# Risco Cardiovascular da Mulher Diabética

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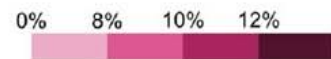Presidente do Departamento de Cardiologia da Mulher da Sociedade Brasileira de Cardiologia

Departamento
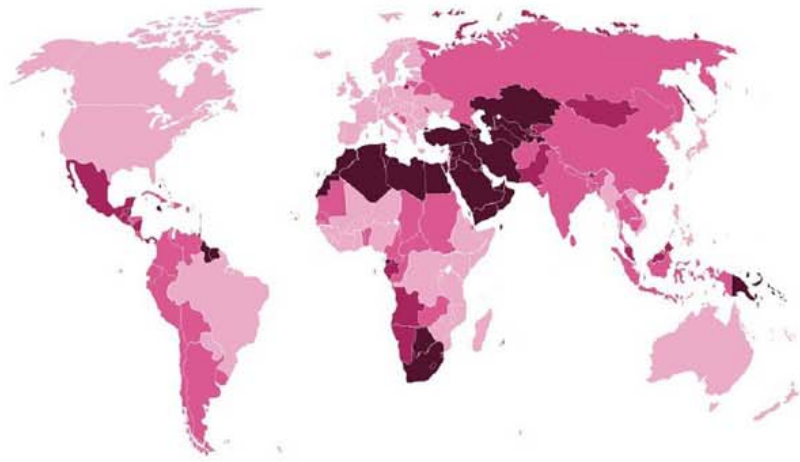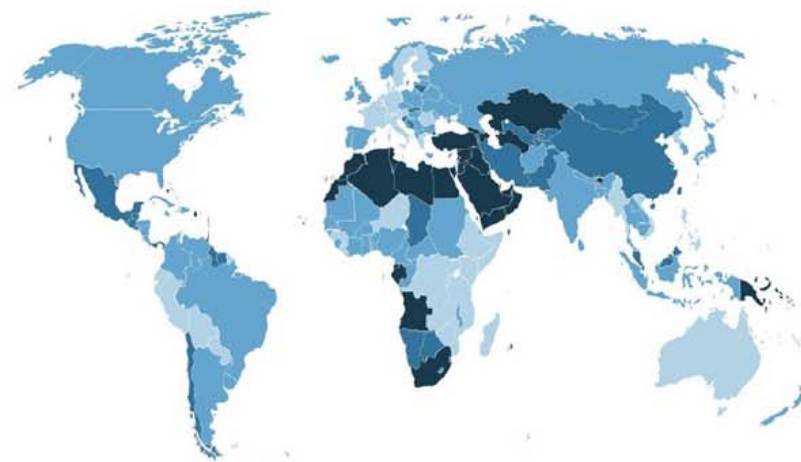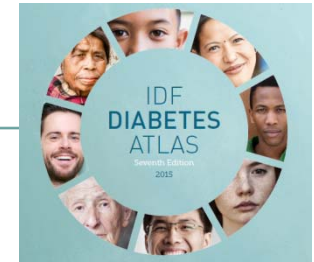de Cardiologia
da Mulher

# Diabetes prevalence



A

Women

Men

0%    8%   10%   12%

0%    8%   10%   12%

# The prevalence of diabetes

## 2015



**One** in **11 adults** has diabetes

## 2040



**One** in **10 adults** will have diabetes

Atlas do Diabetes 2015 - Atualização
7ª edição - IDF

International
Diabetes Federation

Adaptado pela SBD
www.diamundialdodiabetes.org.br.

## Diabetes no Mundo

Em **2015** , o IDF Diabetes Atlas mostra que:

• 1 em cada 11 adultos tem diabetes (415 milhões).
• A cada 2 adultos com diabetes, 1 ainda não foi diagnosticado.
• 12% das despesas de saúde no mundo é gasto com diabetes (USD 673 bilhões).
• 1 em cada 7 nascidos é afetado pelo diabetes gestacional.
• 3/4 das pessoas com diabetes vivem em países de baixa renda.
• 542.000 crianças têm diabetes tipo 1.
• A cada 6 segundos 1 pessoa morre devido ao diabetes.

Em **2040**, o IDF estima que :

• 1 em cada 10 adultos terá diabetes (642 milhões).
• As despesas de saúde relacionadas com a Diabetes será superior a USD 802 bilhões.
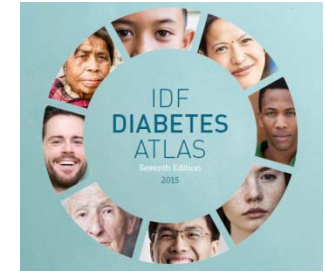
**Diabetes**

Number of **men** with diabetes



**2015** 215.2 million
**2040** 328.4 million

Number of **women** with diabetes



**2015** 199.5 million
**2040** 313.3 million

**Diabetes no Brasil**

- Pessoas com Diabetes em 2015 — **14,3 milhões**
- Pessoas com Diabetes em 2040 — **23,2 milhões**
- % população nacional com Diabetes — **9.4%**
- Gastos com saúde com a diabetes — **US$ 21,8 bilhões**
- Mortalidade devido ao Diabetes — **130.700 pessoas**
- Crianças com Diabetes Tipo 1 (0-14 anos) — **30.900 crianças**

**Metade ainda não foi diagnosticado.**

# Dados do Vigitel



Aumento da obesidade

Brasileiros estão ficando mais pesados desde 2006

■ HOMENS    ■ MULHERES    ■ TOTAL

EM (%)

Adultos com excesso de peso (IMC acima de 25)

56,5
52,5
49,1
47
43
39

2006  2007  2008  2009  2010  2011  2012  2013  **2014**
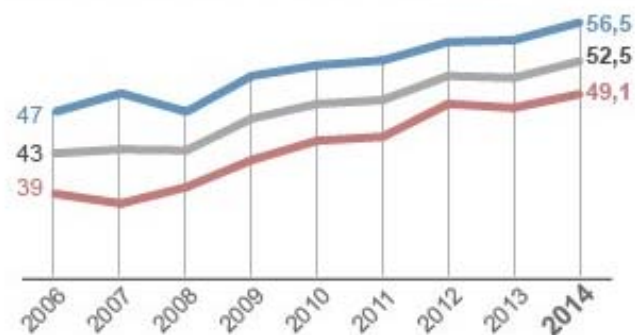
Fonte: Vigitel
Infográfico atualizado em 15/4/2015



Evolução da frequência de diabetes autorreferido

■ 2006  ■ 2007  ■ 2008  ■ 2009  ■ 2010  ■ 2011  ■ 2012  ■ 2013

**Total**
5,5  5,8  6,2  6,3  6,8  6,3  7,4  6,8

**Masculino**
4,6  5,4  5,7  5,8  6,1  5,9  6,5  6,5

**Feminino**
6,3  6,2  6,7  6,8  7,4  6,6  8,1  7,2
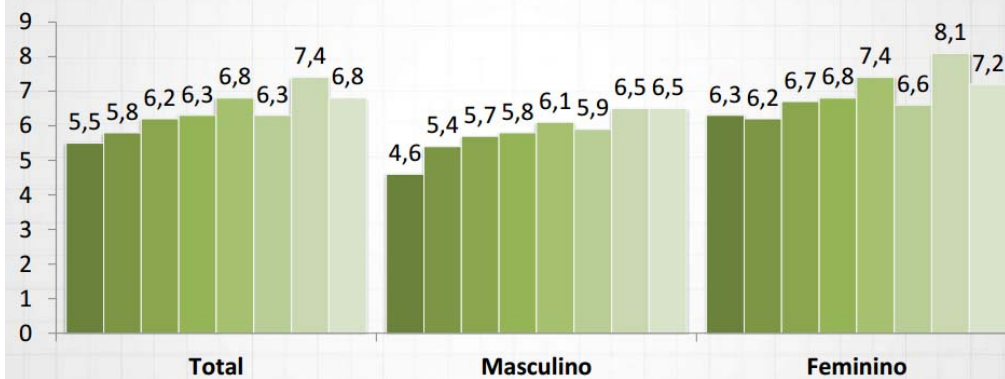
Aumento significativo em todos os estratos (2006-2013) → p <0,05

Vigitel 2013

# High prevalence of diabetes and intermediate hyperglycemia The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).
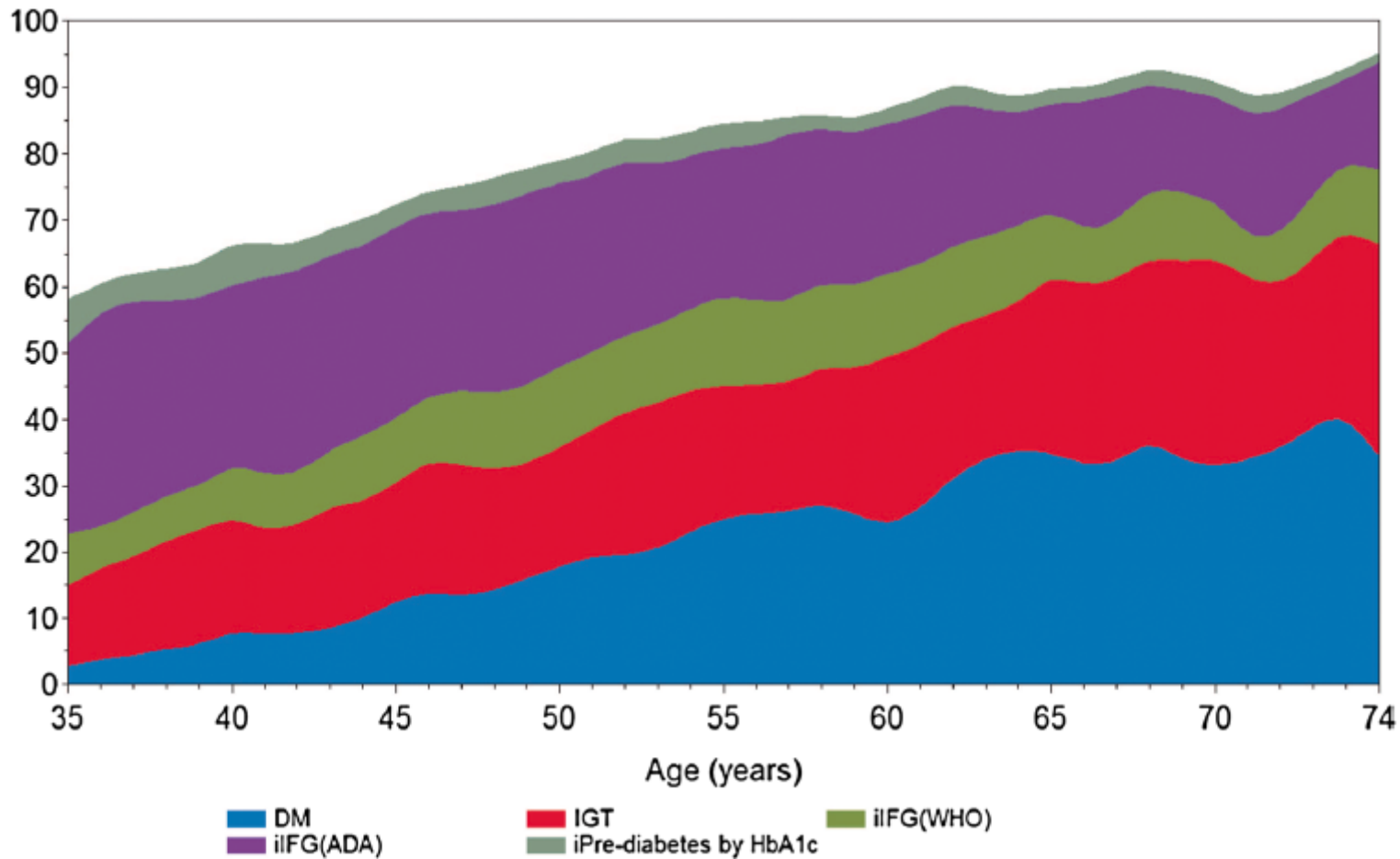
# Prevalência de pré diabetes, diabetes e sobrepeso/obesidade em homens e mulheres
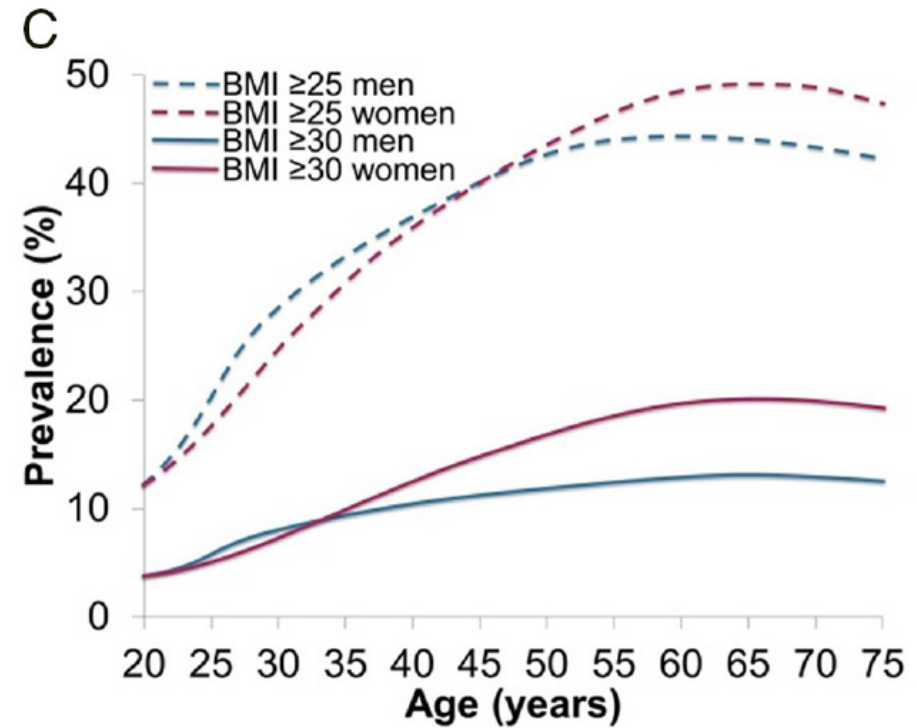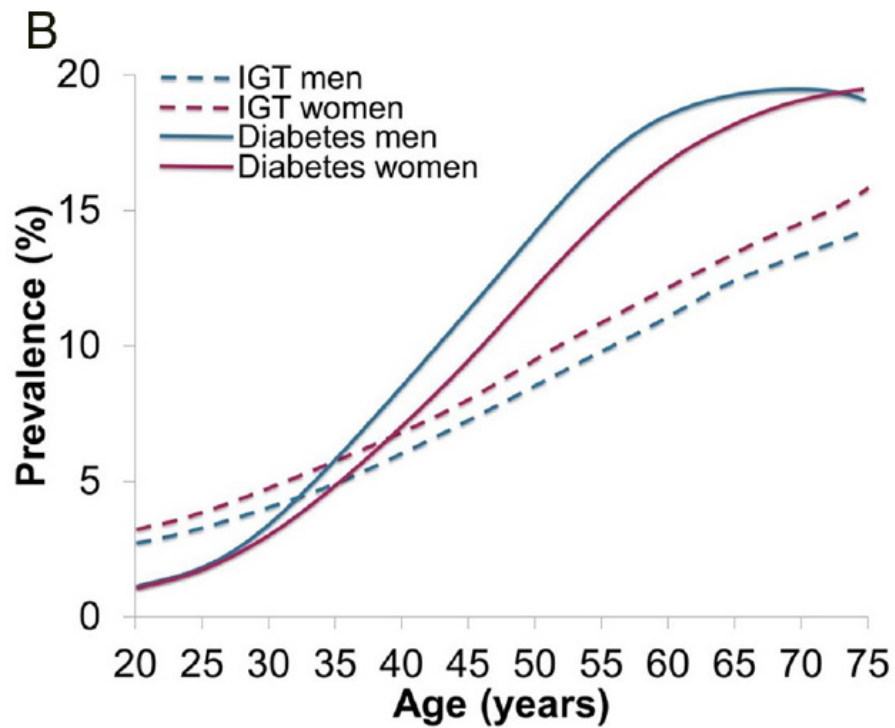
# Prevalência de obesidade entre homens e mulheres em países europeus



% BMI ≥ 30
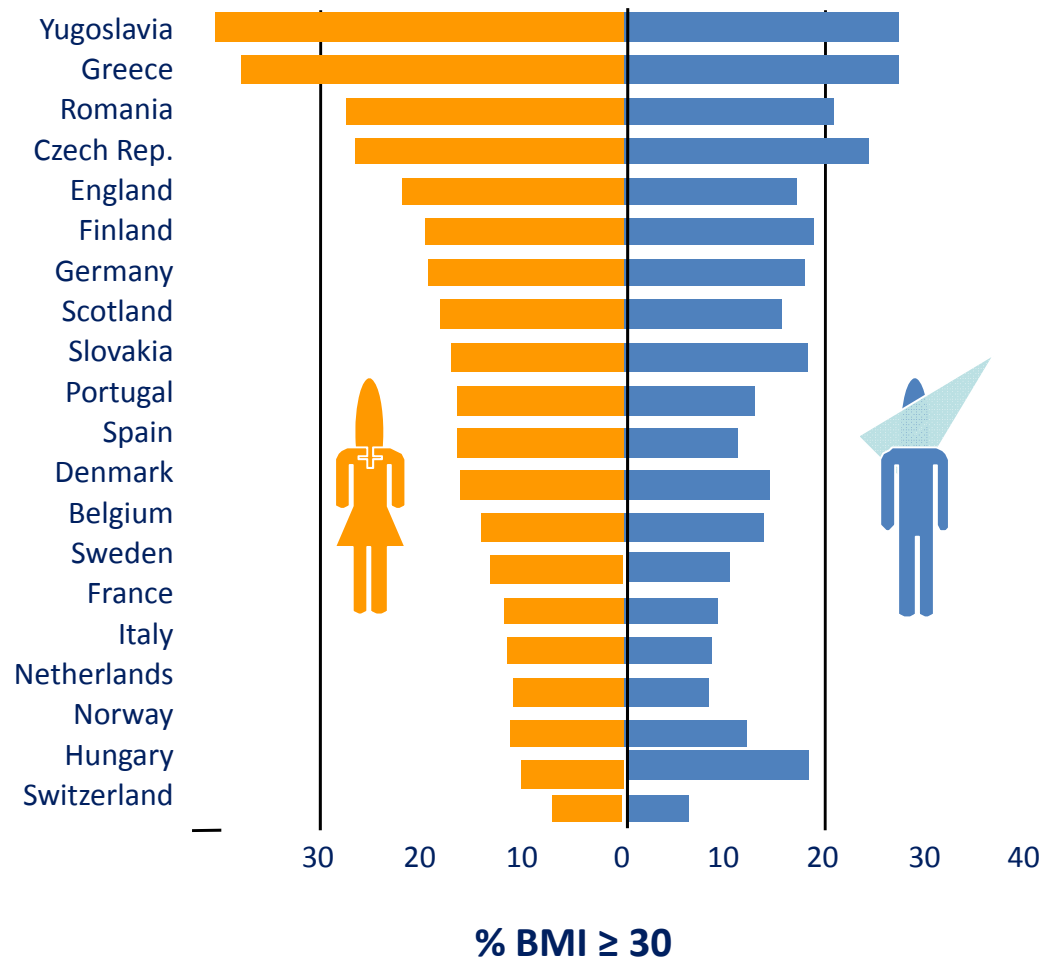
**Type 2 diabetes,**
the **metabolic syndrome** and **cardiovascular disease** in Europe

# Prevalence of people with diabetes by age and sex, 2015
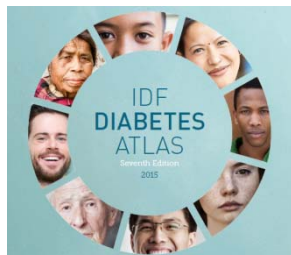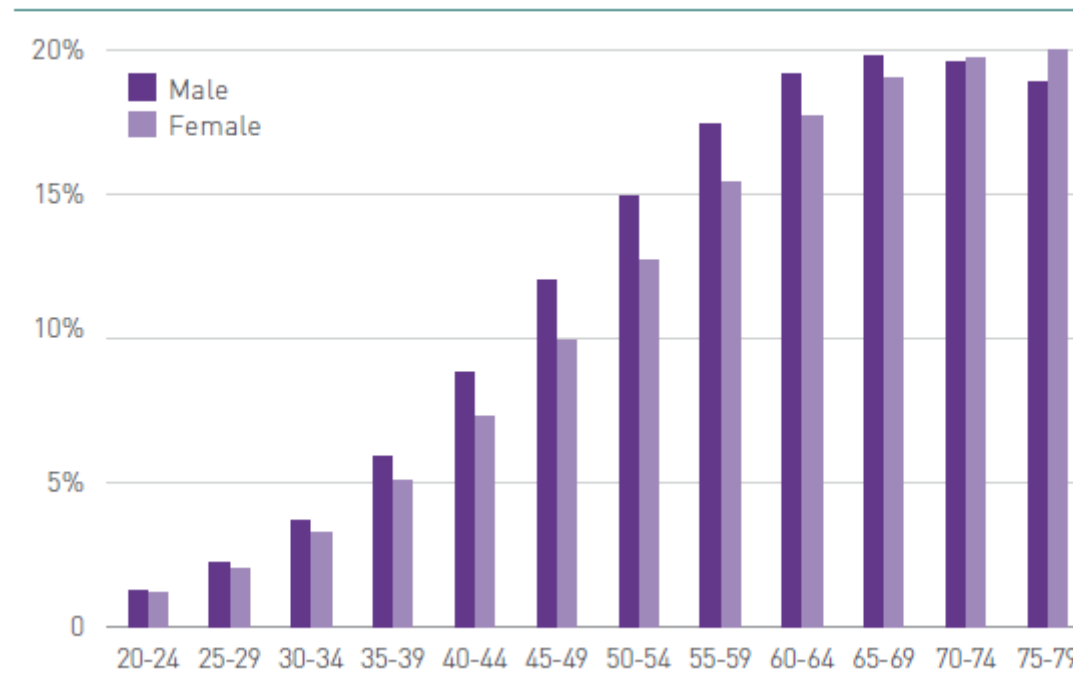
# A Mulher e o Diabetes - Fatos

1. 2013: 184 mi  →  2030: 288mi

2. 9ª causa de mortes (2,1mi)

3. 60% dos pobres são mulheres (desnutrição 2X; analfabetismo 2/3)

4. Maior incremento em população de mulheres diabéticas será no Oriente Médio e Norte da  África (96%), África (90,4%) e Sudeste da Ásia (74,4%)

5. 2 em cada 5 mulheres diabéticas estão em idade reprodutiva, cerca de 60mi

International Diabetes Federation

## Diferenças de Sexo no Risco Cardiovascular do Diabético

DM: > morbidade e mortalidade para DCV em ambos os sexo

♂ é um fator de risco independente para DCV na população geral

♀ mais protegidas

♀ diabéticas: risco CV >

DCV é a maior causa de morbidade e mortalidade em diabéticos

Principalmente DAC (angina, IM), DAOP, MCP diabética e AVC

Associação de fatores de risco: HAS, DLP e obesidade

# INTERHEART: Association of risk factors with acute MI in women and men

Adjusted for age, sex, geographic region
Note: odds ratio plotted on a doubling scale

Yusuf S et al. *Lancet*. 2004;364:937-52.

# Diabetes mellitus

**DAC: 3,7** ♀ **X 1,5** ♂

Kannel WB, Wilson PW. Comparison of risk profiles for cardiovascular events: implications for prevention. Adv Intern Med. 1997;42:39-66.

**DAOP: 6,4** ♀ **X 3,4** ♂

**ICC: 8,0** ♀ **X 4,4** ♂

**Rancho Bernardo Study** ♀ **RR: 3,5**

♂ **RR: 2,4**

Why women have less heart disease than men and how diabetes modifies women's usual cardiac protection
A 40-year Rancho Bernardo Cohort Study – Global Heart 2013 Vol 8 (2):95-104

# RR de morte cardiovascular de acordo com o sexo e o status diabético

| References | RR in men with DM/men without DM | RR in women with DM/women without DM |
|---|---|---|
| (1) | 1.99 (1.69–2.35) | 3.12 (2.34–4.17) |
| (2) | 2.54 (1.84–3.49)[*] | 2.03 (1.60–2.59)[*] |
|  | 2.04 (1.46–2.84)[†] | 2.0 (1.37–2.92)[†] |
| (4) | 1.0 | 2.8 |
| (5) | 1.9 | 3.3 |
| (6) | 2.4 | 3.5 |
| (7) | 1.7 | 3.3 |
| (9) | 1.85 (1.47–2.33) | 2.58 (2.05–3.26) |
| (10) | 2.16 (1.82–2.56) | 2.82 (2.35–3.38) |
| (11)[a] | 1.23 (1.14–1.34) | 1.41 (1.27–1.56) |
| (12) | 1.17 (0.71–1.94) | 3.61 (1.97–6.61) |
| (14) | 2.1 (1.3–3.3) | 3.8 (2.2–6.6) |
| (15)[a] | 2.67 (2.43–2.95) | 4.26 (3.68–4.94) |
| (16) | 1.3 (0.9–2) | 1.8 (1.2–2.7) |
| (17) | 2.75 (2.05–3.70) | 9.54 (5.39–16.87) |
| (19) | 3.79 | 4.72 |
| (20) | 2.31 (1.91–2.85) | 2.92 (2.22–3.84) |

CVD, cardiovascular disease; CHD, coronary heart disease; AR, absolute risk; DM, diabetes mellitus; RR, relative risk.
[a]This study refers to the risk of myocardial infarction.
[*]for death from CHD; [†]for death from stroke.

Cardiovascular risk in women with type 2 diabetes mellitus and prediabetes: is it indeed higher than men? European Journal of Endocrinology (2014) 171, R245–R255

# Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events

Sanne A. E. Peters · Rachel R. Huxley · Mark Woodward

**Conclusions/interpretation**: Women with diabetes have more than a 40% greater risk of incident CHD compared with men with diabetes. Sex disparities in pharmacotherapy are unlikely to explain much of the excess risk in women, but future studies are warranted to more clearly elucidate the mechanisms responsible for the substantial sex difference in diabetes-related risk of CHD.

# Diabetes Mellitus

♀ **Tolerância diminuída a glicose, TOTG ⟶ disfunção de cel. β**

♂ **GJ ⟶ Resistência a insulina (RI)**

**Hiperglicemia pós-prandial: correlação com DCV**

**Testosterona**

♀ **Extremos são preditores de risco CV**

♂ **Níveis baixos são preditores de risco CV**

**Why women have less heart disease than men and how diabetes modifies women's usual cardiac protection A 40-year Rancho Bernardo Cohort Study – Global Heart 2013 Vol 8 (2):95-104**

**Predictors of Cardiovascular Risk in Women. Women's Health. 2013;9(5):491-498.**

# Diabetes mellitus
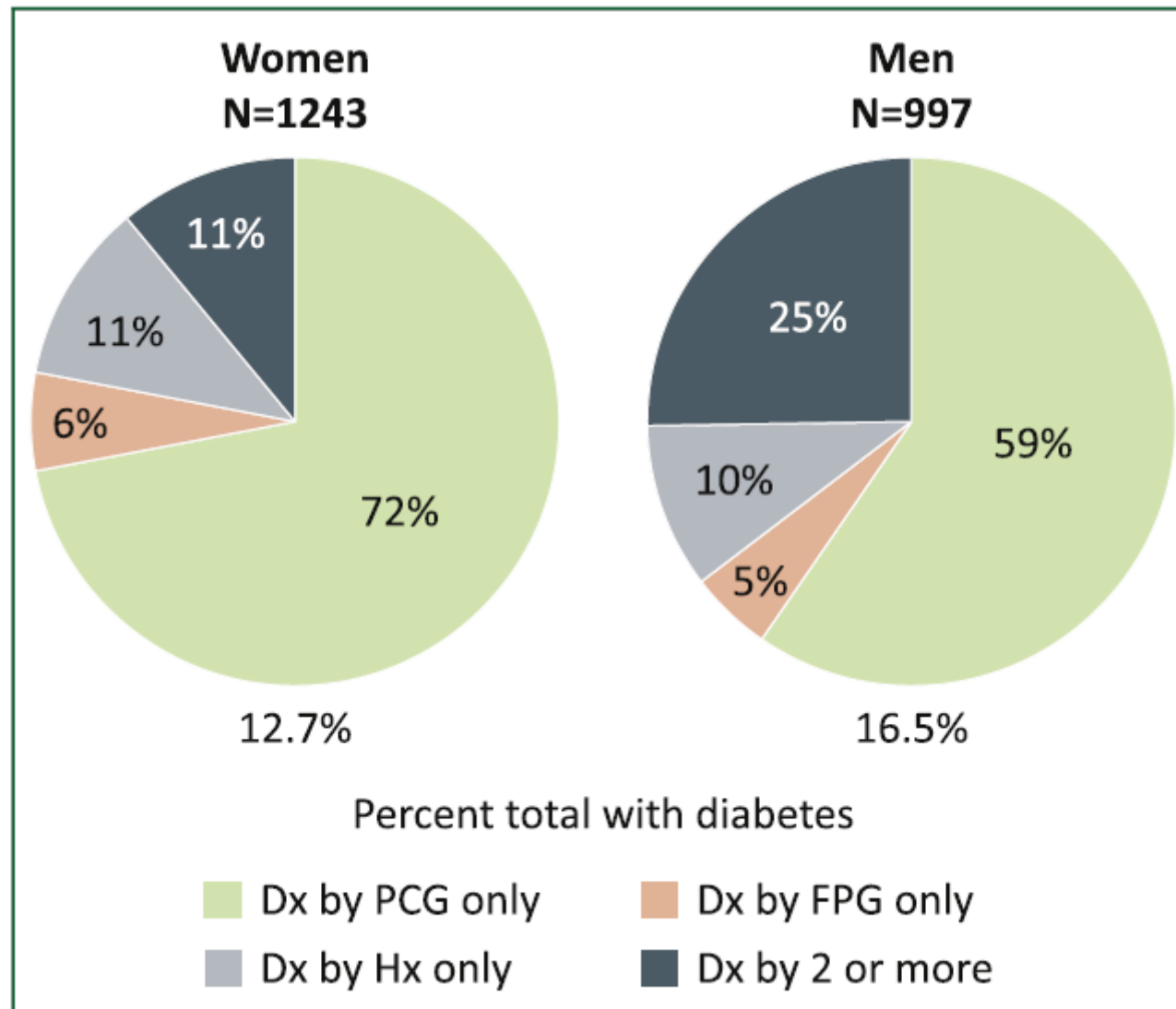


Women N=1243 / Men N=997 — pie charts showing percent total with diabetes. Women 12.7%, Men 16.5%. Categories: Dx by PCG only, Dx by FPG only, Dx by Hx only, Dx by 2 or more.

**Why women have less heart disease than men and how diabetes modifies women's usual cardiac protection A 40-year Rancho Bernardo Cohort Study – Global Heart 2013 Vol 8 (2):95-104**

# Diabetes mellitus

**Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes.**

**Conclusão:** O risco para AVC associado ao diabetes é significativamente maior nas mulheres do que nos homens, independemente da presença de outros grandes fatores de risco. Estes dados adicionam evidência de que homens e mulheres expressam diferentemente as doenças relacionadas ao diabetes e sugerem a necessidade de trabalhos futuros para esclarecer os mecanismos biológicos , comportamentais e social envolvidos

# Risco Global para DM2

**Obesidade**
**Sedentarismo**
**Predisposição genética**

→ ♀ **Afetada**
**desproporcionalmente**

Sex differences in type 2 diabetes: focus on disease course and outcomes
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2014:7 409–420

# Risco Cardiovascular

♀ **4X**          ♂ **3X**

1. Mulheres tem > associação de fatores de risco para DM2

2. Perfil metabólico da mulher diabética:  HAS, DLP aterogênica (TGC ), HDL baixo

3. Obesidade abdominal é um fator de risco mais importante para as mulheres

4. Mulheres obesas com DM2 tem > prevalência de disfunção de VE e > rigidez arterial

5. Mulheres diabéticas tem > mortalidade por todas as causas

6. Mulheres ten um controle glicêmico pobre

# Fatores de Risco DM2

Idade, história familiar e HDL ⟶ igual para ambos os sexos

Consumo de álcool, tabagismo e HAS ⟶ homens

Circ. Abdominal, TG e sedentarismo ⟶ ♀

## Diferenças sexuais na fisiopatologia hormonal

**Cortisol**
**Testorterona**
**SHBG**
**Estrogeno**
**GH e IGF-1**
**Adiponectina**
**Leptina**

Sex differences in type 2 diabetes: focus on disease course and outcomes
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2014:7 409–420

# Diferenças fisiológicas no metabolismo e homeostase energética entre homens e mulheres



**Physiologic Sex-Differences**

| Homem | Mulher |
|---|---|
| ↓ HPA Axis Activity | ↑ HPA Axis Activity |
| ↓ ARC POMC | ↑ ARC POMC |
| ↑ Central Insulin Sensitivity | ↑ Central Leptin Sensitivity |
| ↑ Food Intake | ↓ Food Intake |
| ↑ Energy Expenditure | ↓ Energy Expenditure |
| ↓ BAT mass and activity | ↑ BAT mass and activity |
| ↓ Subcutaneous fat mass | ↑ Subcutaneous fat mass |
| ↑ Visceral fat mass | ↓ Visceral fat mass |
| ↑ Liver fat | ↓ Liver fat |
| ↑ Muscle mass | ↓ Muscle mass |
| ↓ Adiponectin & Leptin | ↑ Adiponectin & Leptin |
| ↓ Peripheral Insulin Sensitivity | ↑ Peripheral Insulin Sensitivity |
| ↑ Glucose oxidation during excersice | ↑ FFA oxidation during exercise |
| ↑ FFA oxidation at rest | ↑ FFA storage in TG at rest |
| ↑ Fasting glucose | ↑ 2h Glucose (OGTT) |
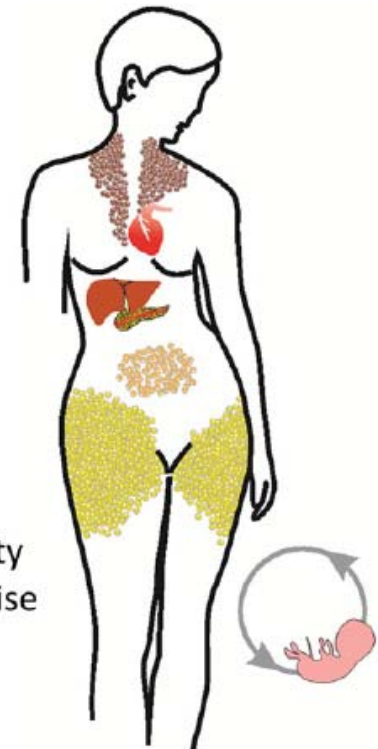
# Diferenças patológicas no metabolismo e homeostase energética entre homens e mulheres



Pathologic Sex-Differences

↑ IFG Incidence
↑ Diabetes Incidence
↑ Diabetes at earlier Age
↑ Overweight Incidence
↑ Metabolically unhealthy obese
↑ Fatty liver
↓ Depression
↓ Androgens
↑ Erectile Dysfunction
↑ Neuropathy, Diabetic foot
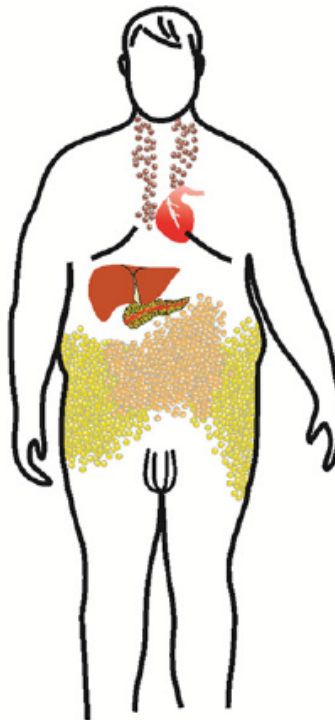
↑ IGT Incidence
↓ Diabetes Incidence
↑ Diabetes at higher BMI
↑ Obesity Incidence
↑ Metabolically healthy obese
↕ Fatty liver
↑ Depression
↑ Androgens
↑ PCOS
↑ RR Cardiovascular disease

# Dimorfismo Sexual

| Risk Factors | Diabetes risk | | Notes |
|---|---|---|---|
| | Men | Women | |
| BMI | + | + | Men: Diabetes diagnosis at lower BMI. |
| | | | Stronger Obesity-Diabetes Risk association in women. |
| | | | Better predictor of T2DM in men. |
| Waist Circumference (WCR) | + | 2+ | Better predictor of T2DM in women. |
| | | | More prominent increase with increasing age in women. |
| Clustering of metabolic risk factors, "metabolic syndrome (MetS)" | + | + | Similar prevalence but sex-dimorphic clustering of risk factors: higher prevalence of hypertension and adiposity in women and of low HDL-cholesterol and higher uric acid levels in males. In younger subjects the combination of dyslipidemia with increased WCR was most prevalent in females, but with hypertension in males. |
| No-Leisure time physical activity (LTPA) | + | 2+ | Greater impact on obesity and closer association with increased abdominal adiposity in women than men. |
| Prediabetes | + | + | |
| - IFG | 2+ | + | Men: More often (isolated) impaired fasting glucose (highest rates 50–70 yr) |
| - IGT | + | 2+ | Women: More often (isolated) impaired glucose tolerance (until 80 yr) |

| Risk factor | Men | Women | Comments |
|---|---|---|---|
| Higher testosterone | − | + | Meta-analysis: 60% higher diabetes risk in women, 42% lower diabetes risk in men. |
| | | | Sexual-dimorphic risk of hyperandrogenism |
| Low sex hormone-binding globulin (SHBG) | + | 2+ | Stronger association with diabetes risk in women |
| | | | SHBG gene polymorphisms relate to diabetes risk. |
| | | | Hyperinsulinemia and increased liver fat strongly relate to low circulating SHBG. |
| Prior GDM | n.a. | 2+ | 71% higher incidence of T2DM among prediabetic women |
| | | | Meta-analysis: 7fold greater risk of development of T2DM compared to women who maintained normal glucose tolerance during pregnancy |
| PCOS | n.a. | 2+ | 4fold higher risk for T2DM |
| Shift-work (related to sleep deprivation) | | | Overall controversial results, sex-dimorphic impact of chronotypes. |
| | 2+ | + | Greater diabetes risk in men in a meta-analysis |
| | + | 2+ | Greater diabetes risk in women in other studies: In women BMI mainly influenced the association with T2DM. |
| | | | Greater association of night-work exposure and incident T2DM in women in some studies. |
| Job strain | | | |
| High work demands | − | 0 | Protective in men |
| Low decision latitude | 0 | + | Higher diabetes risk in women, particularly greater in combination with high demands |
| High strain* | 0 | + | Lower diabetes risk in non-obese men and higher diabetes risk in obese women. |
| Active Job** | − | 0 | Protective in men |
| Low Education | 0 | + | Higher diabetes risk in women |
| High Occupation | 0 | − | Occupation, women's autonomy and empowerment appear more protective against obesity for women than education on its own |
| Low SES | + | 2+ | Inverse association between SES and prevalence of obesity and diabetes in developed countries with stronger association in women, especially in white young women. |
| Low Childhood SES | 0 | + | |
| Smoking | + | + | Comparably increased diabetes risk, but 25%greater increase of cardiovascular risk in women |

# Sex-specific differences in Complications and Comorbidities of Diabetes

| | | | |
|---|---|---|---|
| Coronary heart disease (CHD) | + | 2+ | Diabetic women bear a 40% greater risk of CHD compared with male counterparts. Greater risk for both fatal and non-fatal events. |
| Stroke | | Diabetic women experience a 27% greater relative risk of stroke compared with men. Greater risk for both fatal and non-fatal events. | (273) |
| Mortality | + | 2+ | More years of life lost at age of 40 in diabetic women than men. |

# Miocardiopatia

Prevalência

Susceptibilidade

Hipertrofia e ICpFE

Obesidade, HAS e Diabetes $\longrightarrow$ > dano

MCP dilatada

Approach to management
of hyperglycemia:

More
stringent

Less
stringent

Patient attitude and
expected treatment efforts

Highly motivated, adherent,
excellent self-care capacities

Less motivated, non-adherent,
poor self-care capacities

Risks potentially associated
with hypoglycemia, other
adverse events

Low

High

Disease duration

Newly diagnosed

Long-standing

Life expectancy

Long

Short

Important comorbidities

Absent

Few/mild

Severe

Established vascular
complications

Absent

Few/mild

Severe

Resources, support system

Readily available

Limited

AMERICAN DIABETES ASSOCIATION STANDARDS OF MEDICAL CARE IN DIABETES—2016

GOALS FOR GLYCEMIC CONTROL

INDIVIDUALIZE GOALS

**A1C ≤ 6.5%**

For patients without concurrent serious illness and at low hypoglycemic risk

**A1C > 6.5%**

For patients with concurrent serious illness and at risk for hypoglycemia

# GLYCEMIC CONTROL ALGORITHM

## LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

| Entry A1C < 7.5% | Entry A1C ≥ 7.5% | Entry A1C > 9.0% |
|---|---|---|

### MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

### DUAL THERAPY*

MET or other 1st-line agent

+

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

### TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent

+

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

### SYMPTOMS

| NO | YES |
|---|---|
| DUAL Therapy OR TRIPLE Therapy | INSULIN ± Other Agents |

### ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

### LEGEND

- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

\* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

## PROGRESSION OF DISEASE

# PROFILES OF ANTIDIABETIC MEDICATIONS

| | MET | GLP-1 RA | SGLT-2i | DPP-4i | AGi | TZD (moderate dose) | SU / GLN | COLSVL | BCR-QR | INSULIN | PRAML |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HYPO | Neutral | Neutral | Neutral | Neutral | Neutral | Neutral | Moderate/Severe / Mild | Neutral | Neutral | Moderate to Severe | Neutral |
| WEIGHT | Slight Loss | Loss | Loss | Neutral | Neutral | Gain | Gain | Neutral | Neutral | Gain | Loss |
| RENAL/GU | Contra-indicated CKD Stage 3B,4,5 | Exenatide Not Indicated CrCl < 30 | Not Effective with eGFR < 45 — Genital Mycotic Infections | Dose Adjustment Necessary (Except Linagliptin) | Neutral | Neutral | More Hypo Risk | Neutral | Neutral | More Hypo Risk | Neutral |
| GI Sx | Moderate | Moderate | Neutral | Neutral | Moderate | Neutral | Neutral | Mild | Moderate | Neutral | Moderate |
| CARDIAC — CHF | Neutral | Neutral | Possible Benefit | Neutral | Neutral | Moderate | Neutral | Neutral | Neutral | Neutral | Neutral |
| CARDIAC — ASCVD | Benefit | Neutral | Possible Benefit | Neutral | Neutral | Neutral | ? | Neutral | Safe | Neutral | Neutral |
| BONE | Neutral | Neutral | Neutral | Neutral | Neutral | Moderate Fracture Risk | Neutral | Neutral | Neutral | Neutral | Neutral |

Legend:
- 🟩 Few adverse events or possible benefits
- 🟨 Use with caution
- 🟧 Likelihood of adverse effects
- 🟨? Uncertain effect

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## DYSLIPIDEMIA

**LIFESTYLE THERAPY** (Including Medically Assisted Weight Loss)

**LIPID PANEL: Assess ASCVD Risk**

**STATIN THERAPY**
If TG > 500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

| Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies | Repeat lipid panel; assess adequacy, tolerance of therapy | Intensify therapies to attain goals according to risk levels |
|---|---|---|

| RISK LEVELS | HIGH | DM but no other major risk and/or age <40 | VERY HIGH | DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking) or ASCVD* |
|---|---|---|---|---|
| | DESIRABLE LEVELS | | DESIRABLE LEVELS | |
| LDL-C (mg/dL) | <100 | | <70 | |
| Non-HDL-C (mg/dL) | <130 | | <100 | |
| TG (mg/dL) | <150 | | <150 | |
| TC/HDL-C | <3.5 | | <3.0 | |
| Apo B (mg/dL) | <90 | | <80 | |
| LDL-P (nmol/L) | <1200 | | <1000 | |

**IF NOT AT DESIRABLE LEVELS:** Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

| | |
|---|---|
| **TO LOWER LDL-C:** | Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin |
| **TO LOWER Non-HDL-C, TG:** | Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin |
| **TO LOWER Apo B, LDL-P:** | Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin |
| **TO LOWER LDL-C in FH:\*\*** | Statin + PCSK9i |

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

\* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED    \*\* FAMILIAL HYPERCHOLESTEROLEMIA

## HYPERTENSION

**GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg**

ACEi or ARB

For initial blood pressure >150/100 mm Hg: **DUAL THERAPY**

ACEi or ARB + 
- Calcium Channel Blocker ✓
- ß-blocker ✓
- Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, ß-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

# A demora na Intensificação da Terapia em 6 Meses Aumenta o Risco Cardiovascular em Pacientes com Diabetes Tipo 2

## Datalink da Pesquisa na Prática Clínica no Reino Unido

**Diagnóstico de DMT2 n=110.543**

**HbA$_{1c}$ >7% após 1 ano**

**Demora de 6 meses na intensificção da terapia + 2 OAD / OAD + Insulina**

**Intensificação imediata da terapia + 2 OAD / OAD + Insulina**

**5 anos**

**Aumento no risco Intensificação tardia vs imediata da terapia**

**20%**

**26%**

**Doença CV**

**IM**

Paul S, et al. *Diabetologia* 2013; 56(Suppl1):S534