | 74.5* | 30.7* |
| Co-Medication[c] (%) | | |
| Antihypertensives | 55.5 | 56.3 |
| Lipid-lowering drugs | 32.3 | 30.1 |
| Antithrombotic agents | 17.7* | 21.7* |

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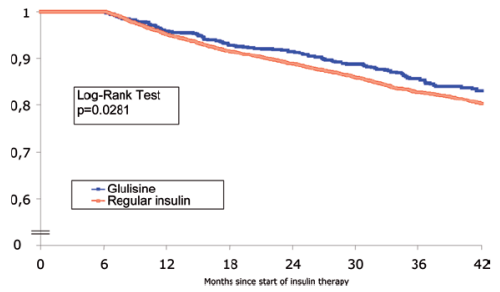
Kress S. Int J Clin Pharm Ther. 2012;50:821

## Sobrevida libre de enfermedad cardiovascular

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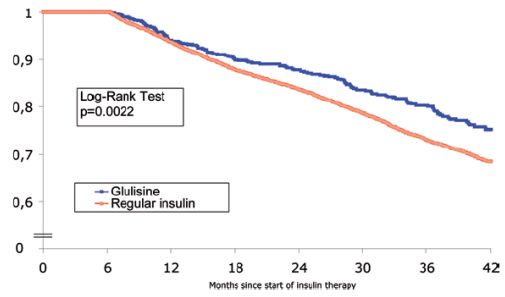
Kress S. Int J Clin Pharm Ther. 2012;50:821

## Sobrevida libre de enfermedad microvascular

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Kress S. Int J Clin Pharm Ther. 2012;50:821

## Caraterísticas basales

| Variable | IA N=2 764[b] | HI N=4 193[b] | p-value[c] |
|---|---|---|---|
| duration of follow-up on IA or HI treatment from index date [days], mean (SD) | 1 891 (698) | 1 835 (608) | 0.266 |
| age [years], mean (SD) | 61.0 (11.3) | 64.7 (10.5) | <0.001 |
| males [%] | 56.9 | 53.5 | 0.006 |
| private health insurance [%] | 8.0 | 3.3 | <0.001 |
| treated by diabetologist [%] | 23.5 | 22.7 | 0.424 |
| treated in West Germany [%] | 73.8 | 71.3 | 0.022 |
| urban residency (>100 000 inhabitants) [%] | 23.6 | 22.8 | 0.411 |
| **type of insulin treatment [%]** | | | |
| multiple daily injection therapy | 88.2 | 86.0 | 0.008 |
| use of long-acting insulin analogue | 53.6 | 29.8 | <0.001 |
| HI/IA treatment before the index date[d] | 25.7 | 9.7 | <0.001 |
| **concomitant oral medications* [%]** | | | |
| biguanides | 50.5 | 53.2 | 0.028 |
| sulfonylurea | 26.1 | 36.5 | <0.001 |
| diuretics | 46.7 | 52.8 | <0.001 |
| β-blockers | 49.6 | 55.2 | <0.001 |
| calcium channel blockers | 35.2 | 38.1 | 0.016 |
| ACE inhibitors | 57.6 | 62.5 | <0.001 |
| angiotensin II receptor antagonists | 28.2 | 26.7 | 0.177 |
| lipid-lowering agents | 52.1 | 52.3 | 0.907 |
| acetyl salicylic acid | 35.1 | 38.8 | 0.002 |

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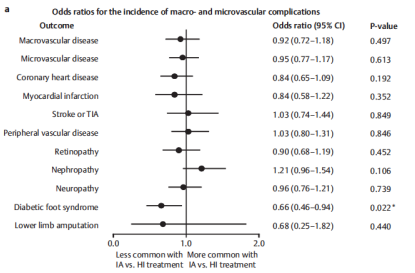
Rathman W. Exp Clin Endocrinol Diabetes. 2014;122:92

## Análogos ultrarrápidos

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Rathman W. Exp Clin Endocrinol Diabetes. 2014;122:92

## ANÁLOGOS BASALES VS ANÁLOGOS ULTRARRÁPIDOS: HEART 2D

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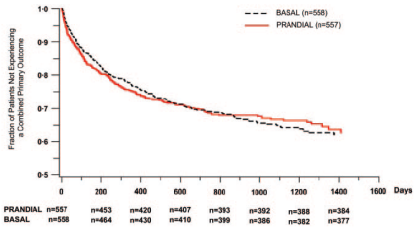


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Raz I. Diabetes Care. 2009;32:381

**DOSIS DE INSULINAS**

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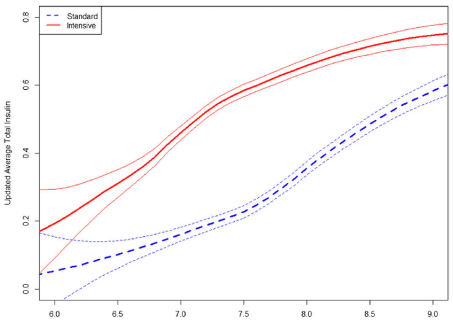
## ACCORD: dosis insulina y Hba1c

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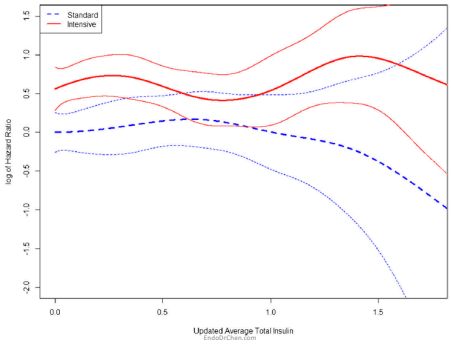
Siraj ES. Diabetes Care. 2015;38:2000

## ACCORD: dosis insulina y mortalidad CV




Gamble JM. Lancet Diabetes Endocrinol. 2017;5:43-52

## Dosis de insulina y eventos cardiovasculares

- Base de datos del Reino Unido
- 6072 adultos
- Edad promedio 60 años
- 54% hombres
- 6% con eventos cardiovasculares previos
- Hba1c promedio 8.5%
- Seguimiento promedio 3.1 años

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Gamble JM. Lancet Diabetes Endocrinol. 2017;5:43-52

| | <25 units per day (n=774) | 25–<50 units per day (n=2277) | 50–<75 units per day (n=1491) | 75–<100 units per day (n=833) | 100 units per day or more (n=697) |
|---|---|---|---|---|---|
| Age (years) at insulin initiation | 63·5 (13·2) | 61·1 (12·8) | 59·2 (12·3) | 58·2 (11·5) | 57·0 (10·9) |
| Sex | | | | | |
| Men | 404 (52%) | 1168 (51%) | 804 (54%) | 488 (59%) | 417 (60%) |
| Women | 370 (48%) | 1109 (49%) | 687 (46%) | 345 (41%) | 280 (40%) |
| Measure of deprivation* | | | | | |
| Least deprived | 73 (9%) | 276 (12%) | 159 (11%) | 82 (10%) | 64 (9%) |
| Most deprived | 84 (11%) | 276 (12%) | 189 (13%) | 107 (13%) | 88 (13%) |
| Years of anti-diabetic treatment | 4·1 (2·9) | 3·7 (2·8) | 3·7 (2·7) | 3·7 (2·6) | 3·5 (2·4) |
| Days of metformin overlap | 1014 (736) | 1217 (856) | 1338 (899) | 1474 (924) | 1585 (967) |
| Smoking status | | | | | |
| Current | 145 (19%) | 423 (19%) | 287 (20%) | 146 (18%) | 109 (16%) |
| Former | 204 (26%) | 742 (33%) | 485 (33%) | 294 (35%) | 285 (41%) |
| None | 294 (38%) | 757 (33%) | 470 (32%) | 255 (31%) | 219 (31%) |
| Unknown | 131 (17%) | 355 (16%) | 249 (17%) | 138 (17%) | 84 (12%) |
| BMI (kg/m²) | 30·6 (6·6) | 30·8 (6·5) | 32·5 (7·1) | 33·5 (6·4) | 35·8 (7·3) |
| Physician visits per year | | | | | |
| 1–12 | 400 (52%) | 1206 (53%) | 828 (56%) | 459 (55%) | 348 (50%) |
| 13–24 | 246 (32%) | 724 (32%) | 448 (30%) | 237 (29%) | 222 (32%) |
| 25 or more | 128 (17%) | 347 (15%) | 215 (14%) | 137 (17%) | 127 (18%) |
| History of vascular disease | 234 (30%) | 568 (25%) | 336 (23%) | 214 (26%) | 194 (28%) |
| Charlson index | | | | | |
| 1 | 643 (83%) | 1992 (88%) | 1314 (88%) | 727 (87%) | 599 (86%) |
| 2 | 96 (12%) | 221 (10%) | 132 (9%) | 83 (10%) | 71 (10%) |
| 3+ | 35 (5%) | 64 (3%) | 45 (3%) | 23 (3%) | 27 (4%) |

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| | Person-years of follow-up | Events (n) | Crude incidence rate per 1000 person-years | Crude HR (95% CI) | | Adjusted* HR (95% CI) | |
|---|---|---|---|---|---|---|---|
| **Major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death)** | | | | | | | |
| <50 units per day | 5008 | 234 | 47 | .. | Reference | .. | Reference |
| 50 to <100 units per day | 3551 | 164 | 46 | 1 | (0·82–1·22) | 1·17 | (0·94–1·44) |
| ≥100 units per day | 1513 | 62 | 41 | 0·9 | (0·68–1·19) | 1·06 | (0·78–1·44) |
| **Major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, or all-cause death)** | | | | | | | |
| <50 units per day | 5058 | 321 | 63 | .. | Reference | .. | Reference |
| 50 to <100 units per day | 3598 | 216 | 60 | 0·95 | (0·80–1·13) | 1·13 | (0·94–1·35) |
| ≥100 units per day | 1534 | 73 | 48 | 0·75 | (0·58–0·97) | 0·94 | (0·71–1·25) |
| **Cardiovascular-related death** | | | | | | | |
| <50 units per day | 5446 | 104 | 19 | .. | Reference | .. | Reference |
| 50 to <100 units per day | 3918 | 62 | 16 | 0·85 | (0·62–1·16) | 1·68 | (1·17–2·42) |
| ≥100 units per day | 1688 | 31 | 18 | 1 | (0·67–1·51) | 2·65 | (1·65–4·25) |
| **Myocardial infarction** | | | | | | | |
| <50 units per day | 5322 | 71 | 13 | .. | Reference | .. | Reference |
| 50 to <100 units per day | 3818 | 37 | 10 | 0·72 | (0·48–1·07) | 0·86 | (0·57–1·31) |
| ≥100 units per day | 1633 | 23 | 14 | 1·02 | (0·63–1·66) | 1·28 | (0·76–2·17) |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Stroke** | | | | | | | |
| <50 units per day | 5161 | 121 | 23 | .. | Reference | .. | Reference |
| 50 to <100 units per day | 3684 | 86 | 23 | 0·98 | (0·74–1·29) | 1·09 | (0·81–1·47) |
| ≥100 units per day | 1586 | 30 | 19 | 0·78 | (0·52–1·17) | 0·88 | (0·57–1·36) |
| **Heart failure** | | | | | | | |
| <50 units per day | 5182 | 122 | 24 | .. | Reference | .. | Reference |
| 50 to <100 units per day | 3715 | 81 | 22 | 0·96 | (0·72–1·27) | 1·13 | (0·85–1·52) |
| ≥100 units per day | 1585 | 43 | 27 | 1·24 | (0·87–1·76) | 1·36 | (0·93–1·99) |
| **Arrhythmia** | | | | | | | |
| <50 units per day | 5259 | 130 | 25 | .. | Reference | .. | Reference |
| 50 to <100 units per day | 3804 | 77 | 20 | 0·76 | (0·57–1·01) | 0·86 | (0·64–1·16) |
| ≥100 units per day | 1634 | 45 | 28 | 0·95 | (0·68–1·35) | 1·15 | (0·79–1·66) |
| **Revascularisation** | | | | | | | |
| <50 units per day | 3381 | 560 | 166 | .. | Reference | .. | Reference |
| 50 to <100 units per day | 2384 | 376 | 158 | 1·01 | (0·88–1·15) | 1·05 | (0·91–1·20) |
| ≥100 units per day | 895 | 153 | 171 | 1·17 | (0·97–1·40) | 1·15 | (0·95–1·39) |

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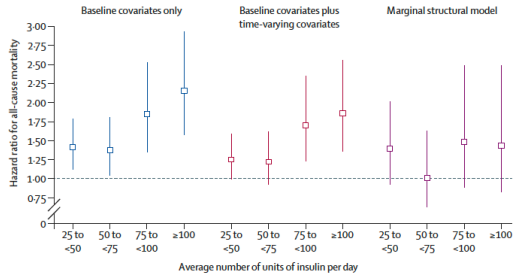
## Mortalidad total y dosis de insulina

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## Interpretación

- Se debe tener cuidado al ajustar el análisis con base a las características iniciales del paciente
  - –Las condiciones cambian con el tiempo y es uno de los grandes confusores
  - –IMC, tabaquismo, hipoglicemias

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**METANÁLISIS**

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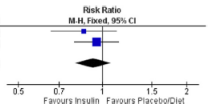
## Metanálisis: mortalidad total insulina vs placebo

| Study or Subgroup | Insulin Events | Insulin Total | Placebo/Diet Events | Placebo/Diet Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| UGDP | 104 | 414 | 60 | 205 | 29.5% | 0.86 [0.68, 1.12] |
| UKPDS 33 1998 | 184 | 911 | 190 | 896 | 70.5% | 0.95 [0.80, 1.14] |
| **Total (95% CI)** | | **1325** | | **1101** | **100.0%** | **0.92 [0.80, 1.07]** |
| Total events | 288 | | 250 | | | |

Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.02 (P = 0.31)

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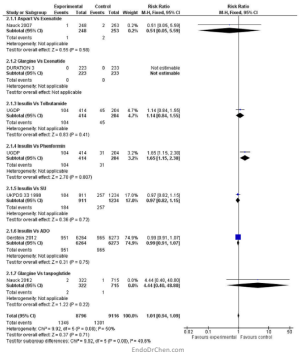
## Metanálisis: mortalidad total insulina vs ADO

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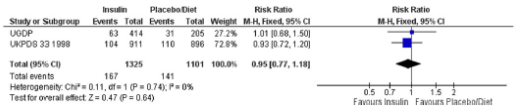
## Metanálisis: muerte CV insulina vs placebo

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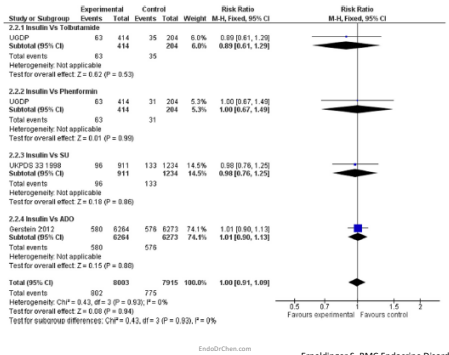
## Metanálisis: muerte CV insulina vs ADOs

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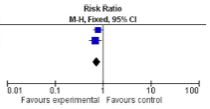
## Metanálisis: ceguera e IRC insulina vs placebo

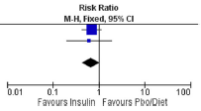
| Study or Subgroup | Experimental Events | Experimental Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| UGDP | 100 | 293 | 67 | 156 | 46.2% | 0.79 [0.62, 1.01] |
| UKPDS 33 1998 | 72 | 911 | 101 | 896 | 53.8% | 0.70 [0.53, 0.94] |
| **Total (95% CI)** | | **1204** | | **1052** | **100.0%** | **0.74 [0.62, 0.90]** |
| Total events | 172 | | 168 | | | |

Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 3.06 (P = 0.002)




| Study or Subgroup | Insulin Events | Insulin Total | Pbo/Diet Events | Pbo/Diet Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| UGDP | 35 | 414 | 25 | 205 | 80.6% | 0.69 [0.43, 1.13] |
| UKPDS 33 1998 | 5 | 911 | 8 | 896 | 19.4% | 0.61 [0.20, 1.67] |
| **Total (95% CI)** | | **1325** | | **1101** | **100.0%** | **0.68 [0.43, 1.06]** |
| Total events | 40 | | 33 | | | |

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)

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## Metanálisis

- No diferencias en amputaciones, muerte súbita, IAM, ictus, muerte por cáncer
- Aumento de riesgo de hipoglicemias

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## Conclusiones

- Los estudios aleatorizados controlados muestran que la insulina es segura
- Los estudios epidemiológicos tienen muchos factores confusores para sacar conclusiones, incluyendo diferencias entre los pacientes con insulinas y agentes orales
- Seguridad cardiovascular debe ser evaluado de manera crítica al igual que con todos los otros tratamientos en diabetes

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**Preguntas…**
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