

Research Article

Study of Factors Associated with Silent Myocardial Ischemia in Hypertensive Diabetic Patients Followed up in the Cardiology Department of Yalgado Ouédraogo Teaching Hospital

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Submitted: July 23, 2025

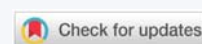
Approved: August 04, 2025

Published: September 03, 2025

How to cite this article: Kologo KJ, Tall-Thiam A, Kabore/Benon LE, Millogo GRC, Kambire Y, Justine KL, et al. Study of Factors Associated with Silent Myocardial Ischemia in Hypertensive Diabetic Patients Followed up in the Cardiology Department of Yalgado Ouédraogo Teaching Hospital. J Cardiol Cardiovasc Med. 2025; 10(5): 106-112. Available from: <https://dx.doi.org/10.29328/journal.jccm.1001217>

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Keywords: Chemoprophylaxis; SMI; Hypertensive diabetic; CHUYO; Burkina Faso



Abstract

Objective: Study the association between anti-ischemic chemoprophylaxis (ACE inhibitor, statin, and antiplatelet agent) and the reduced risk of the occurrence of silent myocardial ischemia in hypertensive diabetic subjects.

Methodology: This was an observational, retrospective, prospective case-control study conducted from January 1 to November 30, 2018. It involved 94 patients distributed into 47 cases and 47 controls following the result of the exercise stress test performed in the cardiology department of Yalgado Ouédraogo Teaching Hospital in Ouagadougou, Burkina Faso.

Results: The average age of the cases was 55.98 ± 8.6 years against 56.11 ± 7.57 years for the controls; the sex ratio was in favor of women in both groups. Anti-ischemic chemoprophylaxis was found in 25% of cases and 15% of controls. The assessment of the cardiovascular risk showed a high cardiovascular risk level in 34% of cases, against 35% of controls; an intermediate risk level in 34% of cases, against 41% in controls. Risk factors such as age, dyslipidemia, smoking, and hyperuricemia were not associated with silent myocardial ischemia. Multivariate analysis revealed an association (odds ratio = 0.29; $p = 0.048$) between chemoprophylaxis and reduction of 71% of the risk of silent myocardial ischemia.

Conclusion: Our work highlights the importance of pharmacological treatment of hypertensive diabetic patients as a primary cardiovascular prevention.



Introduction and problem statement

According to the data of the World Health Organization (WHO) in 2014 [1], 422 million adults were living with diabetes. Developing countries are witnessing the emergence of non-communicable diseases, including diabetes. The International Diabetes Federation estimates that the prevalence rate could reach a total of 15 million African diabetic patients by 2025. In 2016, the Ministry of Health in Burkina Faso estimated the prevalence of diabetes at 4.9%; the study "STEPS" found an in-hospital prevalence of 8.5% in 2015 [2]. Apart from obesity, hypertension is the main cardiovascular risk factor associated with diabetes. The "Africa Interheart" study reveals that diabetes and hypertension are the factors highly associated with the occurrence of myocardial infarction in African populations. Furthermore, the coronary risk equivalent term refers to the presumption of the existing coronary heart disease when type 2 diabetes is associated with renal dysfunction, such as proteinuria, microalbuminuria, and/or reduced glomerular filtration rate, or rather with several other cardiovascular risk factors [3].

The association of diabetes and arterial hypertension would therefore deserve a specific preventive attitude aimed at reducing the cardiovascular risk through poly-medication, including a conversion enzyme inhibitor, a statin, and an antiplatelet agent, as recommended in certain studies [4-6]. Coronary artery disease in diabetic patients is characterized by multi-vessel damage, with stenoses of the left coronary trunk, the anterior interventricular, and the circumflex. In this case, coronary surgery has shown excellent short- and medium-term results [6]. This treatment is not available in our working environment. The alternative remains prevention through hygienic-dietary measures and chemoprophylaxis. We therefore propose to study the effect of the association of a converting enzyme inhibitor, statin, and an antiplatelet agent on the reduction of coronary risk characterized by the occurrence of myocardial ischemia in hypertensive diabetic patients in our country, through a case-control study.

Methods

The study took place in the consultation unit of the departments of Cardiology and Physical Medicine of Yalgado Ouédraogo Teaching Hospital.

Study population

This was an observational, case-control (1 case for 1 control), unpaired study with predominantly retrospective and prospective data collection.

The cases included in the study: hypertensive diabetic patients with silent myocardial ischemia diagnosed by a clinically positive exercise stress test by the occurrence of typical angina, or electrically positive with ST-segment depression ≥ 0.1 mmV lasting 60 to 80ms, or T-wave tripling.

The controls included in the study: hypertensive diabetic patients with no silent myocardial ischemia confirmed by a negative exercise stress test.

Operational definitions

- **Silent myocardial ischemia:** It has been defined by a positive exercise stress test clinically by the occurrence of typical angina during the exercise stress test or electrically by T wave tripling, significant ST-segment depression, or ST-segment elevation.
- **Exposure:** This was a therapeutic combination based on an enzyme conversion inhibitor, statin, and an antiplatelet agent like aspirin.
- **Event:** referred to as silent myocardial ischemia
- **Hypertensive:** Any patient suffering from known and documented arterial hypertension.
- **Active smoking:** defined as active tobacco consumption or weaned off less than three years.
- **Lipid standards :** according to the «health authorities » in 2017, the following values were defined [7]:
 - Cholesterol total: 4.10-5.20 mmol/l or 1.6-2.0g/l
 - Triglycerides: 0.40-1.70 mmol/l or 0.35-1.50g/l
 - HDL-cholesterol: > to 1.0 mmol/l or > to 0.40g/l
 - LDL-cholesterol: < to 4.9 mmol/l or < to 1.90 g/l
- **Dyslipidemia:** these are abnormal quantitative lipids reflected by total hypercholesterolemia and/or hypercholesterolemia at LDL > 1.8 mmol, particularly defined by the hypolipidemic treatment goal of the European Society of Cardiology 2016 and/or hypertriglyceridemia [8].
- **Abnormal waist circumference = abdominal perimeter:** men ≥ 102 cm and women ≥ 88 cm.
- **Kidney failure:** defined by creatinine clearance < 60 ml/minute according to the health authorities [9].
- **Hyperuricemia:** uricemia was > 460 $\mu\text{mol/L}$ in men and > 360 $\mu\text{mol/L}$ in women.
- **Diabetes control:** defined based on the glycated hemoglobin value. Glycated hemoglobin is high if > 7% [10].
- **Cardiovascular risk at 10 years:** calculated using the Framingham score.
- **Therapeutic association studied:** this was defined as the combination of ACE inhibitor-statin-platelet antiaggregant, or the antagonistic association of the receptors of angiotensin-statin-antiplatelet agents

Data entry and analysis

A microcomputer equipped with SPSS and STATA software was used to record the data and analyze them, using the chi-square and Fisher tests to compare proportions and averages, while considering a significant threshold of 0.05. Logistic regression was performed to minimize confounding bias. We calculated the population attributable risk fraction (PARF) to assess the impact of anti-myocardial ischemia chemoprophylaxis combining ACE inhibitors, statins, and antiplatelet agents in our study population.

Results

Socio-demographic characteristics of the study population

Age: The average age of cases was 55.98 ± 8.6 ($p = 0.576$) with extremes ranging from 41 to 73 years ($p = 0.576$) against 56.11 ± 8.06 with extremes from 41 to 69 years for controls ($p = 0.099$).

Sex: The sex ratio of silent myocardial ischemia cases was 11/36, corresponding to 0.30 against 18/29 or 0.62 ($p = 0.118$) for controls. In both groups, the sex ratio was in favor of women.

Socio-professional status

Civil servants accounted for 12 (25%) of cases and controls. Housewives were found in 17 cases (36%) and 11 controls (21%).

Cardiovascular risk factors

The association of diabetes and hypertension: The association between hypertension and diabetes less than 5 years old was found in 55% of cases and 49% of controls.

Diabetes control: Glycated hemoglobin was normal in 55% of cases and 55% of controls ($p < 0.05$).

Other cardiovascular risk factors

Among these risk factors, the duration of diabetes exceeding 10 years was observed in 11 cases (23%), dyslipidemia was observed in 35 cases (74%), and 19 cases (40%) of women with silent myocardial ischemia were over 55 years of age (Table 1).

Table 1: Proportions of risk factors in cases and controls.

Variables	Cases n (%)	Controls n (%)	p
Age > 45 years in men	10 (21)	16 (34)	0.86
Age >55 years in women	19 (40)	17 (36)	0.63
Dyslipidemia	35 (74)	36 (76)	0.89
Hyperuricemia	1 (2)	8 (17)	
Smoking	2 (4)	2 (4)	
Age of the diabetes >10 years	11 (23)	15 (31)	0.35

Distribution of silent myocardial ischemia cases and controls according to the cumulative number of other cardiovascular risk factors

Among these other cardiovascular risk factors, 51% of cases accumulate one other factor, 31% of cases accumulate 2 associated factors, and none accumulate 4 other risk factors (Table 2).

Global cardiovascular risk

The Intermediate global cardiovascular risk was observed in 11 cases (23%) and 9 controls (19%). 14 cases (29%) and 14 controls (29%) had high cardiovascular risk factors (Table 2).

Averages of paraclinical variables in cases and controls

The average blood glucose level of cases was estimated at 7.61 mmol/L against 8.27 found in controls; the average creatinine level for cases was 100 μ mol/L against 90.19 μ mol/L found in controls; and the average total cholesterol level for cases was 5.11 mmol/L against 5.01 mmol/L found in controls.

Treatment

Hypoglycemic treatment: 26 cases (55%) and 26 controls (53%) were taking antidiabetic treatment with biguanides.

Cardiological treatment: The proportion of cases on ACE was 77% and that of controls was 47%. Combined statin and antiplatelet agent therapy was taken by 30% of cases and by 21% of controls. Table 3 shows the distribution of cases and controls according to the cardiological treatment taken (Treatment III).

Myocardial anti-ischemic chemoprophylaxis

25% of cases and 15% of controls were exposed to myocardial anti-ischemic chemoprophylaxis.

Table 2: Distribution of silent myocardial ischemia cases and controls according to the global cardiovascular risk level.

CVR level	Cases n (%)	Controls n (%)	p
Low	11 (27)	8 (21)	0.34
High	30 (73)	31 (79)	
Intermediate			

Table 3: Distribution of cases and controls according to the cardiological treatment.

Drugs	Cases n (%)	Controls n (%)	p
ACE or ARAII	36 (77)	22 (47)	8.824
Statin	15 (32)	11 (23)	0.85
Antiplatelet agent	15 (32)	11 (23)	
Statin antiplatelet agent	14 (30)	10 (21)	0.89
Beta-blocker	9 (19)	16 (34)	2.670

Impact of cardiovascular risk factors and chemoprophylaxis on the occurrence of silent myocardial ischemia

Predictive factors of silent myocardial ischemia: The multivariate analysis has enabled us to represent the odds ratios of the predictive factors of silent myocardial ischemia in the following table (Table 4).

Table 4: Distribution of cases and controls according to the sociodemographic variables.

Variables	Cases	Controls	p
Sex ratio	0,3	0,62	0,118
average age	55,98 ans	56,11 ans	0,576
Extremes age	41-73 ans	41-69 ans	0,099
Civil servants	25%	25%	
House wives	36%	21%	

Diabetes of more than 10 years duration doubled the occurrence of silent myocardial ischemia. Furthermore, we also found an association between anti-ischemic chemoprophylaxis and the occurrence of silent myocardial ischemia (odds ratio = 0.29 $p = 0.048$).

Impact of myocardial anti-ischemic chemoprophylaxis on cardiac and renal function

Calculating the attributable fraction in the population has enabled us to estimate the benefit of the myocardial anti-ischemic chemoprophylaxis on renal and cardiac protection. This treatment would reduce renal function impairment by 14% and cardiac function impairment by 9.36%.

Impact of myocardial anti-ischemic chemoprophylaxis on the occurrence of silent myocardial ischemia

The association between myocardial anti-ischemic chemoprophylaxis and the occurrence of silent myocardial ischemia was established. This could mean, in other words, that there would be a 71% reduction in the risk of occurrence of silent myocardial ischemia characterized by an odds ratio of 0.29 in our overall population and an odds ratio = 0.12 in women, corresponding to a reduction of 88%. In addition, calculating the etiological fraction in the general population and in the exposed population led to the conclusion that if all diabetic hypertensive patients were put on the above-mentioned treatment, the burden of morbidity linked to silent myocardial ischemia would be reduced by 41% and 48.95%.

Discussion

Epidemiological profile of cases and controls

Age: The average age of cases was 55.98 ± 8.6 ($p = 0.576$) with extremes from 41 to 73 years ($p = 0.576$), and that of controls was 56.11 ± 8.06 with extremes from 41 to 69 years ($p = 0.099$). The average age we found for cases and controls

was similar. Similarly, this average age is comparable to that of Purifine A S in Côte d'Ivoire in 2017, who found an average age of $56.2 \text{ years} \pm 11.7$ [11] in a dietary habits study in type 2 diabetic patients attending Abidjan diabetes center. It is also comparable to that of Mbaye A, in Senegal, in 2011, about screening silent myocardial ischemia in type 2 diabetic patients having high cardiovascular risk in Senegal (58.8 y) [12]. However, in Burkina Faso, the study of Ouédraogo T in 2017 about the contribution of exercise stress test in screening silent myocardial ischemia in type 2 diabetic patients, and that Sagnan Y in Burkina Faso in 2014 about the prevalence and factors associated with erectile dysfunction in diabetic patients respectively found an average age of 53.82 ± 9.66 and 52.3 ± 11.1 years which is below ours. In 2018, the ASCEND study in Oxford, when evaluating the effect of aspirin as a primary prevention in type 2 diabetic patients over a sample of 15,000 participants divided into 2 groups, where one was receiving aspirin and the other placebo, found a higher average age of $63.2 \text{ years} \pm 9.2$ in the treatment group and $63.3 \text{ years} \pm 9.2$ in the other one. Similarly, Koo B K in Korea, in 2013, in a 4-year prospective community-based study comparing the risk of coronary heart disease in asymptomatic diabetic and non-diabetic subjects with chest pain, found an average age above ours, estimated at $59 \text{ years} \pm 9$ in the diabetic group with coronary heart disease during follow-up [13]. Finally, the ACCORD trial in 2007, about designs and methods aimed at controlling cardiovascular risk in diabetic patients, also found a higher average age estimated at 62 years [14]. This difference in average age found in the studies between Western countries and African countries, and particularly in Burkina Faso, may reflect life expectancy in these countries.

Gender: The sex ratio of our study population was predominantly female for cases (0.30) and controls (0.62). This female predominance was found by Yaméogo T in 2014 during his study on the clinical characteristics of volunteers for diabetes screening at 0.7 [15]. This predominance was also reported by Ouédraogo T at 0.73 [16], by Mbaye A at 0.41 for echocardiographic screening of silent myocardial ischemia [12], and by Aké Tano S at 0.61 on risk factors associated with diabetes in Côte d'Ivoire [11]. However, our result is different from those reported by Vernstrom L in 2018 in Denmark (sex ratio = 2) [17], by Kreutzenberg S in 2017 in Italy (sex ratio = 1.17) [18], and by Gu A in the United States (sex ratio = 1.03) [19]. Female predominance women in our sample could be explained by the same demographic predominance in Burkina Faso [20].

Cardiovascular risk

Diabetes in a patient confers a high cardiovascular risk, defined by a 10-year coronary event risk of more than 20% [3]. In addition, the association of diabetes with hypertension is responsible for an increased risk and degenerative impairment of diabetes [21]. The cardiovascular risk concept has emerged in the field of occupational medicine. Therefore,



assessing the global cardiovascular risk is of paramount importance in subjects with at least one risk factor, and several models are used for this assessment. However, the Framingham score remains the most widely used model in cardiology [22]. In our study, the Framingham score helped in assessing the cardiovascular risk. The proportion of the high cardiovascular risk level was the same for both cases and controls at 29%, and that of intermediate cardiovascular risk was also identical in the 2 groups, estimated at 34%. The proportion of cases at low cardiovascular risk was 23%. This was higher than the proportion of low-risk controls.

Otherwise, the intermediate cardiovascular risk level was the highest in both groups. Kirk J's study on the predicted risk of coronary heart disease in diabetic patients has also estimated cardiovascular risk using the Framingham score, which gave an overall moderate risk of 17% [21].

Other cardiovascular risk factors

Dyslipidemia: Dyslipidemia of type 2 diabetes is a dyslipidemia secondary to the immune disorder, lifestyle changes, and advanced age of this population [23]. Free radicals play a role in its pathogenesis [24]. In our study, 74% of cases were found to have LDL dyslipidemia, against 76% for the controls. These results are higher than those of MBaye M (64.2%) and Ouédraogo T 53.9% [12,25]. Indeed, the pathophysiology of diabetic dyslipidemia is characterized by the presence of hypertriglyceridemia, secondary to an increased hepatic production of VLDL, and decreased plasma levels of HDL cholesterol, related to increased catabolism of HDL. There was also the qualitative feature of great, great-sized VLDL (VLDL1), relatively rich in triglycerides and dense in LDL [26,27]. On the other hand, we had an average HDL of 1.19 in the cases against 1.12 in the controls. The reduction of HDL levels during diabetes is variable [28].

Duration of diabetes

In our study, 23% of cases and 36% of controls have had diabetes for more than 10 years. This result is comparable to that of Aké Tano S, who found a percentage of 20% in his series [11]. However, it is significantly higher than that of Ntyonga-Pono P in Gabon, who found a prevalence of 18% in patients with known diabetes for at least 10 years [16]. The results differed, probably due to the age inclusion criteria.

Diabetes control

Most cases and controls had good glycemic control (55%). Cardiovascular risk is linked to glycemic control. Indeed, an approximation shows that a 1% rise in glycated hemoglobin above normal increases cardiovascular risk by 18% [10]. On the other hand, according to the UKPDS study, a 1% fall in glycated hemoglobin does not improve cardiovascular risk, but glycemic control does improve the occurrence of long-term cardiovascular events [29].

Impact of cardiovascular predictive factors on the occurrence of silent myocardial ischemia

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in diabetic patients. Early detection of this disease in type 2 diabetic patients, therefore, seems to be a beneficial approach to prevent the progression and occurrence of the CHD-related clinical events. Therefore, criteria have been defined to screen silent myocardial ischemia [30]. In our study, there was no statistically significant difference in the factors associated with silent myocardial ischemia [31]. Similarly, Goff D in the ACCORD study found that diabetes is an independent risk factor associated with classical risk factors such as hypercholesterolemia, smoking, and hypertension [32]. The studies "Detection of ischemia in Asymptomatic Diabetics study (DIAD)" by Scognamiglio R and Aké-Tano S also dealt with the predictive factors associated with the occurrence of myocardial ischemia in diabetic subjects. Their findings focused on the lack of association of most traditional risk factors except for the presence of an association with males, age > 65 years, and low HDL cholesterol levels [11,33]. In addition, erectile dysfunction was a predictive factor for coronary heart disease undetectable on exercise stress test in Jackson G's study [34]. On the other hand, Ouédraogo T found an association between arterial hypertension, smoking, obesity, overweight, dyslipidemia, heredity, sedentary lifestyle, alcohol, and silent myocardial ischemia [25]. The lack of correlation between classic risk factors and myocardial ischemia may be related to the lack of risk factors weighing according to their severity, duration, and possible treatment [30].

The impact of chemoprophylaxis on reducing the risk of the occurrence of silent myocardial ischemia

Primary prevention in diabetic patients through pharmacological treatment using antihypertensives, statins, and antiplatelet agents has been tackled by several studies aimed at reducing the cardiovascular risk associated with diabetes [35,36].

Our study showed an association between our chemoprophylaxis and a reduction in the risk of the occurrence of silent myocardial ischemia (odds ratio = 0.29, 95% confidence interval = 0.08 - 0.99, $p = 0.048$), meaning that this cardio protective treatment would reduce the occurrence of silent myocardial ischemia by 71%. Our figures are comparable to those of Coca A, who found a reduction of 69%. Otherwise, our chemoprophylaxis has been studied in order to establish a primary prevention based on the increase of the global cardiovascular risk assessed by the Framingham score, UKPD [35]. There's also the notion of combined therapy, where a single tablet may contain antihypertensive, statin, and antiplatelet agents, which corresponds to our chemoprophylaxis. As a result, some

studies have also found a reduction in the occurrence of myocardial ischemia by 72%, 66% [7,37]. Newman J's study reported a reduction of 53%, a rate below ours. However, this reduction was reached after combining hygienic and dietetic measures with pharmacological treatment. According to the scientific societies, the use of statins as a primary prevention is recommended for diabetic patients with no cardiovascular events, on the basis of an assessment of the global cardiovascular risk [22].

The use of aspirin as a primary prevention is controversial [36]. Indeed, according to ACC/AHA, it is a class IIa recommendation, while the ADA considers it as a class C recommendation [17,38,39]. These disparities regarding the percentage reduction could be explained by the differences in the study types and duration. Aspirin has demonstrated its efficacy in reducing cardiovascular risk, but the beneficial effects are counterbalanced because of its hemorrhagic effects, which makes its prescription controversial. Similarly, the primary prevention of diabetes complications first and foremost includes hygienic and dietary measures, followed by the control of other associated risk factors. Dr R Belaid's study on diet and cardiovascular risk in type 2 diabetic patients found an association between sucrose ($r = 0.25$; $p = 0.03$) and fasting blood glucose, glycated hemoglobin and protein intake ($r = 0.28$ $p = 0.03$); cholesterol intake > 200 mg/d (OR = 5.08; 95% CI [0.99 - 26]; $p = 0.03$). He concluded that adequate nutritional management was needed to reduce cardiovascular risk [40].

Conclusion

Diabetes is an independent cardiovascular risk factor. Hypertension associated with diabetes increases cardiovascular risk. Cases and controls were quite similar, considering their socio-demographic characteristics, and even some clinical and paraclinical parameters were similar. There was no statistically significant difference between cardiovascular risk factors and silent myocardial ischemia. Patients did not have good glycemic control. The association between anti-ischemic chemoprophylaxis and the reduced risk of silent myocardial ischemia was found with a statistically significant difference. A cohort study is desirable to investigate the efficacy of anti-ischemic myocardial chemoprophylaxis in hypertensive diabetic patients.

Ethic

The protocol was submitted to and approved by the National Ethics Committee. Informed consent was obtained orally from each patient after a clear explanation of the study's objectives and relevance. All participants gave their verbal consent knowingly and voluntarily.

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