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# Achievement of cardiovascular risk factor targets according to sex and previous history of cardiovascular disease in type 2 diabetes: A population-based study

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ABSTRACT

*Aims:* The main objective was to assess, using real-practice primary care records, the degree of control of cardiovascular risk factor targets. Records were stratified by the presence of previous history or cardiovascular disease (CVD), and sex differences in the fulfillment profile were analyzed.
*Methods:* This is a cross-sectional population-based study conducted in Spain. Type 2 diabetes patients over 20 years old (n = 32,638) were identified from primary care electronic health records, and the following information was extracted: glycated hemoglobin (HbA1c), systolic and diastolic blood pressure (SBP and DBP), LDL and HDL cholesterol levels, triglycerides, BMI and smoking history.
*Results:* Patients with CVD had worse control of HbA1c than patients without it, (HbA1c < 7% 56.9% vs. 61.2%) but better control of BP (<130/80: 43.5% vs 38.2%) and lipids. In the group without prior CVD history, women had worse control of HbA1c, LDL, HDL, BMI and triglycerides and better control of blood pressure and smoking. These differences were maintained or accentuated in the group with previous CVD.
*Conclusions:* Women had poorer control of CV risk factors in both groups, and the sex-gap is accentuated in patients with previous CVD.



## 1. Introduction

The International Diabetes Federation estimates that 425 million people, or 8.8% of the world's population, between 20 and 79 years old has diabetes, a number that is expected to grow to 629 million people by 2045.[1] Diabetes mellitus (DM) is a major source of health complications, induces comorbidities and reduces the quality of life of the population.

Diabetes is an important and independent risk factor for cardiovascular disease (CVD).[2,3] Furthermore, patients with diabetes and with a previous history of cardiovascular disease are at a higher risk for a recurrent event.[4] Although the control of cardiovascular risk factors has proven to be effective in the reduction of CVD risk, there are several recent studies showing that there is still a gap between the guideline's recommendations and clinical practice.[5–7]

Increasing amounts of literature are demonstrating the differences in how diabetes affects CVD risk between women and men.[3,8,9] Two recent meta-analyses showed how the increased risk of CVD due to diabetes is higher in women.[10,11] They showed that diabetes is attributed a 44% increased risk for incident CHD and a 27% increased risk of stroke in women compared with men. They argue that this excess of risk is due to a combination of factors, including biological and behavioral factors and differences in received health care.

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The implementation and generalization of electronic medical record systems allows for the realization of population-based studies using large real-practice databases. These registers have proven to be a valid and useful source of information for characterizing patients with diabetes and the degree of achievement of control targets,[7,12] even linking it with socioeconomic status.[13]

Although there is growing literature about sex-differences in cardiovascular prevention and the excess of risk that diabetes causes in women,[14] there is little research focusing on patients with previous CVD and analyzing the sex effects in this population. The fact of having had a cardiovascular event could modify the behavior of patients and clinicians, altering the previous paradigm.

The aim of this population-based study is the assessment, using real-practice primary care records, of the achievement of cardiovascular risk factor targets according to sex and previous history of CVD, establishing whether sex differences in the achievement profile differ by the presence of previous CVD.

## 2. Material and methods

This is a cross-sectional study conducted in Navarra, a community of over 600,000 inhabitants situated in northern Spain. The Regional Health Service of Navarre – Osasunbidea, part of the National Health Service, is a public health system financed by general taxes. Primary care was developed in Spain in the 1980s, providing practically universal coverage to the population.

The source of information for this study was the Electronic Medical Record System of Primary Care of the Regional Health Service of Navarre, named Atenea. It contains patient data about diagnoses, clinical variables, lifestyles, laboratory results and prescriptions, and its coverage is of about 97% of the population. These electronic medical records were established in the early 2000s and have been thoroughly used by all professionals since 2008. Electronic prescription was established in 2013.

The study population is all patients registered in the Atenea system with a diagnosis of type 2 diabetes (International Classification of Primary Care (ICPC), T90) as of May 15th, 2014. The following patient information was extracted: glycated hemoglobin (HbA1c), systolic and diastolic blood pressure (SBP and DBP), LDL and HDL cholesterol levels, triglycerides, weight, height, body mass index (BMI), smoking history, medications, date of registration in the information system, date of diabetic onset, and birth date. We obtained the latest results available within the 15 months prior to the data extraction date. Cardiovascular event was defined as a composite event including ischemic heart disease (ICPC: K74, K75, K76), cerebrovascular disease (K89, K90, K91) and peripheral vascular disease (K92).

Main treatment goals were based on Spanish guidelines[15] and are in line with international standards[16]: HbA1c < 7%, BP < 140/90 mmHg; LDL < 100 mg/dL and LDL < HDL > 35 mg/dL in men and > 45 mg/dL in women; triglycerides < 150 mg/dL and BMI < 30 kg/m$^2$. Other treatment goals used in previous studies[6,7] were also studied: HbA1c < 8%, HbA1c > 10% and BP < 130/80. Two combined targets were also considered: Combined target A: HbA1c < 7% and BP < 140/90 mmHg and LDL < 100 mg/dL; Combined target B: (HbA1c < 7% if <75 yr and HbA1c < 8% if ≥75 yr) and BP < 140/90 mmHg and LDL < 100 mg/dL.

### 2.1. Statistical analysis

Continuous variables included in the study were summarized by the mean and standard deviation, and categorical variables were summarized by frequency and percentage. Sex differences in the control variables were estimated using logistic regression models adjusted first by age then by age and glucose-lowering treatment, stratified by presence of CVD. Similar results were obtained in both models, so finally only age-treatment adjusted model data were included. The difference of sex-effects between both groups was evaluated including presence of CVD and CVD-sex interaction term in the logistic models, both age and treatment adjusted. Statistical analyses were conducted with IBM-SPSS 20 and R 3.2.2.

## 3. Results

The number of patients over 20 years of age with type 2 diabetes registered by Navarre Regional Health Service was 32,638, including 56.5% men and 43.4% women. The prevalence of type 2 DM, over all population of Navarra older of 20 years, was 6.6% (95% CI: 6.5–6.7), with 7.5% (95% CI: 7.4–7.6) in males and 5.6% (95% CI: 5.5–5.7) in females. The prevalence of previous history of CVD in the population with type 2 diabetes was 25.13%, (95% CI: 24.67–25.61). This prevalence was higher in men, 29.0% (95% CI: 28.5–29.5), than in women, 20.2%, (95% CI: 19.8–20.6), with $p < 0.001$.

Demographic and clinical characteristics by presence of previous CVD and sex are summarized in Table 1. Patients with a previous history of CVD were older than those without, with a mean age of 74.3 years vs. 67.9 years, respectively ($p$-value<0.001). These patients also had a longer duration of diabetes by an average of two years. There was a smaller proportion of women in the group of patients with CVD than in the CV disease-free group, at 34.6% vs. 45.7%. Regarding glucose-lowering treatment, patients with CVD more frequently received insulin and combined treatment and were less frequently without treatment or with oral hypoglycemic treatment.

**Table 1**
Demographic and clinical characteristics: Mean (standard deviation) or frequency (percentage).

| | CVD | | | No CVD | | |
|---|---|---|---|---|---|---|
| | Total (n = 8203) | Men (n = 5277) | Women (n = 2838) | Total (n = 24,435) | Men (n = 12,911) | Women (n = 11,180) |
| Age (years) | 74.31 (10.73) | 72.29 (10.40) | 78.08 (10.31) | 67.87 (13.07) | 65.27 (12.26) | 70.95 (13.24) |
| Treatment | | | | | | |
| No treatment | 1557 (19.0%) | 965 (18.3%) | 548 (19.3%) | 5891 (23.6%) | 3060 (23.7%) | 2625 (23.5%) |
| Non-insulin | 4201 (51.2%) | 2878 (54.5%) | 1297 (45.7%) | 14,350 (59.1%) | 7853 (60.8%) | 6387 (57.1%) |
| Insulin | 926 (11.3%) | 508 (9.6%) | 409 (14.4%) | 1350 (5.6%) | 635 (4.9%) | 705 (6.3%) |
| Combined | 1519 (18.5%) | 926 (17.5%) | 584 (20.6%) | 2844 (11.7%) | 1363 (10.6%) | 1463 (12.1%) |
| Diabetes duration (years) | 11.86 (7.65) | 11.47 (7.95) | 11.88 (7.69) | 9.64 (7.03) | 9.07 (7.08) | 9.71 (7.19) |
| Smoking | 451 (13.9%) | 372 (17.1%) | 77 (7.3%) | 1539 (16.8%) | 1147 (23.11%) | 382 (9.24%) |
| HbA1c (%) | 7.29 (5.32) | 7.30 (6.26) | 7.29 (2.83) | 7.03 (1.41) | 6.99 (1.33) | 7.07 (1.48) |
| Diastolic BP (mmHg) | 73.09 (10.61) | 73.19 (10.49) | 72.92 (10.76) | 76.39 (10.33) | 77.10 (10.27) | 75.63 (10.30) |
| Systolic BP (mmHg) | 134.26(18.41) | 134.01(17.90) | 135.04 (17.56) | 135.09 (16.90) | 135.14 (16.24) | 135.04 (19.16) |
| HDL (mg/dL) | 42.58 (11.84) | 41.18 (11.35) | 45.25 (12.24) | 46.42 (12.53) | 44.27 (11.90) | 48.86 (12.77) |
| LDL (mg/dL) | 97.88 (31.58) | 93.96 (29.36) | 105.28 (34.22) | 113.55 (33.56) | 111.44 (32.38) | 115.92 (34.67) |
| BMI (kg/m$^2$) | 29.93 (8.33) | 29.72 (7.92) | 30.38 (9.09) | 30.64 (9.36) | 30.29 (7.96) | 31.05 (10.73) |
| TGs (mg/dL) | 147.08 (89.40) | 142.88 (91.41) | 155.102 (84.92) | 146.89 (101.30) | 147.28 (116.84) | 146.31 (80.38) |

**Table 2**
Cardiovascular risk factor targets by sex and presence of CVD. Percentage of fulfillment and age and treatment-adjusted odds ratio for fulfillment (men vs. women).

| | CVD | | | | No CVD | | | | *p*-Value[+] |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Men | Women | $OR_{adj}$ (95% CI) | Total | Men | Women | $OR_{adj}$ (95% CI) | |
| HbA1c ≤ 7% | 56.9 | 58.3 | 54.1 | 1.11 (0.97, 1.25) | 61.2 | 62.4 | 60.0 | 1.09 (1.01, 1.16) | 0.89 |
| HbA1c ≤ 8% | 80.7 | 81.9 | 78.2 | 1.22 (1.05, 1.42) | 83.6 | 84.1 | 83.2 | 1.07 (0.97, 1.17) | 0.19 |
| HbA1c > 10% | 3.7 | 3.4 | 4.3 | 1.30 (0.97, 1.75) | 3.3 | 3.3 | 3.3 | 1.09 (0.91, 1.30) | 0.26 |
| SBP ≤ 130 mmHg | 46.3 | 47.0 | 44.9 | 1.08 (0.97, 1.20) | 44.1 | 43.6 | 44.5 | 0.87 (0.81, 0.92) | 0.039 |
| DBP ≤ 80 mmHg | 81.7 | 81.5 | 82.2 | 1.27 (1.11, 1.46) | 72.6 | 70.1 | 75.2 | 0.96 (0.89, 1.03) | <0.001 |
| BP ≤ 130/80 mmHg | 43.5 | 44.2 | 42.3 | 1.12 (1.01, 1.25) | 38.2 | 37.4 | 38.9 | 0.91 (0.86, 0.97) | 0.015 |
| BP ≤ 140/90 mmHg | 70.6 | 71.2 | 69.5 | 1.05 (0.94, 1.18) | 69.6 | 69.5 | 69.7 | 0.92 (0.86, 0.98) | 0.17 |
| LDL < 100 mg/dL | 57.5 | 62.4 | 48.4 | 1.79 (1.60, 2.00) | 34.7 | 37.1 | 31.9 | 1.38 (1.29, 1.47) | <0.001 |
| LDL < 130 mg/dL | 85.2 | 89.2 | 77.8 | 2.41 (2.07, 2.80) | 71.5 | 73.9 | 68.7 | 1.42 (1.33, 1.52) | <0.001 |
| HDL (≥35 M, ≥45 W)[a] | 63.7 | 71.9 | 48.2 | 2.76 (2.46, 3.10) | 71.3 | 80.9 | 60.6 | 2.90 (2.71, 3.11) | 0.86 |
| TGs < 150 mg/dL | 63.9 | 66.6 | 58.7 | 1.67 (1.49, 1.87) | 64.8 | 66.4 | 63.0 | 1.33 (1.24, 1.41) | 0.001 |
| BMI < 30 kg/m$^2$ | 55.7 | 57.5 | 51.7 | 1.49 (1.31, 1.71) | 51.6 | 53.2 | 50.0 | 1.30 (1.21, 1.39) | 0.15 |
| Not smoking | 86.1 | 82.9 | 92.7 | 0.49 (0.38, 0.64) | 83.2 | 76.9 | 90.8 | 0.42 (0.37, 0.48) | 0.25 |
| Combined targets[b]: | | | | | | | | | |
| A | 19.7 | 22.9 | 14.0 | 1.71 (1.47, 1.99) | 11.8 | 13.2 | 10.3 | 1.36 (1.23, 1.49) | <0.001 |
| B | 24.0 | 27.1 | 18.5 | 1.72 (1.50, 1.97) | 13.8 | 14.9 | 12.6 | 1.33 (1.22, 1.46) | <0.001 |

[+] *p*-Value of the sex-CVD interaction term in the full model.
[a] Target: ≥35 mg/dL in men and ≥45 mg/dl in women.
[b] Combined targets:

- A: HbA1c < 7% & BP < 140/90 mmHg & LDL < 100 mg/dL.
- B: (HbA1c < 7% if <75 yr & HbA1c < 8% if ≥75 yr) & BP < 140/90 mmHg & LDL < 100 mg/dL.

The achievement of cardiovascular risk factor goals by the presence of CVD and sex is shown in Table 2. In the group with previous CVD, 56.9% and 80.7% of patients had HbA1c level below 7% and 8% respectively, while in the group without CVD, it was 61.2% and 83.6% of patients. There was a poor lipid control among patients without CVD, 34.7% of patients with LDL < 100 (37.1% in men 31.9% in women) and it is better among patients with previous CVD (57.5%). 43.5% of patients with CVD had combined BP levels below 130/80, while in the group without CVD there were 38.2% of them. There was a high percentage of non-smokers in both groups, 86.1% in the CVD group and 83.2% in the no-CVD one. Finally, in the combined targets, the fulfillment percentages were low in both groups and sexes; only 14% of the disease-free patients (14.9% in men, 12.6% in women) and 24% of the CVD group patients (27.1% in men, 18.5 in women) met B combined target.

Stratified by the presence of CVD, sex-effects in the fulfillment of cardiovascular risk factor goals are shown in Table 2 and Fig. 1, with age and treatment adjusted odds ratios ($OR_{adj}$). Women had slightly worse glycemic control in both groups: for instance, with the <7% goal, $OR_{adj}$ was 1.11 (0.97, 1.25) in the CVD group and 1.09 (1.01, 1.16) in the group without CVD. Women had also worse control of HDL and LDL, and this difference in LDL control was accentuated in the CVD group: $OR_{adj}$ 2.41 vs. 1.42 in the LDL < 130 goal and $OR_{adj}$ 1.79 vs. 1.38 in the LDL < 100 goal. Women showed worse control of BMI and triglycerides in both groups, and this difference was also more intense in the group with previous history of CVD. Apropos of blood pressure control, diverse fulfillment profiles were found. In the group with a previous history of CVD, women were less likely to have controlled BP levels than men, but they nevertheless showed better control within the group of patients without CVD. Women were also

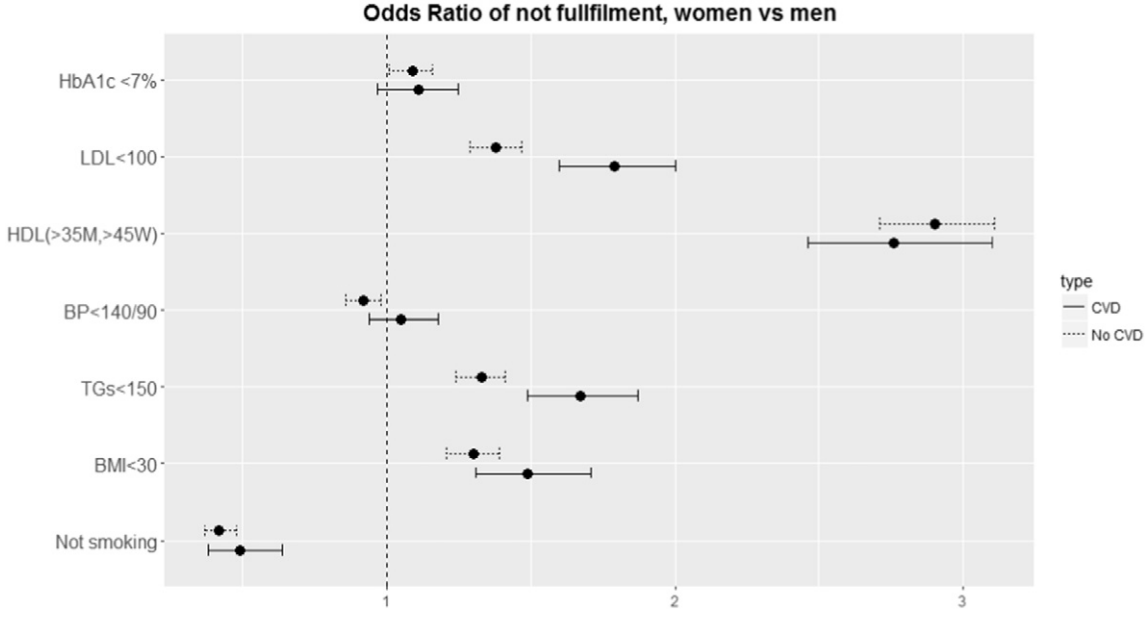


**Fig. 1.** Age and treatment adjusted odds ratio for no fulfillment for different cardiovascular risk factors, (women vs. men).

much less frequently smokers, with $OR_{adj}$ 0.49 (0.38, 0.64) in the CVD group and 0.42 (0.37, 0.48) in the group without CVD. Finally, in the combined targets, women showed worse fulfillment, especially within the group of patients with CVD, with differences of up to 9% in the B target.

## 4. Discussion

There is a sex effect in the control of cardiovascular risk factors in patients with previous CVD and without and these sex effects differ between both groups. On the one hand, in the group without prior CVD history, women had worse control of HbA1c, LDL, HDL, BMI and triglycerides, and better control of blood pressure and smoking. On the other hand, in the group with previous history of CVD the sex differences observed in the group without previous CVD were maintained and even accentuated against women, even for BP, where women no longer had better control than men.

Our results regarding sex differences in risk factor target achievement by CVD are in accord with those obtained in other published studies. In a similar population-based cross-sectional study performed in another Spanish region,[17] women also had worse control of BMI and LDL, better control of smoking, and the size of these effects were also very similar, with and without CVD. In their study, control of HbA1c was only worse for women in the CVD group. Furthermore, a similar BP control pattern was found, with women having better control in the group without CVD and worse control in the CVD group in their study. In another study from the US,[18] sex-differences were also higher in the group with previous CVD. In the group without prior CVD, control of LDL and SBP was similar in both sexes, but women were more likely to have uncontrolled LDL and SBP in the group with prior CVD. Similarly to our study, no noticeable differences in the achievement of HBA1c control targets were found.

There is growing evidence that diabetes has a greater impact on cardiovascular risk in women than in men, but there is no consensus about the main reasons behind this difference. On the one hand, the existence of sex differences in the management of diabetes has been mentioned[19]; women were 15% less likely to meet recommended care processes. On the other hand, they add that even when women and men are treated equally, women are less likely to achieve control targets, hypothesizing that management differences alone could not explain the excess of CV risk among women with diabetes. We observed that women were in a higher percentage in the more intensive treatments in both groups, and the difference is slightly greater in the prevalent group.

In a recent review,[14] it is suggested that women experience a larger deterioration in major cardiovascular risk factors and weight during their transition to DM2. In another review about sex differences in diabetes,[20] they mention that European men are diagnosed with diabetes at an earlier age and lower BMI than women. One possible explanation to this gender gap in cardiometabolic risk could be that for a mixture of lower perception of disease and biological factors, women are diagnosed in a worse state, and this difference is not reduced after. In this work, we confirm the worse control of cardiovascular risk factors among women and that this sex difference is greater in patients with a previous history of CVD.

This study has some limitations. Our study cohort is from a region of Spain, and all the data comes from users of the Public Regional Health Services; thus, there are no data from private practice users or from those with undiagnosed diabetes. Due to the high coverage of the public health system and the fact that in patients with a mixed insurance the monitoring of chronic pathologies is usually done in the public system, we do not expect this could lead to a selection bias. That this is a retrospective study based on real clinical practice could lead to information bias, especially for some variables such as tobacco use, because the process is more dependent on the physicians' procedures. The fact that this is a cross sectional study makes it necessary to be cautious when inferring causality in the presented associations. The presence of CVD is basically a stratification of the population into groups that may have different characteristics. We have not information regarding the date at which the CVD took place, and so we cannot guarantee that a minimum time-period between the CVD date and the analytic date has passed for all patients, making difficult to interpret results as secondary prevention results for the CVD group. Nevertheless, we do not expect a high percentage of incident CVD cases just previously to the extraction date. The absence of antihypertensive or lipid treatment information is also a limitation. The lack of information at the time of the diagnosis of diabetes does not allow the analysis of the actual effect of the health system in the control of risk factors. The main strengths of the study are that it used data from real clinical practice with a large number of entries available and that it covered almost the totality of registered DM of the region under study.

## 5. Conclusions

The results of our study confirm that overall control of cardiovascular risk factors is poorer in women compared to men, and that these sex-differences are greater in the group of patients with previous history of CVD than in the group without it, especially for LDL and TG, even when age and treatment differences are accounted for. This could suggest that actual secondary prevention management does not diminished sex-differences, although this subject should be corroborated with a longitudinal study design.

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