People's Democratic Republic of Algeria
Ministry of High Education and Scientific Research
University of Kasdi Merbah Ouargla
Faculty of Medicine
Department of Medicine

Prevalence of electrocardiographic abnormalities and their relation to clinical features and cardiac symptoms in patients with type 2 diabetes without known CVDs: a cross-sectional study during the period 20/12/2023 - 29/02/2024 in Ouargla

DISSERTATION SUBMITTED TO OBTAIN A DOCTORATE DEGREE IN MEDICINE

Presented by:

LAKHDARI Mohammed El-Fadhil

SANDALI Fatma Zohra

Supervised by:

M.D HAMCHAOUI Kamel — **Assistant professor of Internal medicine**

In front of the jury members consisting of:

M.D KAHEL Abdelhak	**President**	**Assistant professor of internal medicine**
M.D OUCHENE Samia	**Examinator**	**Assistant professor of internal medicine**
M.D RAHMI Amine	**Examinator**	**Assistant professor of anesthesia and resuscitation**

Academic year: 2023-2024

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ACKNOWLEDGMENTS

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Mr. Hamchaoui Kamel

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DEDICATIONS

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In the name of ALLAH, the most gracious, the most merciful

May peace and blessings be upon his prophet Muhammed, the best of messengers

Completing this research has been a long marathon where I don't like running, yet for the sake of contributing to the greater good of academic research and positive impact, I took the run willingly.

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To my father Ammar, a true hero and a great soul in my world.

To the most amazing girls in humankind, the cutest supporters that I have ever had, to their voices who call inside of me to stay strong my lovely sisters: to the greatest lead Salsabil, to the most fashionable Mounira, the smartest and my lovely secret box hibat Arrahmane and the source of joy and fights Manel

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To every Palestinian mother and Palestinian martyr, to every soul that stands steadfastly to protect the honor of our holy land, I dedicate this work to you may Allah protect you proud Palestine.

Sandali Fatma Zohra

DEDICATIONS

In the name of ALLAH, the most gracious, the most merciful

May peace and blessings be upon his prophet Muhammed, the best of messengers

I dedicate my work to my beloved family: my amazing father, a true hero. Despite his illness, you never stopped fighting for us. Your courage and determination have taught me the true meaning of strength. I am forever grateful for your love and sacrifice, to my lovely Mother, whose unwavering love and support have made all my dreams possible. Thank you for working tirelessly to provide for me and for always believing in me. Your sacrifices will never be forgotten. To my caring Sisters Khadidja and Fatima and especially to my little sister, Amina. Your love, support, and unwavering belief in me have been the greatest gifts in my life. Thank you for always being there, for listening to my ramblings, for celebrating my successes, and for comforting me through my failures. Your presence has made me the person I am today, and I am eternally grateful for your love.

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Lakhdari Mohammed EL-Fadhil

LIST OF ABBREVIATIONS

List of abbreviations

Akt: A key player in cell survival and growth.

ASCVD: Atherosclerotic cardiovascular disease.

ARVC: Arrhythmogenic right ventricular cardiomyopathy.

ADVANCE: a model used in assessing cardiovascular risk in T2DM patients (Action in Diabetes and Vascular Disease: Preterax and diamicron MR controlled evaluation).

ACCORD: Action to control cardiovascular risk in diabetes study.

ACS: Acute coronary syndrome.

ADA: American Diabetes Association.

ATP: Adenosine Triphosphate.

AGE: Advanced glycated end-products.

ApoB: Apolipoprotein B.

BMI: Body mass index.

BP: Blood pressure.

CAD: Coronary artery disease.

CVD: Cardiovascular disease.

CD4+ T cell: A critical component of the immune system that plays a role in coordinating the body's immune system.

CD8+ T cells: T cell that plays a role in cell-mediated immune response called killer T cells or cytotoxic T cells.

CVOTs: Cardiovascular outcome trials.

CKD: Chronic kidney disease.

COX-2: A key enzyme in inflammation that is involved in the production of prostaglandins.

CAROLINA trial: Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Type 2 diabetes.

CARMELINA trial: Cardiovascular and Renal Microvascular Outcome study with Linagliptin.

DCCT: Diabetes Control and Complications trial.

DIAL: a model used in assessing cardiovascular risk in T2DM patients (Diabetes Lifetime perspective model).

DIGAMI: Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial.

DM: Diabetes mellitus.

DPP-4 I: Dipeptidyl peptidase-4 Inhibitors.

ECG: Electrocardiogram**.**

EURODIAB: A collaborative effort involving multiple European diabetes

eNOS: Endothelial nitric oxide synthase.

eGFR: Estimated glomerular filtration rate.

EPC: Endothelial progenitor cells.

ESC: European society of cardiology.

EASD: European Association for the Study of Diabetes.

FQRS: Fragmented QRS complex.

FFAs: Free fatty acids.

Factor NF-kB: Nuclear Factor kappa B, the master regulator of inflammation

GAD: Glutamic acid decarboxylase.

GDM: Gestational diabetes mellitus.

GLUT4: Glucose transporter 4.

GLP-1 RAs: Glucagon-like peptide-1 receptor agonists.

HF: Heart failure.

HDL-C: High-density lipoprotein cholesterol.

HBP: Hypertension (High Blood Pressure).

HbA1c: Hemoglobin A1c.

Hsp: Hexosamine pathway.

IDF: International diabetes federation.

IGT: Impaired glucose tolerance.

IFG: Impaired fasting glucose.

IRS: Insulin receptor substrate 1.

IS: Insulin sensitivity.

IR: Insulin resistance.

LDL: Low-density lipoprotein.

MENA: Middle East and North Africa.

MACE: Major adverse cardiovascular events.

MetS: Metabolic syndrome.

MENA: Middle East and North Africa.

NO: Nitric oxide.

OGTT: Oral glucose tolerance test.

ORIGIN: Outcome Reduction With Initial Glargine Intervention.

PG: Prostaglandin.

PAD: Peripheral artery disease.

PPARg: Peroxisome proliferator-activated receptor gamma.

PROactive Study: PROspective pioglitAzone Clinical Trial in Macrovascular Events

Ser1177: a key phosphorylation site.

PA: Physical activity.

PI3K: Phosphatidylinositide 3-kinase.

p66Shc: A key player in cellular stress response.

ROS: Reactive oxygen species.

RAGE: Receptor of advanced glycated end-products.

ROS: Reactive oxygen species.

SGLT2 inhibitors: Sodium-glucose co-transporter-2 inhibitors.

SR-B: Scavenger receptor B.

T2DM : Type 2 diabetes mellitus.

T1DM : Type 1 diabetes mellitus.

TG: Triglycerides.

tPA: Tissue plasminogen activator.

TZD: Thiazolidinedione.

TH1 cells: T helper cell that plays a role in cell-mediated immune response.

UKPDS: UK Prospective Diabetes Study.

UACR: Urinary albumin-to-creatinine Ratio.

VLDL: Very low-density lipoprotein.

WHO: World Health Organisation.

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ABSTRACTS

Abstract

Introduction: Type 2 Diabetes Mellitus (T2DM) is a pervasive and increasingly prevalent chronic condition, significantly elevating the risk of cardiovascular complications. T2DM is recognized as a cardiovascular disease risk equivalent, with patients facing a markedly increased risk of premature atherosclerotic cardiovascular disease (CVD). Despite the high incidence of cardiovascular involvement among diabetics, many remain asymptomatic. Electrocardiogram (ECG) abnormalities are critical in identifying hidden ischemic changes that may not present with symptoms but indicate a higher risk of cardiac mortality and morbidity.

Aim: This study aims to investigate the prevalence and types of ECG abnormalities in patients with Type 2 DM and to explore the relationship between these abnormalities and clinical features, and cardiac symptoms.

Materials and Methods: A cross-sectional study was conducted involving 191 T2DM patients from Ouargla. All participants were assessed for ECG abnormalities and clinical features such as age, gender, smoking status, physical activity, Body Mass Index, and blood pressure. The study focused on identifying the prevalence and types of ECG abnormalities and their association with cardiac symptoms and diabetes-related clinical features.

Results: Among the 191 T2DM patients, 151 exhibited abnormal ECG findings (79,1%). The most prevalent abnormalities were ischemic changes and repolarization abnormalities (57.1%), with fragmented QRS complexes being the most common abnormality observed between all abnormalities (40,85%). The study found no significant correlation between the presence of ECG abnormalities and the reported cardiac symptoms in the patients. The prevalence of these ECG abnormalities underscores the hidden risk posed by T2DM, highlighting the importance of routine ECG screening in this population, Patients with mild, high, and very high risk according to the SCORE2-Diabetes were more likely to present ECG abnormalities. Biological findings, such as ACR and eGFR, were correlated with the presence of abnormalities; however, HbA1c and fasting glucose were not. The highest prevalence of abnormalities was found in the older age group, between 80 and 90 years old.

Conclusion: The high prevalence of ECG abnormalities among Type 2 DM patients, particularly the frequent occurrence of fragmented QRS complexes, underscores the significant cardiovascular risk inherent in this condition. Despite the lack of a direct correlation between ECG abnormalities and cardiac symptoms, the findings emphasize the critical role of ECG in identifying subclinical cardiac issues in diabetic patients. Regular ECG monitoring is essential for early detection and management of potential cardiovascular complications in individuals with T2DM.

Keywords: ECG abnormalities, Type 2 diabetes mellitus, Fragmented QRS, FQRS.

Résumé

Introduction : Le diabète de type 2 (DT2) est une affection chronique de plus en plus répandue, augmentant considérablement le risque de complications cardiovasculaires. Le DT2 est reconnu comme un équivalent de maladie cardiovasculaire, avec un risque marqué d'athérosclérose précoce chez les patients. Bien que de nombreux diabétiques présentent des complications cardiovasculaires, beaucoup restent asymptomatiques. Les anomalies de l'électrocardiogramme (ECG) sont cruciales pour identifier les changements ischémiques cachés qui peuvent ne pas se manifester par des symptômes évidents mais indiquer un risque accru de mortalité et de morbidité cardiaques.

Objectif : Cette étude vise à étudier la prévalence et les types d'anomalies de l'ECG chez les patients atteints de diabète de type 2 et à explorer la relation entre ces anomalies et les caractéristiques cliniques, ainsi que les symptômes cardiaques.

Matériels et Méthodes : Une étude transversale a été réalisée avec 191 patients atteints de DT2 provenant de Ouargla. Tous les participants ont été évalués pour des anomalies de l'ECG et des caractéristiques cliniques telles que l'âge, le sexe, le tabagisme, l'activité physique, l'indice de masse corporelle (IMC) et la pression artérielle. L'étude a porté sur l'identification de la prévalence et des types d'anomalies de l'ECG ainsi que leur association avec les symptômes cardiaques et les caractéristiques cliniques liées au diabète.

Résultats : Parmi les 191 patients atteints de DT2, 151 ont présenté des anomalies sur l'ECG. Les anomalies les plus fréquentes étaient les changements ischémiques et les anomalies de repolarisation (57.1%), avec des complexes QRS fragmentés étant l'anomalie la plus courante observée entre tous les anomalies (40,85%). L'étude n'a trouvé aucune corrélation significative entre la présence d'anomalies de l'ECG et les symptômes cardiaques rapportés par les patients. La prévalence de ces anomalies de l'ECG souligne le risque caché associé au DT2, mettant en évidence l'importance du dépistage régulier par ECG dans cette population Aussi, les patients présentant un risque moyen, élevé et très élevé selon le SCORE2-Diabetes étaient plus susceptibles de présenter des anomalies à l'ECG. Les résultats biologiques, tels que l'ACR et le DFG, étaient corrélés à la présence d'anomalies ; cependant, l'HbA1c et la glycémie à jeun ne l'étaient pas. La prévalence la plus élevée d'anomalies a été trouvée dans le groupe d'âge le plus avancé, entre 80 et 90 ans.

Conclusion : La forte prévalence des anomalies de l'ECG chez les patients atteints de DT2, en particulier la fréquence des complexes QRS fragmentés, souligne le risque cardiovasculaire significatif inhérent à cette condition. Malgré l'absence de corrélation directe entre les anomalies de l'ECG et les symptômes cardiaques, les résultats mettent en évidence le rôle crucial de l'ECG pour l'identification des problèmes cardiaques subcliniques chez les patients diabétiques. La surveillance régulière par ECG est essentielle pour la détection précoce et la gestion des complications cardiovasculaires potentielles chez les personnes atteintes de DT2.

Mots clés : Anomalies de l'ECG, Diabète type deux, QRS fragmenté.

الملخص

المقدمة: يعد مرض السكري من النوع الثاني (T2DM) من الحالات المزمنة المتزايدة الانتشار، مما يزيد بشكل كبير من خطر حدوث مضاعفات قلبية. يُعتبر السكري من النوع الثاني معادلاً لخطر الأمراض القلبية الوعائية، حيث يواجه المرضى خطرًا ملحوظًا للإصابة بأمراض تصلب الشرايين المبكرة. على الرغم من ارتفاع معدل الإصابة بمشكلات قلبية وعائية بين المصابين بالسكري، إلا أن العديد منهم يظلون بدون أعراض. تعتبر شذوذات تخطيط القلب الكهربائي (ECG) مهمة في الكشف عن التغيرات السريرية المخفية التي قد لا تظهر بأعراض واضحة ولكنها تشير إلى زيادة خطر الوفاة والامراض القلبية.

الهدف: تهدف هذه الدراسة إلى التحقيق في انتشار وأنواع شذوذات تخطيط القلب الكهربائي لدى المرضى المصابين بداء السكري من النوع الثاني واستكشاف العلاقة بين هذه الشذوذات والميزات السريرية، فضلاً عن الأعراض القلبية.

الأساليب والمواد: تم إجراء دراسة مقطعية شملت 191 مريضًا مصابًا بداء السكري من النوع الثاني من ورقلة. تم تقييم جميع المشاركين لاكتشاف شذوذات تخطيط القلب الكهربائي وميزات سريرية مثل العمر، الجنس، حالة التدخين، النشاط البدني، مؤشر كتلة الجسم (BMI)، وضغط الدم. ركزت الدراسة على تحديد انتشار وأنواع شذوذات تخطيط القلب الكهربائي وعلاقتها بالأعراض القلبية والخصائص السريرية المرتبطة بالسكري.

النتائج: من بين 191 مريضًا مصابًا بداء السكري من النوع الثاني، أظهر 151 منهم شذوذات في تخطيط القلب الكهربائي. كانت الشذوذات الأكثر شيوعًا هي التغيرات الإقفارية والشذوذات في إعادة الاستقطاب (57.1%)، حيث كانت مركبات QRS المقطعة هي الشذوذ الأكثر شيوعًا الذي تم ملاحظته بين جميع الشذوذات (40,85%). لم تجد الدراسة أي علاقة ذات دلالة إحصائية بين وجود شذوذات في تخطيط القلب الكهربائي والأعراض القلبية المبلغ عنها من قبل المرضى. إن انتشار هذه الشذوذات في تخطيط القلب الكهربائي يسلط الضوء على الخطر الخفي المرتبط بداء السكري من النوع الثاني، مما يبرز أهمية الفحص الدوري بتخطيط القلب الكهربائي في هذا المجتمع الإحصائي. كذلك كان المرضى الذين لديهم مخاطر متوسطة وعالية جدًا وفقًا لمقياس SCORE2-Diabetes أكثر عرضة للإصابة باضطرابات في تخطيط القلب الكهربائي .كانت النتائج البيولوجية، مثل نسبة الألبومين إلى الكرياتينين (ACR) ومعدل الترشيح الكبيبي(eGFR) ، مرتبطة بوجود الاضطرابات، في حين لم تكن مستويات الهيموجلوبين السكري (HbA1c) والجلوكوز الصائم كذلك . وُجد أن أعلى نسبة انتشار للاضطرابات كانت في الفئة العمرية الأكبر سنًا، بين 80 و 90عامًا.

الخاتمة: إن الانتشار العالي لشذوذات تخطيط القلب الكهربائي بين المرضى المصابين بداء السكري من النوع الثاني، وخاصة تكرار مركبات SQR المقطعة، يبرز الخطر القلبي الوعائي الكبير المرتبط بهذه الحالة. على الرغم من عدم وجود علاقة مباشرة بين شذوذات تخطيط القلب الكهربائي والأعراض القلبية، فإن النتائج تبرز الدور الحاسم لتخطيط القلب الكهربائي في الكشف عن المشكلات القلبية تحت السريرية لدى المرضى المصابين بالسكري. إن المراقبة الدورية باستخدام تخطيط القلب الكهربائي ضرورية للكشف المبكر وإدارة المضاعفات القلبية الوعائية المحتملة لدى الأفراد المصابين بداء السكري من النوع الثاني.

الكلمات المفتاحية: شذوذات تخطيط القلب الكهربائي، السكري النوع الثاني، مركب كيو ار اس مقطع.

INTRODUCTION

Introduction :

Diabetes mellitus is a common metabolic condition, characterized by excessive glucose in the blood. This disease affected 537 million individuals worldwide in 2021 (10.5% prevalence), and this is expected to rise to 783 million cases by 2045 (1).

Type 2 diabetes is the most common cause of diabetes (90% of the diabetes population) and is usually caused by insulin resistance coupled with 'relative' insulin deficiency, resulting in raised glucose levels in the blood. Individuals with Type 02 Diabetes Mellitus can be asymptomatic and can be diagnosed after presenting with Cardiovascular complications.

The correlation between diabetes mellitus (DM) and cardiovascular diseases (CVDs) stands as a primary factor contributing to illness and death among individuals with diabetes. The connection between them is complex and involves various factors, such as autonomic dysfunction, remodeling of the atria and ventricles, and molecular changes, also, hyperglycemia and insulin resistance provoke metabolic imbalance and oxidative stress which leads to augmentation of inflammation and endothelial dysfunction. Additionally, dysglycemia, dyslipidemia, and hyperinsulinemia change metabolic profiles and cellular signaling of the cardiovascular system. These factors collectively elevate the susceptibility of individuals with diabetes to cardiovascular diseases (CVDs). According to the American Heart Association, the risk of CVDs is heightened by 2 to 4 times in individuals with Type 2 Diabetes Mellitus (T2DM) compared to those without diabetes and it is also responsible for 24–30% of hospitalization and about one-third of deaths.(2) From which coronary artery disease (CAD) accounts for 75–90% of deaths(3) Therefore, it is mandatory to screen all patients with CVD for the presence of diabetes.

Electrocardiogram (ECG) is the recording of cardiac electrical activity which provides the duration and amount of electrical activity of heart as a muscle. It is frequently used in evaluating patients with suspected cardiovascular disease as a primary Diagnostic Tool. Usually, physicians do not routinely screen diabetic patients for arteriosclerosis unless the disease is suspected. Associations between minor and major electrocardiographic (ECG) abnormalities and incident cardiovascular disease (CVD) are widely observed in patients including patients with T2DM.

Few studies have assessed the prevalence and determinants of ECG abnormalities with type 2 diabetes (T2D) in the world and at least one associated the Clinical Features of it. To our knowledge, there are no local studies that were conducted to assess the ECG abnormality and its associated clinical features. This is what prompted us to carry out this work to know the prevalence and Clinical Features of ECG Abnormalities in Patients with Type 2 Diabetes in the population of Ouargla with as objectives:

Main objective:

Prevalence of electrocardiographic abnormalities in patients with type 2 diabetes and their relation to clinical features and cardiac symptoms without cardiovascular diseases: a cross-sectional study during the period 20/12/2023 -29/02/2024 in Ouargla.

Secondary objectives:

- Describe cardiac clinical features associated with ECG abnormalities.
- Determine the relationship between cardiac symptoms and ECG abnormalities.
- Elaborate recommendations to emphasize the cardiac medical health of T2DM patients.

LITERATURE REVIEW

01. Definition of diabetes mellitus :

Diabetes mellitus, DM is a metabolic disorder characterized by an elevated level of blood glucose due to defects in insulin secretion, action, or both which leads to metabolic disturbances.(4). The diagnosis of diabetes can be confirmed by demonstrating increased concentrations of glucose in venous plasma or increased A1C in the blood.

02. Epidemiology:

An estimated 537 million adults aged 20–79 years worldwide (10.5% of all adults in this age group) have diabetes. By 2030, 643 million, and by 2045, 783 million adults aged 20–79 years are projected to be living with diabetes. Thus, while the world's population is estimated to grow by 20% over this period, the number with diabetes is estimated to increase by 46%.

The incidence and prevalence of youth-onset type 2 diabetes vary by ethnicity and other factors. Populations with high incidence and prevalence of type 2 diabetes in youth also have a higher risk of type 2 diabetes among adults.

The incidence of type 2 diabetes is extremely low among pre-pubertal children but rises gradually at puberty, likely due to hormonal changes and insulin resistance associated with puberty.

MENA region:

Estimates were made for 21 countries and territories in the IDF Middle-East and North Africa (MENA) Region. A total of 31 data sources from 18 countries were used to estimate diabetes prevalence in 20–79 year-old adults in the Region.(5). Eight countries: Afghanistan, Bahrain, Egypt, Jordan, Lebanon, Morocco, Pakistan, and Tunisia, had studies conducted within the past five years. MENA Region has the highest regional prevalence at 16.2% and the second highest expected increase (86%) in the number of people with diabetes, reaching a predicted 136 million by 2045. The MENA Region has the highest percentage (24.5%) of diabetes-related deaths in people of working age. Despite being home to 13.6% of people with diabetes worldwide, only 32.6 billion USD was spent on diabetes in the MENA Region, representing 3.4% of the total spent worldwide.(5).

03. Physiopathology :

The human body maintains glycemic equilibrium around the clock, regulating glucose levels in the bloodstream and within cells. Glucose, serving as the primary energy source, undergoes conversion into pyruvate via the Krebs cycle, ultimately yielding ATP (adenosine triphosphate). Cellular uptake of glucose is facilitated by insulin, a pancreatic hormone produced by beta cells, regulating its entry. Surplus glucose is stored as triglycerides in adipose tissue and as glycogen in the liver. During periods of energy demand, glycogen is converted back into glucose through glycogenolysis, orchestrated by the pancreatic hormone glucagon. In cases of insulin deficiency or high insulin resistance, glucose accumulates in the bloodstream outside the cells, leading to cellular starvation and necessitating the search for alternative energy sources.(6) Hyperglycemia, characterized by elevated blood glucose levels, poses a significant health risk if left untreated, potentially leading to coma and even death due to the brain's inability to tolerate prolonged energy deprivation. The symptoms of both hypoglycemia and hyperglycemia share similarities, such as dizziness, blurred vision, weakness, and fatigue. However, a key distinguishing factor is the physical presentation: hypoglycemic individuals typically exhibit cold, clammy skin with heavy sweating, whereas hyperglycemic individuals often present with warm, dry skin due to dehydration resulting from excessive urination triggered by high blood glucose levels.

I. Type 1 diabetes mellitus :

Type 1 diabetes mellitus is known by the autoimmune reduction of insulin-producing cells in the pancreas by CD4+ and CD8+ T cells and macrophages which infiltrate the islets. Various features classify type 1 diabetes mellitus as an autoimmune disease:

- Immune-competent and accessory cells present and infiltrate in pancreatic islets.
- The associated susceptibility for the disease with class II genes of major histocompatibility complex and human leucocyte antigen.
- Islet-specific autoantibodies are present.
- The remarked alteration of T cell-mediated immune regulation, especially in the CD4+ T cell compartment
- The participation of monokines and TH1 cells which aid in the production of interleukins in the disease process.

- The response of the disease to immunotherapy.
- Usual occurrence of other organ-specific auto-immune disease in the affected person.

The majority of islet antibodies move against glutamic acid decarboxylase (GAD) inside the pancreatic B cells. As a result of the autoimmune destruction of the pancreatic beta cells; a deficiency in insulin secretion, which leads to metabolic derangement linked with type 1 diabetes mellitus. Besides the loss of insulin secretion, the main function of pancreatic alpha cells seems abnormal which leads to excessive secretion of glucagon. In normal cases, hyperglycemia results in a reduction of glucagon secretion, although, in type 1 diabetes mellitus patients, the glucagon secretion is not suppressed by hyperglycemia. Therefore, the result is the inappropriate elevation of glucagon which exacerbates metabolic defects because of insulin deficiency. However, insulin deficiency is considered as the primary defect in type 1 diabetes mellitus, also it was found that there is a defect in the administration of insulin. The consequences of insulin deficiency are uncontrollable lipolysis and elevation in free fatty acids in the plasma, which lead to suppression in glucose metabolism, especially in peripheral tissues, for instance, skeletal muscle. Thus, this mainly impairs the proper utilization of glucose and insulin deficiency and also reduces their function to express several genes that are significant to respond normally to insulin, such as Glucokinase which is present in the liver only and has its main function in storage of glucose as glycogen, which aids in phosphorylation of glucose to enter glycolysis and gain more ATP. In addition, it results in poor expression of the GLUT 4 class of glucose transporters which are present in the adipose tissue.(7).

II. Type 2 diabetes mellitus :

The main consequences in the pathology of type 2 diabetes are impaired insulin secretion via a dysfunction of the pancreatic beta cells, in addition, impairment of insulin action through insulin resistance. In cases where insulin resistance dominates, the mass of beta cells has been transformed and has the capability to increase the insulin supply, compensation for the excessive and anomalous demand. In other words, the plasma insulin concentration has been elevated in both fasting and feeding states.

Insulin resistance: It is believed through the primary events, that there is an initial deficit in insulin secretion and mainly this relative insulin deficiency associated with peripheral insulin resistance. The significant resistance to the insulin leads to impaired insulin-mediated glucose uptake in the peripheral, in addition, to incomplete suppressed hepatic glucose

output and impaired triglyceride uptake by fat. In order to overcome insulin resistance, a significant increase in islet cells leads to an increase in the amount of insulin secreted. Patients with type 2 diabetes have elevated and accelerated endogenous glucose production or impairment in fasting glucose. This increase happens in hyperinsulinemia.

04. Diagnosis of diabetes :

Diabetes mellitus in general, and in a very high number of cases, it is an asymptomatic condition that undiagnosed in over 40% of adults worldwide (ranging from 24% to 75% across regions)(8), for the rest of the cases, it can be suspected that the person or the patients is having different symptoms such as polyuria, polydipsia, fatigue, blurred vision, weight loss, poor wound healing, and recurrent infections(9).

Most guidelines use the standard diagnostic criteria proposed by IDF and the World Health Organization (WHO). The American Diabetes Association (ADA) considered HbA1c as part of the diagnostic criteria for diabetes and prediabetes. WHO supports the use of HbA1c ≥ 6.5% for diabetes diagnosis but not for intermediate hyperglycemia. Currently, WHO and IDF recommend the use of a 75-gram oral glucose tolerance test (OGTT) with measurement of both fasting and two-hour plasma glucose to detect **IGT** and **IFG**. However, there is accumulating evidence favoring the use of the one-hour 75-gram OGTT, which may be a more sensitive method capable of identifying intermediate hyperglycemia.(10).

A. Fasting glucose :

Fasting glucose ≥7.0 mmol/L (≥126 mg/dL) indicates diabetes, usually confirmed by two tests without symptoms. For symptomatic patients, one test suffices after 8 hours without food. International guidelines agree on diabetes criteria but differ on pre-diabetes. WHO defines pre-diabetes as fasting glucose 6.1–6.9 mmol/L (110–125 mg/dL), with <6.1 mmol/L (<110 mg/dL) as normal (11) ADA has stricter criteria, considering 5.6–6.9 mmol/L (100–125 mg/dL) pre-diabetic and <5.6 mmol/L (<100 mg/dL) normal glucose(12,13)

B. Two-hour oral glucose tolerance test and random glucose :

Using a 75g oral glucose with a 2 h interval load:

- 2h glucose ≥11.1 mmol/L (≥200 mg/dL) = diabetes.

- 2h glucose 7.8–11.0 mmol/L (140–199 mg/dL) = impaired glucose tolerance, pre-diabetes.

OGTT is not routine due to time constraints; reserved for unclear cases; performed under resting conditions.

Random glucose ≥11.1 mmol/L (≥200 mg/dL) = diabetes with symptoms; two readings needed without symptoms.

One-hour OGTT ≥8.6 mmol/L (≥155 mg/dL) has been suggested as a better predictor of diabetes than 2 h OGTT ≥11.1 mmol/L (≥200 mg/dL), and is associated with vascular complications and mortality.(9,14). However, further validation is required before this new measure is widely adopted.

C. glycated hemoglobin (Hb1c level):

HbA1c is suggested for diabetes diagnosis, endorsed by guidelines. Used in adults; and also in youth. Its advantages are: easy, consistent, and no fasting needed, and its limitations are: inaccurate in specific groups; false negatives in early diabetes; and limited availability in some areas.

Most guidelines agreed that a value of HbA1c ≥48 mmol/mol (≥6.5%) confirms diabetes. While the diagnosis of pre-diabetes uses two different cut-off values. The WHO criteria define pre-diabetes as HbA1c 42–47 mmol/ mol (6.0–6.4%), while the ADA recommends a wider range of 39– 47 mmol/mol (5.7–6.4%) (11) , Combination of Hb1c with fasting glucose in diabetes range confirms diagnosis without a second test but any discordant results need repeat or OGTT.

HbA1c is as good as or better than other tests for predicting cardiovascular risk, based on 73 studies on 294,998 individuals.

05. Classification :

According to ESC 2023, Diabetes is classified conventionally into several aetiological categories: type 1 and type 2 diabetes, Monogenic diabetes, Secondary diabetes and stress hyperglycemia, and Gestational diabetes.(9).

a) Type 1 diabetes :

Type 1 diabetes constitutes 5–10% of individuals with diabetes and is secondary to the destruction of pancreatic β-cells by an autoimmune process, with subsequent insulin deficiency. Recent guidance on diagnosing T1DM has been published.

Briefly, individuals aged ≤35 years presenting with diabetes should be suspected of having T1DM, although this condition can occur at any age. A short history of osmotic symptoms accompanied by weight loss and raised glucose levels in a younger individual is highly suggestive of T1DM. Antibody testing helps to confirm the diagnosis, although this can be negative in 5–10% of individuals with T1DM, while C-peptide helps to assess endogenous insulin production in unclear cases. (15).

b) Type 2 diabetes :

Type 2 diabetes, previously referred to as "non-insulin-dependent diabetes", or "adult-onset diabetes," is a type of diabetes mellitus that is an endocrenienne chronic disease that is defined by an elevated level of blood glucose, this happens because the insuline which is the hormone that controls the level of blood glucose is insufficient, is not used properly by the receptor cells or totally introduced. It is diagosed according to the WHO organization and the ADA association according to certain biological analyses.

Type 2 diabetes is the most common type accounting for over 90% of all diabetes worldwide. This form encompasses individuals who have relative (rather than absolute) insulin deficiency and peripheral insulin resistance and often throughout their lifetime, these individuals may not need insulin treatment to survive.

c) Monogenic diabetes

This comprises many mutations that cause glucose mishandling. Briefly, monogenic diabetes should be suspected in the presence of a strong family history of abnormal glucose metabolism in an autosomal dominant manner (i.e. successive generations with diabetes at a young age) (16). Patients diagnosed with diabetes before the age of 6 months and those not fitting the T1DM or T2DM profiles should be suspected of having monogenic diabetes.

d) Secondary diabetes and stress hyperglycemia :

Diabetes can occur secondary to various conditions and therapies. Stress hyperglycemia is not uncommon in hospitalized patients and can occur in individuals with acute coronary syndrome (ACS) or HF(17). Stress hyperglycemia without diabetes is associated with adverse in-hospital outcomes and should be suspected in those with raised glucose levels during admission and normal HbA1c(18). Such individuals are best investigated using OGTT a few weeks after discharge to rule out diabetes or impaired glucose tolerance. Some

studies suggest performing OGTT before hospital discharge but robust data supporting this approach are lacking (19,20)

e) Gestational diabetes :

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed in the second or third trimester of pregnancy that was not overt diabetes before gestation.(21) While there is still no worldwide consensus regarding the best testing strategy, the 'one-step' 75 g OGTT, also recommended by the WHO, is the preferred test in many countries. (20).

In women with GDM, repeat testing is required in the postpartum period to rule out persistent abnormal glucose metabolism. Women with GDM will require lifelong annual diabetes screening given the high risk of developing diabetes.(22–24). Also, evidence suggests that women with a history of GDM are at increased CV risk, even with normal post-partum glucose levels. Given that GDM is an important precursor of future cardiometabolic complications, women with a history of GDM should regularly be screened not only for diabetes but also for CV health. (25–28).

06. Cardiovascular complications in T2DM:

Among people with diabetes mellitus, the main cause of morbidity and mortality is still suffering from Cardiovascular diseases through microvascular and macrovascular complications. T2DM is the most prevalent form of DM that lasts long and can be undiagnosed for a long period causing them to be at higher risk to contract these complications macro-vascular diseases i.e. coronary heart disease, peripheral vascular disease, cerebrovascular disease and microvascular diseases (Diabetic retinopathy, nephropathy, and neuropathy) and above 70% of T2DM patients die due to CVDs.

As mentioned before, CVD is the first cause of death in people with T2DM, and by that a significant concern for individuals with type 2 diabetes mellitus.

a) **Heart Disease**:

Diabetes increases the risk of coronary artery disease (CAD) or atherosclerosis, which narrows and hardens the arteries that supply blood to the heart. This can lead to angina (chest pain) and, in severe cases, heart attacks.

b) **Stroke**:

People with diabetes are at a higher risk of suffering from a stroke. Elevated blood sugar levels can damage blood vessels and increase the likelihood of blood clots, which can block arteries leading to the brain.

c) **Hypertension (High Blood Pressure):**

Diabetes often goes hand in hand with high blood pressure, which can strain the heart and blood vessels, increasing the risk of heart disease and stroke.

d) **Dyslipidemia**:

Diabetes can lead to abnormal levels of cholesterol and triglycerides in the blood. High levels of "bad" LDL cholesterol and low levels of "good" HDL cholesterol can contribute to atherosclerosis.

e) **Peripheral Artery Disease (PAD**):

Diabetes can cause reduced blood flow to the limbs due to atherosclerosis, leading to symptoms like leg pain, cramping, and, in severe cases, tissue damage or amputation.

f) **Microvascular Complications**:

Diabetes can damage small blood vessels in the body. This includes those in the heart, which can contribute to heart failure over time

g) **Heart Failure**:

The risk of heart failure is higher in people with diabetes. Diabetes can weaken the heart muscle and impair its ability to pump blood effectively.

Other complications can be also serieus such as Neuropathy, Nephropathy, and diabetic retinopathy, which may lead to vision problems, including blindness. Nerve damage and poor circulation can lead to foot ulcers and, in severe cases, amputation. Gastroparesis: A condition in which the stomach takes too long to empty its contents, leading to digestive problems. There is also urgent complications such as diabetic ketoacidosis (DKA) and hyperosmolar hyperosmolar state(HHS).

Some studies suggest a link between diabetes and an increased risk of Alzheimer's disease, and tha There's a higher risk of depression in individuals with diabetes.

07. Molecular basis of cardiovascular disease in diabetes mellitus :

a. The cardiovascular continuum in diabetes mellitus :

The term "continuum" emphasizes that these cardiovascular complications can occur along a spectrum, starting from early stages of endothelial dysfunction and vascular

inflammation, progressing to the formation of atherosclerotic plaques, and eventually leading to more severe events such as myocardial infarction (heart attack) or stroke.

This continuum is driven by various pathophysiological mechanisms, including insulin resistance, hyperglycemia, dyslipidemia, and oxidative stress, which collectively contribute to the increased risk of cardiovascular disease in individuals with diabetes mellitus.

Type 2 diabetes mellitus is characterized by prolonged insulin resistance, compensatory hyperinsulinemia, and varying levels of elevated blood glucose, all of which contribute to an increased risk of cardiovascular issues and the development of macrovascular disease before diagnosis. Early stages of glucometabolic impairment involve a gradual decline in insulin sensitivity and rising glucose levels that fall below the threshold for a T2DM diagnosis, known as impaired glucose tolerance (IGT). The pathophysiological mechanisms behind this form a "glycemic continuum" spanning impaired fasting glucose (IFG), IGT, diabetes mellitus (DM), and cardiovascular disease (CVD).

The progression of cardiovascular disease in individuals with insulin resistance is gradual and marked by early endothelial dysfunction and vascular inflammation, leading to the recruitment of monocytes, formation of foam cells, and eventual development of fatty streaks. Over time, this process evolves into atherosclerotic plaques, which, when accompanied by increased inflammatory activity, become unstable and prone to rupture, leading to the formation of occlusive blood clots. Atheroma in individuals with diabetes mellitus typically exhibits higher lipid content, increased inflammation, and a greater propensity for thrombus formation compared to those without diabetes mellitus. These changes unfold over a span of 20 to 30 years and are paralleled by molecular abnormalities observed in untreated insulin resistance and type 2 diabetes mellitus(9).

b. Pathophysiology of insulin resistance in type 2 diabetes mellitus :

Insulin resistance plays a significant role in the pathophysiology of both type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), with contributions from both genetic predisposition and environmental factors. Obesity is highly prevalent in individuals with T2DM, affecting over 90% of them (29) The release of free fatty acids (FFAs) and cytokines from adipose tissue directly hamper insulin sensitivity. In skeletal muscle and adipose tissue, the production of reactive oxygen species (ROS) induced by FFAs impedes the activation of insulin receptor substrate 1 (IRS-1) and PI3K-Akt signaling pathways. Consequently, this leads to the downregulation of insulin-responsive glucose transporter 4 (GLUT4) (30).

c. Endothelial dysfunction, oxidative stress, and vascular inflammation :

FFA-induced impairment of the PI3K pathway blunts Akt activity and phosphorylation of endothelial nitric oxide synthase (eNOS) at Ser1177, resulting in decreased production of nitric oxide (NO), endothelialdysfunction (31), and vascular remodelling(increasedintima-media thickness), important predictors of CVD (32,33) In turn, the accumulation of ROS activates transcription factor NF-kB, leading to increased expression of inflammatory adhesion molecules and cytokines. (34).Chronic IR stimulates pancreatic secretion of insulin, generating a complex phenotype that includes progressive beta cell dysfunction(30), decreased insulin levels, and increased PG. Evidence supports the concept that hyperglycemia further decreases endothelium-derived NO availability and affects vascular function via a number of mechanisms, mainly involving the overproduction of ROS. (35).The mitochondrial electron transport chain is one of the first targets of high glucose, with a direct net increase in superoxide anion(O2 2)formation. A further increase inO2 2 production is driven by a vicious circle involving ROS-induced activation of protein kinase C (PKC)(36).Activation of PKC by glucose leads to up-regulation of NADPH oxidase, mitochondrial adaptor p66Shc, and COX-2 as well as thromboxane production and impaired NO release (37–39).

Mitochondrial ROS, in turn, activate signaling cascades involved in the pathogenesis of cardiovascular complications, including polyol flux, advanced glycation end-products (AGEs) and their receptors (RAGEs), PKC, and hexosamine pathway (HSP). Recent evidence suggests that hyperglycemia-induced ROS generation is involved in the persistence of vascular dysfunction despite normalization of glucose levels. This phenomenon has been called ’metabolic memory’ and may explain why macro- and microvascular complications progress, despite intensive glycaemic control, in patients with DM. ROS-driven epigenetic changes are particularly involved in this process. (36,40).

d. Macrophage dysfunction :

The heightened accumulation of macrophages in obese adipose tissue is recognized as a critical process in metabolic inflammation and insulin resistance (IR). Additionally, insulin-resistant macrophages upregulate the expression of the oxidized low-density lipoprotein (LDL) scavenger receptor B (SR-B), promoting the formation of foam cells and atherosclerosis. These effects can be reversed by activating peroxisome proliferator-activated receptor gamma (PPARg), which boosts insulin signaling in macrophages. Thus,

macrophage abnormalities serve as a cellular connection between diabetes mellitus (DM) and cardiovascular disease (CVD), exacerbating IR and contributing to the development of fatty streaks and vascular damage.

e. Atherogenic dyslipidemia :

Insulin resistance triggers an increase in the release of free fatty acids (FFAs) to the liver through lipolysis. Consequently, there is a heightened production of hepatic very low-density lipoprotein (VLDL) due to the availability of more substrates, reduced degradation of apolipoprotein B-100 (ApoB), and increased lipogenesis. In individuals with type 2 diabetes mellitus (T2DM) and metabolic syndrome, these alterations result in a lipid profile characterized by elevated triglycerides (TGs), decreased high-density lipoprotein cholesterol (HDL-C), augmented levels of remnant lipoproteins and apolipoprotein B (ApoB) synthesis, and the presence of small, dense LDL particles.(41). This particular subtype of LDL is more susceptible to oxidation, thus playing a significant role in the development of atherosclerosis. Conversely, recent research suggests that the protective effects of HDL may be compromised in T2DM patients due to modifications in the protein component, leading to an inflammatory and pro-oxidant phenotype. (42). In individuals with T2DM, the presence of atherogenic dyslipidemia serves as an independent predictor of cardiovascular risk, surpassing the impact of isolated high triglycerides or low HDL cholesterol levels. (41).

f. Coagulation and platelet function :

In patients with type 2 diabetes mellitus (T2DM), insulin resistance (IR) and hyperglycemia contribute to the development of a prothrombotic state characterized by increased levels of plasminogen activator inhibitor-1 (PAI-1), factor VII and XII, fibrinogen, and reduced tissue plasminogen activator (tPA)(43). This dysregulation is accompanied by endothelial dysfunction and vascular inflammation, mediated by factors such as adipose tissue cytokines, foam cell formation, reactive oxygen species (ROS), protein kinase C (PKC), advanced glycated end-products (AGE), AGE receptor (RAGE), phosphatidylinositide 3-kinase (PI3K), Akt, and nitric oxide (NO). These alterations in the vascular environment contribute to hypertension, diabetic cardiomyopathy, and an increased atherothrombotic risk. Furthermore, in T2DM, platelet hyper-reactivity plays a significant role in the elevated risk of coronary events. (44). Mechanisms underlying platelet dysfunction include abnormalities in platelet adhesion, activation, and aggregation. Hyperglycemia-induced disturbances in platelet calcium homeostasis, cytoskeletal integrity,

and secretion of pro-aggregant factors contribute to this dysfunction. Additionally, upregulation of glycoproteins (Ib and IIb/IIIa), P-selectin, and enhanced P2Y12 signaling are key factors driving atherothrombotic risk in both type 1 and type 2 diabetes mellitus.

g. Diabetic cardiomyopathy :

In patients with type 2 diabetes mellitus (T2DM), reduced insulin sensitivity (IS) predisposes to impaired myocardial structure and function, contributing to the increased prevalence of heart failure in this population. Diabetic cardiomyopathy is a clinical entity characterized by ventricular dysfunction in the absence of coronary artery disease and hypertension. Individuals with unexplained dilated cardiomyopathy are significantly more likely to have T2DM compared to age-matched controls. (45).

Insulin resistance (IR) adversely affects myocardial contractility by reducing calcium influx through L-type calcium channels and altering reverse mode sodium/calcium exchange. Dysregulation of the phosphatidylinositol 3-kinases (PI3K)/Akt pathway, induced by chronic hyperinsulinemia, plays a crucial role in cardiac dysfunction in T2DM. (46).

Hyperglycemia, in conjunction with IR, contributes to cardiac structural abnormalities through the accumulation of reactive oxygen species (ROS), advanced glycated end-products (AGEs) and their receptor (RAGE) signaling, and increased hexosamine flux. Activation of ROS-driven pathways impairs coronary circulation, promotes myocardial hypertrophy, and leads to fibrosis, resulting in ventricular stiffness and dysfunction. (45,47).

h. The metabolic syndrome :

Metabolic syndrome (MetS) is defined as a cluster of risk factors for CVD and T2DM, including raised blood pressure, dyslipidemia (high triglycerides and low HDL cholesterol), elevated PG, and central obesity. Although there is agreement that MetS deserves attention, there has been an active debate concerning the terminology and diagnostic criteria related to its definition. (48). However, the medical community agrees that the term ‘MetS’ is appropriate to represent the combination of multiple risk factors. Although MetS does not include established risk factors (i.e. age, gender, smoking) patients with MetS have a two-fold increase in CVD risk and a five-fold increase in the development of T2DM.

i. Endothelial progenitor cells and vascular repair :

Circulating cells originating from the bone marrow play a pivotal role in endothelial repair processes. Among these cells, endothelial progenitor cells (EPCs), a subset of adult stem

cells, are crucial for maintaining endothelial homeostasis and facilitating the formation of new blood vessels. While the precise mechanisms underlying the cardiovascular protective effects of EPCs remain unclear, studies indicate that impaired function and reduced numbers of EPCs are characteristic features of both type 1 and type 2 diabetes mellitus (T1DM) and (T2DM). Consequently, targeting these cells holds promise as a therapeutic strategy for managing vascular complications associated with diabetes mellitus (49).

In conclusion, Oxidative stress, a key player in the development of both micro- and macrovascular complications in diabetes, arises from the accumulation of free radicals within diabetic patients' vasculature. These radicals trigger harmful biochemical pathways, fostering vascular inflammation and the generation of reactive oxygen species (ROS). Despite the efficacy of intensive glycemic control and multifaceted treatment strategies in mitigating cardiovascular risk, they may not fully eliminate the risk burden. Hence, targeted therapeutic interventions are necessary. These could entail inhibiting crucial enzymes implicated in hyperglycemia-induced vascular damage or activating pathways that enhance insulin sensitivity, offering promising avenues for intervention.

08. Cardiovascular risk assessment in patients with diabetes :

Individuals diagnosed with type 2 diabetes mellitus (T2DM) face a significantly increased risk—two to four times higher—of developing cardiovascular disease (CVD) throughout their lifetime, including conditions such as coronary artery disease (CAD), stroke, heart failure (HF), atrial fibrillation (AF), and peripheral artery diseases (PAD) (50,51) (51). Furthermore, many individuals with CVD may have undiagnosed T2DM. Given the substantial impact on prognosis, particularly when diabetes and CVD occur at a younger age, it is imperative to screen individuals with CVD for diabetes and to thoroughly evaluate cardiovascular risk in those with diabetes. Additionally, assessing for both cardiovascular and kidney diseases in individuals with diabetes is crucial.(52).

01- Evaluation of cardiovascular risk in type 2 diabetes :

When evaluating cardiovascular (CV) risk in individuals with type 2 diabetes mellitus (T2DM), it is essential to consider various factors including medical and family history, symptoms, physical examination findings, laboratory tests, and the presence of atherosclerotic cardiovascular disease (ASCVD) or severe target organ damage (TOD). Currently, there is insufficient robust evidence to support the routine use of assessments such

as coronary artery calcium (CAC) scoring or intima media thickness measurements to reclassify CV risk in individuals with T2DM.

Severe TOD is defined by:

(i) Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m² regardless of albuminuria,

(ii) eGFR 45–59 mL/min/1.73 m² with microalbuminuria (urinary albumin-to-creatinine ratio [UACR] 30–300 mg/g; stage A2),

(iii) Proteinuria (UACR >300 mg/g; stage A3), or

(iv) Presence of microvascular disease in at least three different sites (e.g., microalbuminuria [stage A2] along with retinopathy and neuropathy). Please refer to Section 9.1 for chronic kidney disease (CKD) screening details.(53–55)

02- Cardiovascular risk categories in type 2 diabetes :

Individuals with T2DM should be categorized into different CV risk groups based on the following criteria (table below) :

Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk ≥20% using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 10 to <20% using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 5 to <10% using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk <5% using SCORE2-Diabetes

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Table 1: Cardiovascular risk categories in type 2 diabetes (53–55)

table 01: Cardiovascular risk categories in type 2 diabetes (53–55)

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; SCORE2-Diabetes, type 2 diabetes-specific 10-year CVD risk score; T2DM, type 2 diabetes mellitus; TOD, target-organ

damage; UACR, urinary albumin-to-creatinine ratio. Severe TOD defined as eGFR 300 mg/g; stage A3); or the presence of microvascular disease in at least three different sites [e.g. microalbuminuria (stage A2) plus retinopathy plus neuropathy] (53–55)

03- SCORE2-Diabetes: estimating 10-year cardiovascular disease risk :

In individuals over 40 with type 2 diabetes but without significant cardiovascular or severe organ damage, it's recommended to assess their 10-year cardiovascular disease (CVD) risk using the SCORE2-Diabetes algorithm. While other models like ADVANCE or DIAL were previously suggested(56–58) (57) (58), they have limitations in accurately estimating risk across European populations. These models lack recalibration to current cardiovascular trends and may not adequately reflect regional differences in risk. To address these issues, the current guidelines advocate for using the SCORE2-Diabetes model. This model incorporates traditional CVD risk factors along with diabetes-specific factors to estimate an individual's 10-year risk of heart attacks and strokes.(59,60).

The ESC CVD Risk Calculation App includes SCORE2-Diabetes to facilitate risk estimation and communication between health professionals and individuals with T2DM.

Additional risk scores like the DIAL2 model, designed to estimate lifetime cardiovascular risk in individuals with diabetes and calibrated for different European countries, can also assist in treatment decisions. (61). However, it's important to adapt lifetime risk estimation as new methods emerge. The guidelines provide thresholds for various risk categories, but it's crucial to recognize that no single threshold applies universally. The suggested risk thresholds in these guidelines, particularly for use with the SCORE2-Diabetes model, aim to facilitate discussions between clinicians and patients to guide decisions on treatment intensity and additional interventions to prevent cardiovascular disease. These may include lipid-lowering therapies, SGLT2 inhibitors, or GLP-1 receptor agonists. Nonetheless, it's emphasized that 10-year risk thresholds serve as guidance, and treatment decisions should consider individual patient characteristics regardless of these thresholds.

09. Management of diabetes mellitus and glucose-lowering medications in diabetes:

The management of DM is based on focusing on multiple s points and this also can help to maintain a stable state with this condition and prevent CVD development or at least postpone it :

Lifestyle (which should be based on maintaining a correct BMI, a regular diet and physical activity)

Lifestyle changes are crucial in preventing and managing type 2 diabetes, with interventions like weight loss, exercise, and nutritional counseling showing significant benefits in reducing HbA1c, blood pressure, and microvascular complications. However, long-term effects on cardiovascular events vary, and adherence is essential.(58)

- Weight loss exceeding 5% benefits glycemic control, lipid levels, and blood pressure in obese T2DM patients(62,63). GLP-1 RAs and SGLT2 inhibitors offer significant weight reduction and cardiovascular benefits, making them preferred treatments(64–66) . Bariatric surgery is considered for long-term weight management in T2DM patients with a BMI ≥35 kg/m² (67) .

- Change in diet or nutrition: Nutritional recommendations for T2DM include a Mediterranean-style diet with olive oil or nuts (68–70), reducing sugars and alcohol, and moderating sodium intake. High-protein diets may benefit overweight patients.(71), while reducing salt intake lowers BP and ASCVD risk(72).

- Increasing physical activity and exercise: Regular moderate to vigorous physical activity (PA) benefits T2DM by improving metabolic control and reducing CV risk factors. Combining endurance and resistance exercise reduces HbA1c, while high total PA lowers CV mortality. Structured exercise, tailored to individual needs and comorbidities, is recommended, including interval training for better outcomes. Behavior-based interventions and wearable activity trackers can promote increased PA levels and sustainability.

- Smoking cessation: Smoking cessation significantly reduces mortality in patients with T2DM, with or without CVD, by up to 36%(73–75) . Nicotine replacement therapies like patches or gum are recommended, followed by medications like bupropion if needed. Electronic cigarettes may have a role but limited duration. Continual support is crucial for long-term success despite low efficacy at 12 months.(76).

Glucose control (using different lowering glucuse treatement) :

1. **Role of glycated haemoglobin :**

Reducing HbA1c, particularly to near-normal levels (<7%, <53 mmol/mol), reduces microvascular complications in T2DM, but its impact on macrovascular disease is

intricate(77–80). Studies like DCCT and UKPDS reveal long-term reduction in macrovascular events (81–83), while shorter-term trials like ADVANCE and ACCORD fail to show significant effects. Meta-analyses suggest HbA1c lowering decreases major adverse cardiovascular events (MACE) and microvascular complications, but not stroke or heart failure. However, intensive glycemic control in higher-risk cohorts, as seen in ACCORD, may increase mortality (80). Observational data indicates a U-shaped relationship between HbA1c and clinical outcomes, challenging the notion that lower HbA1c is always better (84,85).

2. **Additional glycaemic targets :**

Hypoglycaemia is associated with an increased risk of vascular events, explaining recent consensus advocating hypoglycaemic exposure at ≤1 % in individuals at high CV risk (85,86). A causal relationship between hypoglycaemia and adverse outcomes is not always clear as low glucose levels can be a marker of ill health (87,88).

3. **Glycaemic control following vascular events :**

High blood sugar after a heart attack is linked to worse outcomes (89), The DIGAMI 1 trial found that closely managing glucose levels after a heart attack reduced mortality (90,91), However, DIGAMI 2, which was not as conclusive due to its smaller size, couldn't replicate these results. Surprisingly, DIGAMI 2 showed a potential increase in mortality among those receiving intensive glucose control, especially in patients using insulin, suggesting that hypoglycemia might harm this group (92).

Therefore, larger studies are needed, using continuous glucose monitoring, to determine if improving blood sugar levels in heart disease and diabetes patients leads to better outcomes. To sum up, managing glucose in people with diabetes and heart disease is complicated. Current evidence suggests the importance of individualizing HbA1c targets, minimizing low blood sugar events, and reducing blood sugar fluctuations.

Atherosclerotic cardiovascular disease risk reduction by glucose-lowering medications in diabetes :

Type 2 diabetes mellitus (T2DM) is prevalent among individuals with atherosclerotic cardiovascular disease (ASCVD) or those at high cardiovascular (CV) risk, and The converse is also true: ASCVD is common in patients with T2DM (93), Recognizing this bidirectional relationship is crucial when devising strategies to mitigate CV risk. Screening

all patients with CVD for T2DM should be the initial step in this process. Many treatment decisions are not solely dependent on glucose management; thus, knowing T2DM status can guide clinical decision-making for CV risk reduction, as highlighted in the current Guidelines (94).

The wealth of data from various dedicated cardiovascular outcome trials (CVOTs) investigating glucose-lowering medications in patients with diabetes and ASCVD or high CV risk enables informed choices regarding the preferred use of specific glucose-lowering drugs to mitigate CV risk, regardless of their impact on glucose levels. When prescribing glucose-lowering medications, two primary intentions may coexist: (i) improving CV outcomes and safety, and (ii) managing glucose levels. Accordingly, in the current Guidelines, recommendations for prescribing these medications are categorized into those aimed at enhancing CV outcomes and those focused on glucose control. These recommendations are grounded in findings from pivotal CVOTs that have elucidated the efficacy and safety profiles of various glucose-lowering therapies in treating T2DM and their impact on CV outcomes.

4. Glucose-lowering medications that have shown cardiovascular efficacy in dedicated cardiovascular outcomes trials include:

01- ISGLT 2 :

The cardiovascular outcomes of sodium-glucose co-transporter-2 (SGLT2) inhibitors have been investigated in several dedicated trials (64,95–99).

A meta-analysis of the six trials investigating SGLT2 inhibitors revealed a reduction in the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke (MACE), particularly notable in patients with established atherosclerotic cardiovascular disease (ASCVD). Interestingly, dapagliflozin and ertugliflozin did not show significant reductions in MACE risk but demonstrated consistent benefits in reducing heart failure (HF) hospitalizations, a benefit observed across the class of SGLT2 inhibitors.

Based on these collective findings, along with evidence from trials of GLP-1 receptor agonists, SGLT2 inhibitors are preferred as glucose-lowering therapy for patients with type 2 diabetes mellitus (T2DM) and ASCVD, irrespective of glucose control considerations and without regard to background metformin use. While the meta-analysis did not show a statistically significant reduction in MACE risk in patients without ASCVD but with

multiple risk factors for ASCVD, the favorable trend persisted in this subgroup. There was no significant interaction by ASCVD status(100–102).

02- Glucagon-like peptide-1 receptor agonists :

The cardiovascular outcomes of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been assessed in several trials (64,66,103–108)

Among the eight GLP-1 RA trials, five demonstrated superior cardiovascular outcomes on the primary composite endpoint of time to the first event of myocardial infarction (MI) and stroke compared to placebo.

A meta-analysis of seven of these completed GLP-1 RA trials showed a pooled estimate indicating a 15% reduction in the primary outcome (HR 0.85; 95% CI, 0.80–0.90). Additionally, GLP-1 RAs reduced the risks of cardiovascular death, MI, stroke, and hospitalization for heart failure.

The meta-analysis suggested a potential greater risk reduction in those with established ASCVD compared to those without, although this difference was not conclusive (100–102).

03- Pioglitazone:

The PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) randomized cardiovascular outcomes trial (CVOT) investigated the cardiovascular effects of the thiazolidinedione (TZD) pioglitazone compared to placebo, irrespective of its impact on glucose control, in patients with type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD). However, it did not achieve statistical significance for its primary composite outcome, which included all-cause death, myocardial infarction (MI), stroke, unstable angina, coronary or peripheral revascularization, and amputation (HR 0.90; 95% CI, 0.80–1.02) (109).

In contrast, for the principal secondary outcome assessing the gold-standard three-point composite endpoint of cardiovascular death, myocardial infarction, and stroke, there was a statistically significant 16% relative risk reduction (HR 0.84; 95% CI, 0.72–0.98) (109).

Pioglitazone, a thiazolidinedione (TZD), has shown potential benefits in individuals with atherosclerotic cardiovascular disease (ASCVD), supported by subsequent meta-analyses and observational studies. These findings align with the cardiovascular benefits

observed with other classes of medications like sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

However, it's important to note that TZDs, including pioglitazone, come with certain risks. They can increase fluid retention, leading to peripheral edema, especially when used alongside insulin or in individuals with kidney issues. Additionally, TZDs raise the risk of heart failure, primarily due to expanded plasma volume, though no evidence suggests myocardial toxicity.

Another concern with TZDs is weight gain, attributed to adipose tissue expansion. However, this weight gain tends to redistribute to less metabolically active areas. Despite these considerations, given the overall benefit-risk assessment, pioglitazone may be considered as a strategy to reduce ASCVD risk in patients with type 2 diabetes and existing ASCVD(110–124).

5. Glucose-lowering medications that exhibit cardiovascular safety without showing additional effectiveness in dedicated cardiovascular outcomes trials :

01- Dipeptidyl peptidase-4 inhibitors :

Five randomized cardiovascular safety trials, conducted in populations with type 2 diabetes mellitus (T2DM) or at high risk of atherosclerotic cardiovascular disease (ASCVD), evaluated the cardiovascular effects of dipeptidyl peptidase-4 (DPP-4) inhibitors. These trials included saxagliptin, alogliptin, sitagliptin, and linagliptin, each compared to placebo, and linagliptin compared to glimepiride (116–119) .

All four of the placebo-controlled trials showed statistical non-inferiority but not superiority for the DPP-4 inhibitors regarding the primary major adverse cardiovascular events (MACE) endpoint. However, in the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53) trial, saxagliptin significantly increased the risk of hospitalization for heart failure compared to placebo (120,122–124) .

02- Lixisenatide and exenatide :

Of the eight glucagon-like peptide-1 receptor agonists (GLP-1 RAs) evaluated in cardiovascular outcomes trials (CVOTs), this two have demonstrated safety without showing incremental efficacy (103,104).

03- Insulin :

Two basal insulins have undergone formal evaluation in dedicated cardiovascular outcomes trials (CVOTs).

In the ORIGIN (Outcome Reduction With Initial Glargine Intervention) trial, 12,537 patients (with a mean age of 63.5 years) at high cardiovascular disease (CVD) risk, presenting with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or type 2 diabetes mellitus (T2DM), were randomized. They received either insulin glargine titrated to achieve a fasting blood glucose level of ≤5.3 mmol/L (≤95 mg/dL) or standard care. After a median follow-up of 6.2 years, there was no significant difference in the incidence of cardiovascular outcomes between the two groups.

Similarly, the DEVOTE (A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events) trial compared the ultra-long-acting once-daily insulin degludec with insulin glargine U100 in 7,637 patients with T2DM who had atherosclerotic cardiovascular disease (ASCVD) or were at high cardiovascular risk. Over a median follow-up of 1.8 years, there was no significant difference in the primary composite outcome of cardiovascular death, non-fatal myocardial infarction (MI), or nonfatal stroke between the two treatment groups. Notably, the degludec arm exhibited a significantly lower frequency of hypoglycemia compared to the glargine arm. (125,126).

04- Glimepiride :

The statistical non-inferiority of linagliptin compared to placebo in the CARMELINA trial, combined with its non-inferiority versus glimepiride as shown in the CAROLINA trial, suggests that glimepiride likely poses a cardiovascular safety profile similar to placebo. Consequently, the historical uncertainty surrounding the cardiovascular safety of sulfonylureas may no longer hold clinical relevance for glimepiride, especially in patients with a shorter duration of diabetes, as observed in the CAROLINA trial (median duration of type 2 diabetes mellitus approximately 6 years) (124,127).

- Cardiovascular considerations of older glucose-lowering medications not tested in dedicated cardiovascular outcomes trials :

05- metformin :

Despite being the recommended first-line treatment for hyperglycemia in patients with type 2 diabetes mellitus (T2DM), metformin has not been rigorously assessed for cardiovascular (CV) safety or efficacy in dedicated randomized trials. Existing trials are often limited by small sample sizes and few CV events, resulting in low statistical power and uncertain estimates.

The largest randomized trial with promising CV outcomes for metformin was a nested study within the UK Prospective Diabetes Study (UKPDS). In overweight or obese patients with newly diagnosed T2DM without previous cardiovascular disease (CVD), metformin reduced the risk of myocardial infarction (MI), coronary death, and stroke over a median follow-up of 10.7 years. However, the precision of these efficacy estimates remains uncertain due to the small number of events in the metformin arm.

Meta-analyses of randomized clinical trials comparing metformin to placebo or active control did not find statistically significant differences in assessed CV outcomes, providing reassurance about the CV safety of metformin. Despite inconclusive evidence on CV effects, metformin is not considered a prerequisite for considering treatment with sodium-glucose co-transporter-2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for CV benefits. However, in patients already on metformin, adding SGLT2 inhibitors and/or GLP-1 RAs is recommended, regardless of additional glucose control needs(83,128–130).

06- Sulphonylureas :

With the exception of glimepiride, which was directly compared to linagliptin in the CAROLINA trial, and gliclazide-modified release, which was assessed against usual care in the ADVANCE trial, other sulfonylureas have not undergone dedicated cardiovascular safety assessments. In the UK Prospective Diabetes Study (UKPDS), which included patients with newly diagnosed type 2 diabetes mellitus (T2DM), chlorpropamide and glibenclamide (also known as glyburide) did not show statistically significant effects on cardiovascular outcomes, and no concerning signals of cardiovascular risk were observed.(UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) (78,79,83,117,118,129,131,132).

Similarly, in the ADVANCE trial, where patients were randomized to more intensive glucose control using gliclazide-modified release, there were no major cardiovascular safety concerns despite the lack of significant improvements in cardiovascular outcomes.

The comparative cardiovascular safety of gliclazide and glimepiride finds some support from contemporary real-world data analyses.

- Special considerations

Hypoglycaemia and cardiovascular risk :

The data based on a cosidered number of studies indicates that the connection between hypoglycemia events and cardiovascular risks (and vice versa) is likely more about association than direct causation, indicating the vulnerability and frailty of high cardiovascular-risk patients. However, in some cases, hypoglycemia might directly impact cardiovascular risk. Nonetheless, it's crucial to avoid hypoglycemia due to its unpleasant patient experience and, in severe cases, life-threatening nature if third-party assistance isn't available.

Effects on weight :

The selection of glucose-lowering therapy is frequently influenced by its impact on weight, especially when weight management is a priority. Insulins, sulfonylureas, and pioglitazone are known to cause weight gain, while metformin, acarbose, and DPP-4 inhibitors are weight-neutral or may lead to minor weight loss. On the other hand, SGLT2 inhibitors and GLP-1 receptor agonists are associated with significant weight loss, with GLP-1 receptor agonists often inducing more pronounced weight reduction compared to SGLT2 inhibitors.

- implications of results from cardiovascular outcomes trials of glucose-lowering medications :

The mechanisms underlying the cardiovascular benefits of novel glucose-lowering medications with established efficacy are not fully understood. For GLP-1 receptor agonists (GLP-1 RAs), cardiovascular efficacy is primarily driven by a reduction in atherosclerotic cardiovascular disease (ASCVD)-related events. On the other hand, SGLT2 inhibitors demonstrate improvements in heart failure (HF)-related endpoints and slowing the progression of kidney disease. Consequently, SGLT2 inhibitors are recommended for

reducing HF hospitalizations in patients with type 2 diabetes mellitus (T2DM) who have HF or chronic kidney disease (CKD) or are at risk of developing HF. In individuals with newly diagnosed T2DM without CVD or other significant cardiovascular risk factors at low or moderate risk, various factors such as affordability, accessibility, side effects, weight benefits, tolerability, and ease of use may influence the choice of glucose-lowering medications more than mitigating cardiovascular and kidney risks.

6. Multifactorial approach to risk-factor management in diabetes :

Management of type 2 diabetes mellitus (T2DM) necessitates meticulous attention to risk factors and lifestyle modifications, alongside prompt identification and treatment of associated conditions. The Swedish National Diabetes Registry highlights the tangible benefits of maintaining key parameters such as HbA1c, LDL-C, albuminuria, smoking status, and blood pressure within specified target ranges. Notably, individuals with advanced T2DM and microalbuminuria experienced a noteworthy reduction in microvascular and macrovascular events through intensive, goal-oriented, multifaceted therapy as demonstrated by the Steno-2 study. However, similar outcomes were not consistently observed in primary care settings or in the early stages of disease progression, as evidenced by the ADDITION and J-DOIT3 trials, and the Look AHEAD trial focusing on lifestyle interventions.

Challenges persist in effectively managing patients with both T2DM and cardiovascular disease (CVD), including underdiagnosis of T2DM among individuals with CVD, inadequate referrals to diabetes specialists, and difficulties in sustaining adherence to treatment regimens. The EUROASPIRE V survey revealed suboptimal rates of adherence to cardioprotective medications and achievement of target blood pressure and lipid levels among patients with T2DM and CVD. The concept of a polypill may offer promise in secondary cardiovascular prevention.

Moreover, maintaining adherence to lifestyle modifications over time remains a challenge, with weight regain commonly observed. The 2021 ESC Guidelines advocate for a stepwise approach to address risk factors and treatment intensification, emphasizing patient-centered care and shared decision-making. Individualized risk assessment, considering comorbidities, age, frailty, and patient preferences, is paramount in tailoring treatment strategies. Notably, a stepwise approach to treatment intensification has shown promise in improving outcomes and patient satisfaction. Multidisciplinary interventions,

such as the Italian Diabetes and Exercise Study 2, underscore the importance of combining behavioral and psychological support with dietary recommendations for optimal outcomes.

Effective clinician-patient communication is essential for fostering understanding, adherence, and motivation. Motivational interviewing techniques and multidisciplinary approaches can enhance patient engagement and treatment adherence. Furthermore, mobile health applications may offer additional support, although further research is needed to ascertain their efficacy, particularly in individuals with both CVD and T2DM. Individualized education methods, such as tailored SMS support programs, may hold promise but require further investigation regarding their impact on glycemic control in poorly controlled diabetes.(133–154) .

10. The Electrocardiogram (ECG) in Diabetes Mellitus: A Window into Cardiovascular Risk :

The electrocardiogram (ECG) is a simple, non-invasive tool that provides valuable insights into the electrical activity of the heart. In the context of diabetes, ECG plays a crucial role in:

Indications for ECG in Diabetes:

1. Screening for Silent Ischemia: Diabetics often experience "silent ischemia," where heart muscle damage occurs without chest pain.
2. Detection of ischemia, prompting further investigation with stress tests or imaging studies.
3. Baseline Assessment: An ECG at the time of diabetes diagnosis establishes a baseline for comparison in future evaluations. It can also help identify pre-existing cardiac conditions.
4. Monitoring Treatment Efficacy: Drugs used to manage diabetes can sometimes have side effects on the heart rhythm. An ECG can be used to monitor for these potential complications.
5. Pre-operative Evaluation: Before undergoing surgery, particularly for non-cardiac procedures, an ECG helps assess the risk of peri-operative cardiac events.
6. Evaluation of Symptoms: If a diabetic patient experiences symptoms suggestive of heart problems, like palpitations, shortness of breath, or chest tightness, an ECG can help identify potential underlying arrhythmias or ischemic events.

ECG Signs in Diabetic Patients:

Fibrotic changes, particularly in the basal region of the left ventricle, have frequently been observed in patients with diabetes, even in cases where cardiac issues are not yet clinically apparent.

Even in individuals without diabetes, high levels of insulin in the blood, a condition known as hyperinsulinemia, can lead to prolonged QTc intervals and a reduction in T-wave area and amplitude. The EURODIAB study, which focused on individuals with diabetes but normal QTc intervals at the outset, revealed that a higher risk of prolonged QTc was associated with female sex, elevated hemoglobin A1C levels, and higher systolic blood pressure. Conversely, physical activity and a normal body mass index served as protective factors. The study also identified a correlation between QT duration and the presence of coronary calcium, primarily driven by the QRS interval rather than the JT interval.

Okin and colleagues found that both QTc prolongation and ST depression were predictive of all-cause mortality in patients with type 2 diabetes. Genetic variations in previously identified candidate genes may be linked to the duration of the QT interval in individuals with diabetes.

Sawicki and his team discovered that QT dispersion was the most significant independent predictor of total mortality and also an independent predictor of cardiac and cerebrovascular mortality. However, these findings were not confirmed in a subsequent study.

In the EURODIAB Insulin-Dependent Diabetes Mellitus Complications Study, which involved 3,250 type 1 diabetes patients with an average diabetes duration of approximately 30 years, the prevalence of left ventricular hypertrophy was three times higher than in the general population of a similar age. In another study led by Okin, almost 9,000 non-diabetic hypertensive patients were followed up. During this follow-up, cases of regression or the persistent absence of left ventricular hypertrophy on the ECG, as a result of antihypertensive treatment, were associated with a reduced incidence of new-onset diabetes mellitus.

There’s also a Fragmented QRS complex: This abnormality suggests the presence of scar tissue within the heart muscle and is associated with a higher risk of complications in diabetics. (155). Though the relationship between fQRS and T2DM isn't fully understood, there are some studies that show that there’s still a connection :

- Increased Prevalence: Studies have shown a higher prevalence of fragmented QRS complex in people with diabetes compared to those without (155).

- Potential Mechanism: Diabetes can contribute to heart muscle damage through various mechanisms like high blood sugar levels and inflammation. This damage can manifest as scar tissue or fibrosis, which is what a fragmented QRS complex might indicate on an ECG.

- Independent Risk Factor: While diabetes can worsen heart health, some studies suggest that a fragmented QRS complex in diabetic patients might be an independent risk factor for adverse outcomes(155). This means that even for diabetics with seemingly well-controlled conditions, a fragmented QRS could indicate a higher risk of complications.

About fragmented QRS:

Fragmented QRS (QoS) is an anomaly detected on an electrocardiogram (ECG) that indicates the presence of scar tissue or fibrosis within the heart muscle (156,157), An ECG is a test that records the heart's electrical activity, whereas a normal tracing displays a specific pattern of waves corresponding to the different stages of the heartbeat. The QRS complex is a series of waves on the ECG representing the electrical impulse spreading through the heart muscle, causing it to contract. In the case of a fragmented QRS complex, it can be defined as the presence of additional R′ waves or a notch in the nadir of the R or S wave (fragmentation) in two contiguous leads corresponding to a coronary territory in a routine 12-lead ECG (0.5–150 Hz). Fragmented wide QRS (f-wQRS) is defined as two or more notches in the R or S wave, in two contiguous leads corresponding to a coronary territory (anterior, lateral, or inferior). The notches should be separated by at least 40 ms. (157,158).

Causes of Fragmented QRS:

A fragmented QRS complex can result from various conditions that damage the heart muscle, including(157,159):

- Coronary artery disease (CAD)

- Myocardial infarction (heart attack)

- Myocarditis (inflammation of the heart muscle)

- Cardiomyopathy (weakening of the heart muscle)

- Dilated cardiomyopathy

- Hypertrophic cardiomyopathy

- Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Clinical Significance of Fragmented QRS:

The presence of a fragmented QRS complex on an ECG is linked to an increased risk of several adverse outcomes, such as (157,159):

- Sudden cardiac death

- Arrhythmias (irregular heartbeats)

- Heart failure

- Worse prognosis in patients with various heart conditions

How is Fragmented QRS Diagnosed:

A fragmented QRS complex is diagnosed through the examination of a 12-lead ECG. There are no specific criteria for diagnosing a fragmented QRS, and it can sometimes be challenging to distinguish it from other ECG abnormalities. However, physicians generally look for the presence of multiple spikes or deflections within the QRS complex, especially in certain leads (electrical views) of the ECG. (156).

Management of Fragmented QRS:

The management of a fragmented QRS complex depends on its underlying cause. If due to CAD, treatment will focus on improving blood flow to the heart with medications, lifestyle changes, or coronary artery bypass surgery. (157) If the fragmented QRS results from another condition, such as myocarditis, treatment will address the underlying cause.

ECG Measures of Cardiac Autonomic Neuropathy:

The most commonly utilized methods for assessing Cardiovascular Autonomic Neuropathy (CAN) involve evaluating baroreflex dysfunction and disturbed heart rate variability. Pop-Busui and their team demonstrated the protective effects of intensive therapy in reducing cardiac complications among patients with type 1 diabetes mellitus. In 24-hour ECG recordings, both time and frequency domain analyses indicated similarities between day and night recordings, primarily due to reduced nighttime vagal modulation of heart rate in these patients. In a prospective study involving the general population, individuals with a high resting heart rate and low heart rate variability were found to be at an increased risk for future development of diabetes mellitus. Ong and colleagues observed that the QTc interval was shorter in patients displaying signs of neuropathy, even though these patients had higher heart rates, and their circadian patterns appeared preserved. Valensi and their team identified an unchanged QTc interval in mild neuropathy, although the circadian day/night QTc pattern was reversed.

Pappachan and colleagues suggested that the QTc interval could reasonably be used to diagnose CAN with a good balance of sensitivity, specificity, and positive predictive value. Grossmann and their team observed a prolonged QTc interval only in diabetic patients with CAN; late potentials were not recorded in any of these patients with CAN. Individuals with CAN who exhibited prolonged variability in QTc, QT, or both experienced a higher incidence of sudden death.

Detection of Silent Ischemia in Diabetic Patients:

Myocardial ischemia often occurs without pain in patients with diabetes mellitus. Resting ECG abnormalities, as well as cardiac autonomic dysfunction, have been identified as predictors of silent ischemia in individuals with asymptomatic type 1 diabetes.

In a study of otherwise healthy diabetic men, conducted over an average follow-up period of 16 years, an abnormal or even equivocal exercise ECG response was associated with a significantly higher risk of all-cause and cardiac mortality and morbidity. This risk was independent of physical fitness and other traditional risk factors. It was observed that physically fit men had a higher rate of survival compared to unfit men.

For asymptomatic type 2 diabetes patients with a normal resting ECG, exercise testing was the preferred method for screening for silent ischemia. Thallium scintigraphy with dipyridamole was considered when exercise testing was either not possible or yielded

inconclusive results. Stress ECG was found to be accurate at 79%, with coronary arteriography serving as the gold standard. Combining stress ECG with myocardial scintigraphy, Cosson and colleagues were able to effectively detect coronary artery lesions in individuals with asymptomatic diabetes mellitus.

The use of screening before initiating an exercise training program for patients with asymptomatic type 2 diabetes mellitus remains a topic of debate and is described as "justifiable but unproven" in a recent scientific statement by the American Heart Association.

Signs of Diabetes Mellitus:

Yli et al. demonstrated a significantly higher prevalence of ST depression in fetal ECGs from mothers with diabetes. In children with an average hemoglobin A1c level exceeding 10%, a reduction in heart rate variability was found to be a predictive indicator for the onset of symptomatic neuropathy.

Shiono and colleagues conducted a study on children and adolescents aged 7 to 20 years who had poor glycemic control (hemoglobin A1c levels exceeding 10%). They used signal-averaged ECG and discovered a prolonged filtered QRS duration and a significantly lower root mean square voltage. These findings highlighted subclinical cardiac impairment in this group.

Diabetic Cardiomyopathy:

The preclinical phase of diabetic cardiomyopathy can be identified by showcasing exercise-induced left ventricular dysfunction, even when the resting cardiac function remains within the normal range. In the early stages of diabetic cardiomyopathy, various metabolic abnormalities and diastolic function issues may already be present. It's common not to find any structural cardiac abnormalities at this point, making subtle ECG changes one of the primary methods for diagnosing early diabetic cardiomyopathy.

MATERIALS AND METHODS

1. Type of study:

This cross-sectional descriptive study employed qualitative and quantitative methods of data collection during the period from 20/12/2023 to 29/02/2024, at the Public diabetic care center in OUARGLA.

2. Study population:

The study involved 215 patients with type 2 diabetes mellitus who are followed in the diabetic care center in Ouargla, Diabetic patients getting follow-up service in this center are usually appointed in two to three months regularly.

3. Subject's inclusion and exclusion criteria:

All the patients aged above eighteen (≥18) however their age or sex that have type 2 diabetes were included.

3.1. Inclusion criteria:

All adult type 2 diabetic patients who were on follow-up at the diabetic care center in Ouargla were a source population. The study population was all randomly selected adult type 2 diabetic patients on follow-up at the center during the study period and who fulfilled the eligibility criteria. All type 2 diabetic patients aged 18 years and above, who had no prior diagnosis of cardiovascular diseases were included in this study.

3.2. Exclusion criteria:

Type 2 diabetic patients who were mentally impaired and unable to give information, or had diagnosed CVDs were excluded.

4. Data collection:

The information that was collected about patients was consulted by the interns after finishing their consultation on a technical file and it was either given by the patient himself or extracted from his medical file that contains the clinical and paraclinical examination, with the recording of a resting ECG using a CardiofaxC ECG-2150 model Device.

4.1. Technical file:

It contains variables such as sociodemographic factors (age, sex, educational status, Addressee or Number), behavioral factors (alcohol, tobacco), factors related to a medical condition (duration of diabetes, other diseases, high blood pressure, atrial fibrillation), patient's Pre-existent CVD or Complications, Family history of coronary artery disease or any lung diseases, Anthropometric variables measurements included height, weight from which Body Mass Index (BMI) was calculated. Systolic and diastolic blood pressures were measured at the upper right/left arm after 5 min of rest with participants in a seated position, using an automatic oscillometric digital blood pressure device.

The abdominal perimeter was not calculated due to the shortness of the consultation.

Cardiac symptoms were described and self-reported, such as dyspnea with its NIHA classification if present, chest pain and its characteristics, palpitation, Syncope & Fainting, and other cardiac symptoms related to diabetes complications if present.

Medication use, Information on medication use was obtained by the name of the drug, prescribed quantity, and dosage, and the Therapeutic Chemical classification code. The use of glucose-lowering medication was classified as no medication, only oral medication, only insulin use, and oral and insulin use, the oral medication and insulin classes were detailed. Other medications such as antihypertension medication were classified according to their effect, and antiplatelets and statins were mentioned.

Hypertension was defined as elevated blood pressure (systolic >140
mmHg or diastolic >90 mmHg) and/or antihypertensive medication. It was also considered present when self-reported by the patients.

The SCORE2 prediction for T2DM CVD's complications provides data on the 10-year risk of fatal and non-fatal CVD events (myocardial infarction [MI], stroke) based on individual patient characteristics. SCORE2-Diabetes serves as a guide for clinical decision-making in patients with T2DM at low, moderate, high, or very high risk, but without clinically overt ASCVD or severe TOD, According to the European Society of Cardiology guidelines, which is based on sex, age, systolic blood pressure, total cholesterol, and smoking status … etc. it was calculated for patients (≤69 years old), for older patients the SCORE OLD PERSON was used.

4.2. Other measurements:

Biological measurements like Glycated hemoglobin (HbA1c), Fasting blood glucose, Total cholesterol, HDL cholesterol, and triglycerides, LDL cholesterol, creatinine, urea were obtained through the medical file (only measurements during the last six months were accepted).

The urinary albumin creatinine ratio (UACR) was obtained if found in the medical file. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation. The eGFR was categorized as high (eGFR >120 ml/min) or normal (eGFR 120-90 ml/min), mildly decreased (eGFR 60–90ml/min), moderately decreased (eGFR 30–60 ml/min) or severely decreased (eGFR <30 ml/min). Albuminuria was categorized as normal to mild (UACR <3 mg/mmol), microalbuminuria (UACR 3–30 mg/mmol), or macroalbuminuria (UACR >30 mg/mmol).

4.3. ECG abnormality:

During the examination, a standard, resting 12-lead ECG was recorded,

Electrocardiography records the heart's electrical activity using the ECG machine by placing electrodes on the surface of the body.

Any ECG change beyond normal sinus rhythm (ST-segment elevation or depression, T-wave aberrations (inversion or tall T-wave), AV nodal block, bundle branch block, chamber enlargement, and dilatation, ventricular hypertrophy, arrhythmias, fQRS, and prolonged QT intervals…. etc).

5. Data analysis:

Data were entered and analyzed in the IBM SPPS statistics program version 25. The illustrations (graphs and charts….) were obtained using Excel Microsoft 2019.

6. Data presentation:

Data were presented as frequency tables and bar graphs.

Inferential statistics were presented in relation to their level of significance.

7. Ethical statement:

No clinical experiment was conducted on humans in this study.

All the patients were informed in advance that participation in the study was voluntary and the identities of those who participated were withheld throughout the study. The purpose of the study was explained to them, and those who were willing to

Participants provided verbal consent in advance.

RESULTS

I. Population:

1. Age distribution:

The bar chart below represents the repartition of the population according to age: the average age of the population was 57 years old with extremes ranging from 26 years to 88 years. the median of our series is 58 Years. The modal age group is between 51 to 60 years.

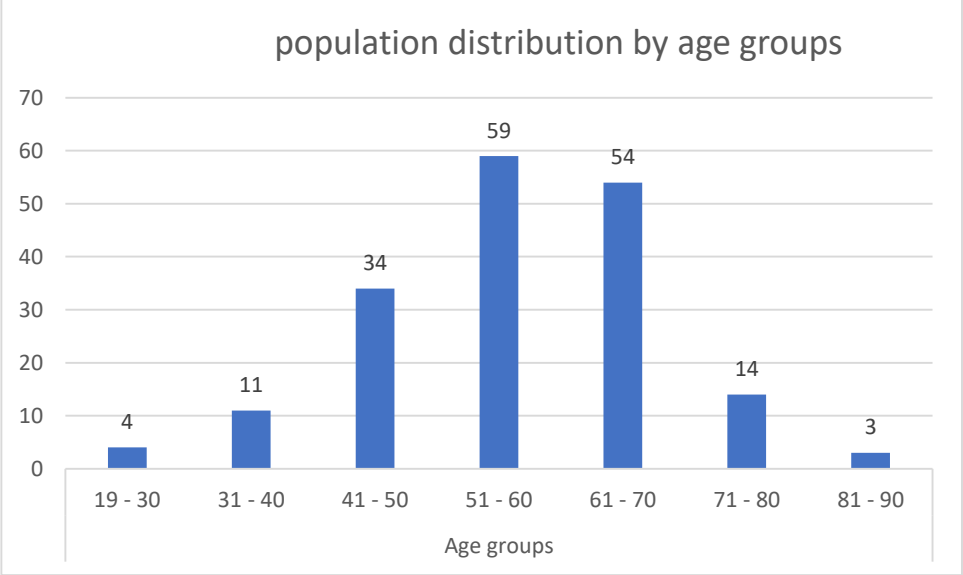

Figure 1: population distribution by age groups

2. Gender distribution:

As presented in the pie chart below the majority of our population was female patients (n= 129. 67,5%) when the percentage of male patients was (n=62. 32,5%).

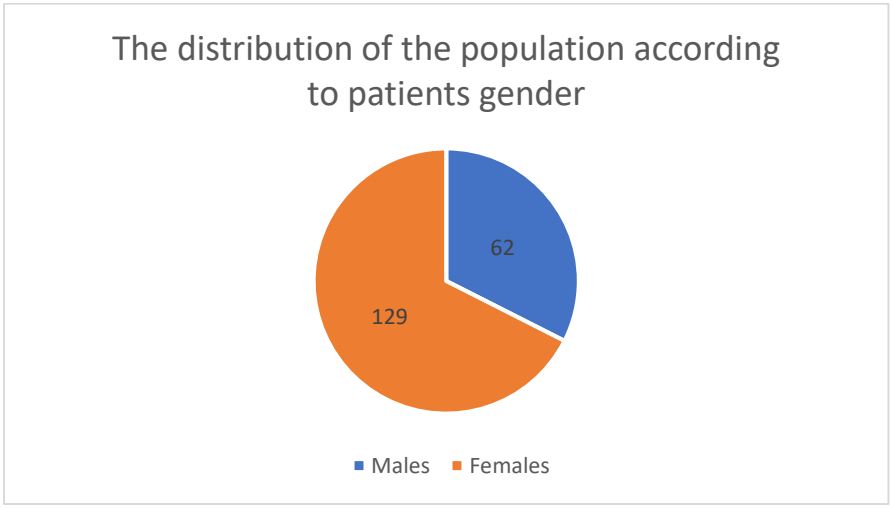

Figure 2: The distribution of the population according to patients' gender

3. Educational level distribution:

Approximately, ¼ of the population was not educated while only 6.8% of them have passed to finish their studies.

Table 2: Educational level distribution

		Frequency	Percent	Valid Percent	Cumulative Percent
Education level	No Education	50	26.2	26.2	26.2
	Primary	44	23.0	23.0	49.2
	Middle	25	13.1	13.1	62.3
	Secondary	59	30.9	30.9	93.2
	University	13	6.8	6.8	100.0
	Total	191	100.0	100.0	

4. Diabetes duration:

The graph below shows the repartition of 191 patients across six categories of diabetes duration:

Most people (n= 138, 73.7 %) have had diabetes for less than 15 years. The distribution across the first five categories (under 20 years with diabetes) is relatively even. There are 16 people (8.4%) in the category with over 20 years of diabetes.

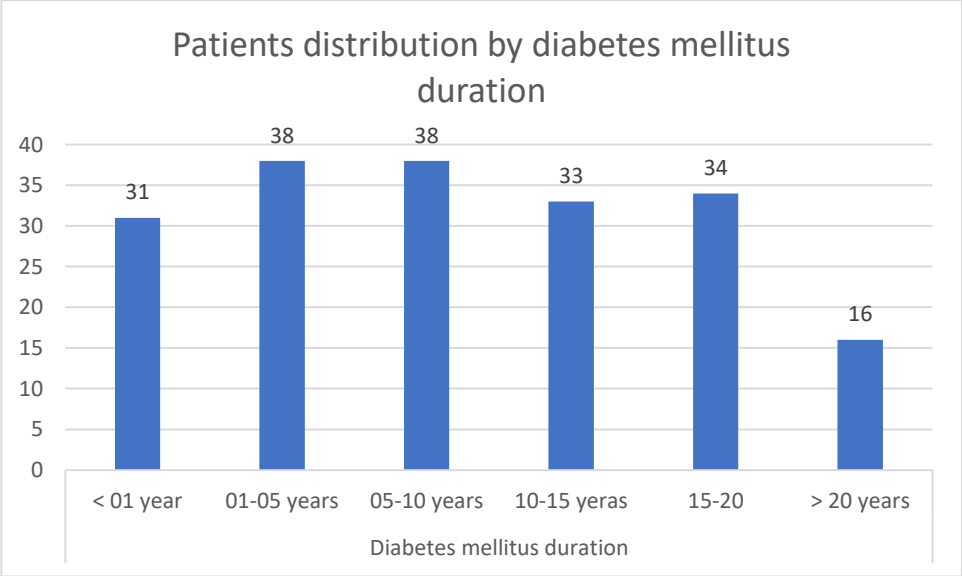

Figure 3: Patient distribution by diabetes mellitus duration

II. ECG ABNORMALITIES DISTRIBUTION IN T2DM PATIENTS:

01. The prevalence of ECG abnormalities in the population of patients with type 2 diabetes mellitus (the research population n=191):

The prevalence of ECG abnormalities in our population is 79.1 % as shown in the bar chart below.

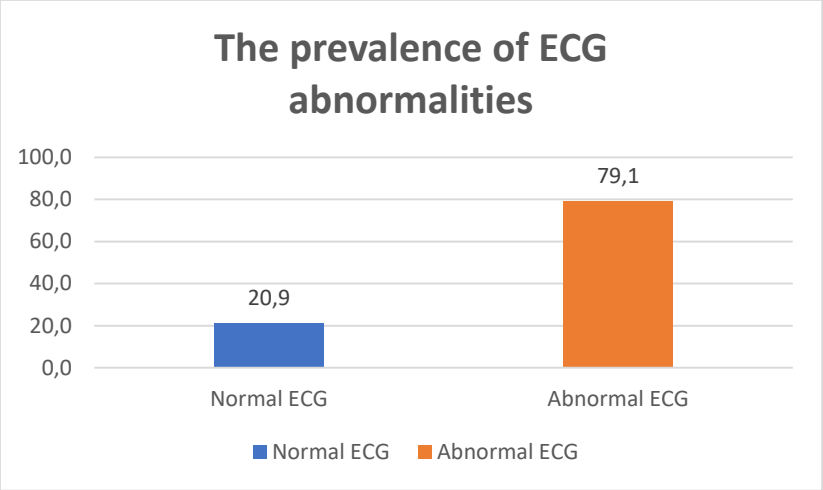

Figure 4: The prevalence of ECG abnormalities

02. The distribution of ECG abnormalities according to the type of abnormality:

The distribution of ECG abnormalities in our population is arranged in the following order: the most present abnormality is FQRS (n=96) followed by ST segment and T wave abnormalities, the least found abnormalities are Atrial Fibrillation and left atrial enlargement, while 0 ECG showed un atrial flutter nor second and third-degree atrioventricular blocks, left fascicular block and premature ventricular contraction are also absent In our population.

Table 3: The distribution of ECG abnormalities according to the type of abnormality

		Count	Percentage
ECG abnormalities	**Left ventriculair Hypertrophy**	**20**	**8.51%**
	Right atrial enlargement	**4**	**1.70%**
	Left atrial enlargement	**1**	**0.43%**
	Atrial fibrillation	**1**	**0.43%**

	Atrial flutter	0	0.00%
	Complete left bundle branch block	3	1.28%
	Complete right bundle branch block	2	0.85%
	First-degree atrioventricular block	5	2.13%
	Second-degree atrioventricular block	0	0.00%
	Third-degree atrioventricular block	0	0.00%
	Incomplete left bundle branch block	2	0.85%
	Incomplete right bundle branch block	11	4.68%
	Left anterior fascicular block	15	6.38%
	Left posterieur fascicular block	0	0.00%
	Premature atrial contraction	2	0.85%
	Premature ventriculair contraction	0	0.00%
	Poor R wave progression	2	0.85%
	ST abnormality	24	10.21%
	Tw abnormality	45	19.15%
	Abnormal Q w	2	0.85%
	FQRS	96	40.85%
	Total	235	100.00%

03. The distribution of ECG abnormalities according to the type of abnormality.

The distribution of ECG abnormalities according to their type in our population is arranged in the following order: the most present type of abnormality is ischemic and repolarization abnormalities (n=121) followed by conduction abnormalities (n= 35), then axis deviation and hypertrophy which are approximately even.

The least type of abnormality is arrhythmias with a percentage of (4.7%)

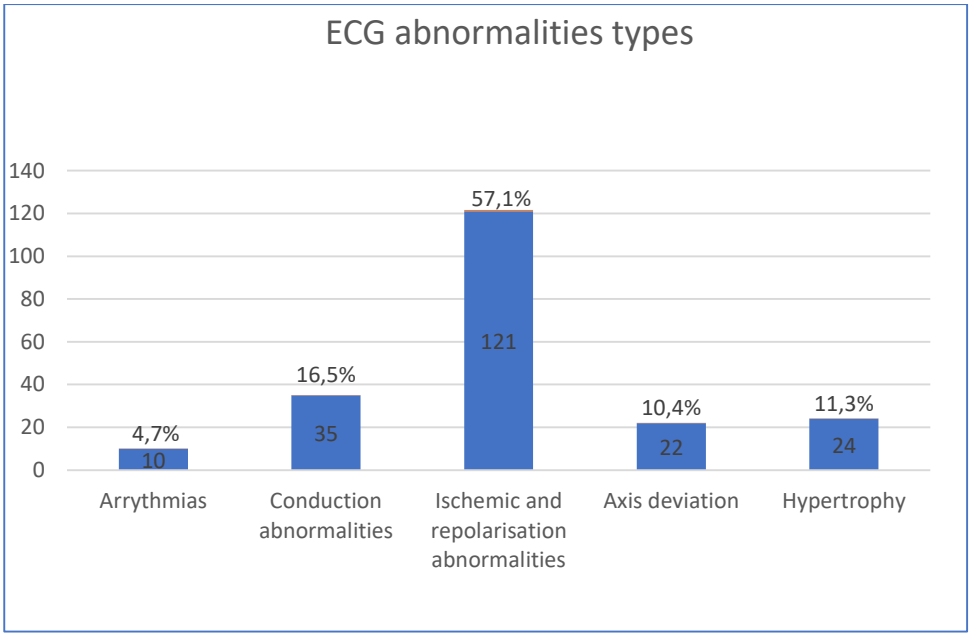

Figure 5: ECG abnormalities types

04. The distribution of ECG abnormalities according to the smoking behavior:

The table below shows the smokers have more abnormal ECG's (88.90 %) compared to non-smokers (78.6%).

Table 4: ECG abnormality according to smoking behavior

		Normal ECG	Abnormal ECG	
Smoking behaviour	**Non-smokers**	**21.4%**	**78.6%**	**100.0%**
	Smokers	**11.1%**	**88.9%**	**100.0%**
Total		**20.9%**	**79.1%**	**100.0%**

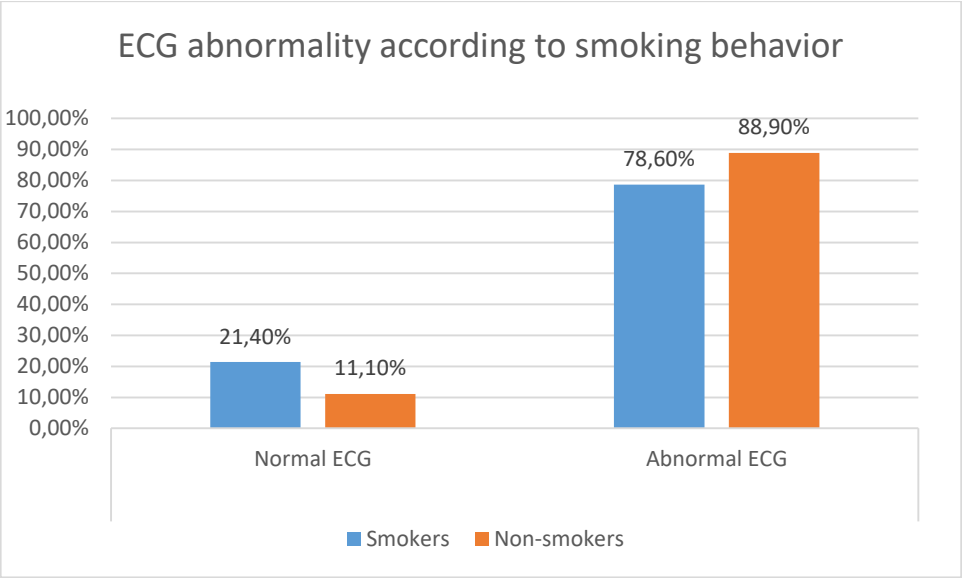

Figure 6: ECG abnormality according to smoking behavior

05. The distribution of ECG abnormalities according to age:

In our population, the highest prevalence is found in the older age group (80 – 90) with 100 % of abnormal ECG while the least prevalence is found in the age group between (31 – 40) with 54.55% abnormal ECG. If we excluded the youngest age group we observe an increase in the prevalence of ECG abnormality with aging.

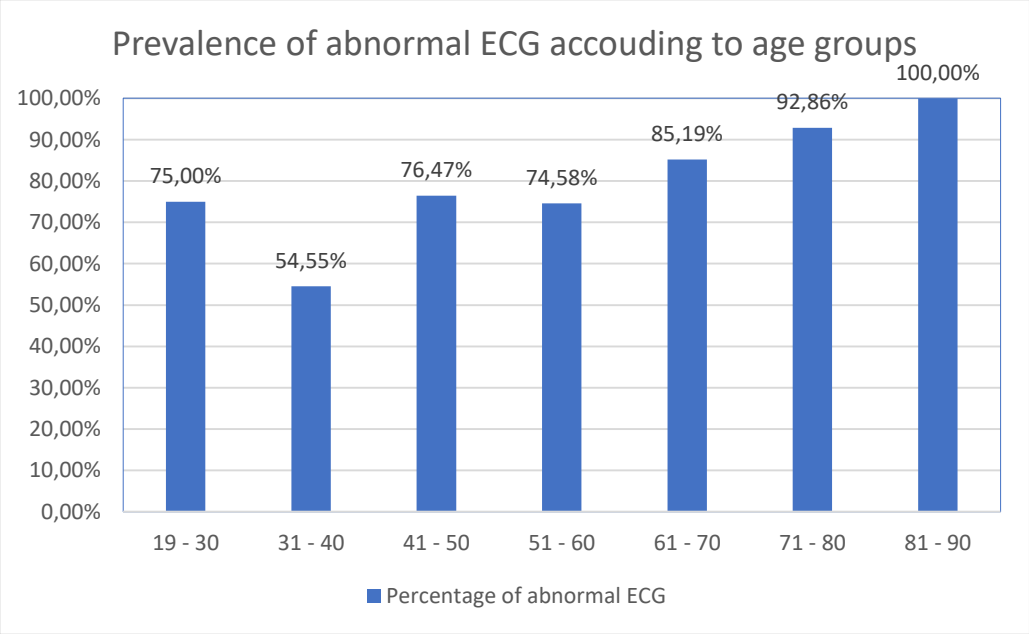

Figure 7: Prevalence of abnormal ECG according to age groups

06. The distribution of ECG abnormalities according to gender:

The table below shows the prevalence of ECG abnormalities according to gender: we note that the majority of them are females (65%).

Table 5: The distribution of ECG abnormalities according to gender

Patient gender	Abnormal ECG percentage
Male	**35%**
Female	**65%**
Total	**100%**

07. The distribution of ECG abnormalities according to age and gender:

The bar chart below shows that in our population both males and females present more ECG abnormality with aging. The highest ECG abnormality prevalence was in the groups aged above 71 years. The smallest ECG abnormality prevalence was in the age groups under 40 years

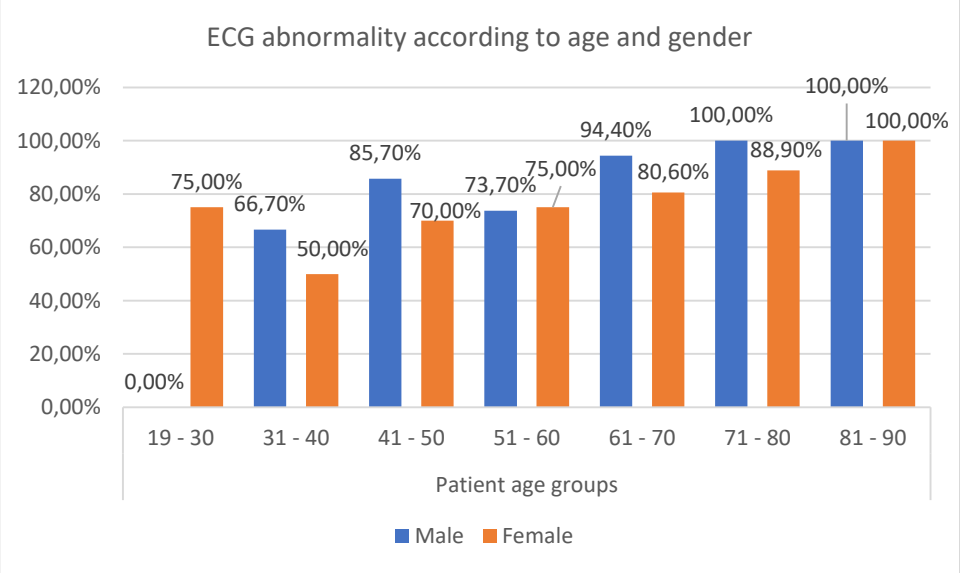

Figure 8: The distribution of ECG abnormalities according to age and gender

08. The distribution of ECG abnormalities according to the duration of diabetes:

In this result, we observe that the prevalence of ECG increases, the longer the duration of T2DM increases with a few exceptions, the highest percentage (93.8%) is observed in the group with the longest duration (over 20 years).

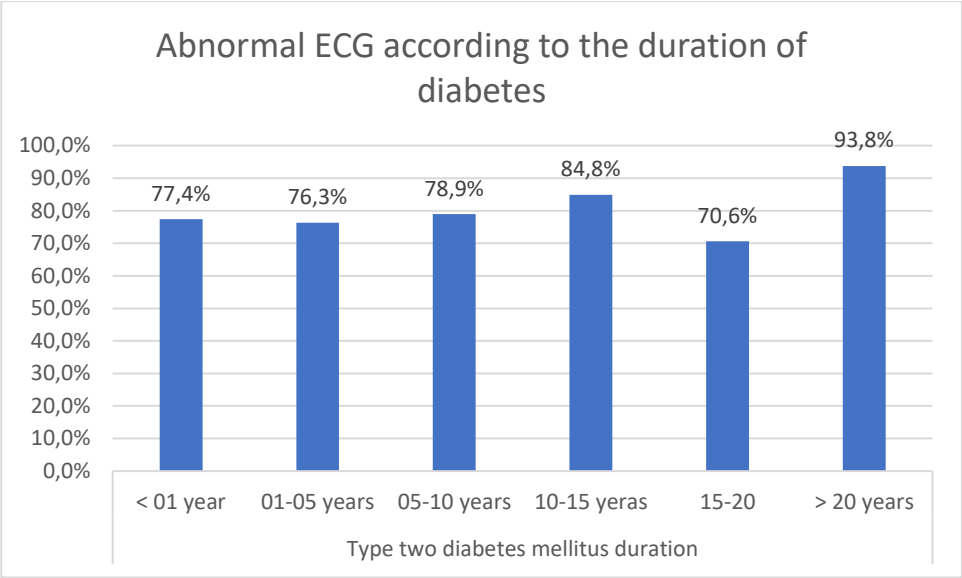

Figure 9: The distribution of ECG abnormalities according to the duration of diabetes

09. The distribution of ECG abnormalities according to score 02 diabetes:

In the group of patients where it was possible to calculate this SCORE, 64.8 % of the patients presented a very high risk representing the majority of the group,

Notably, There are no patients classified as low risk.

A significant portion of the data is missing (71.7 %) due to:

The absence of certain requested information to calculate the SCORE in the patient's profiles.

The group with an age older than 69 years old where the score is not applicable.

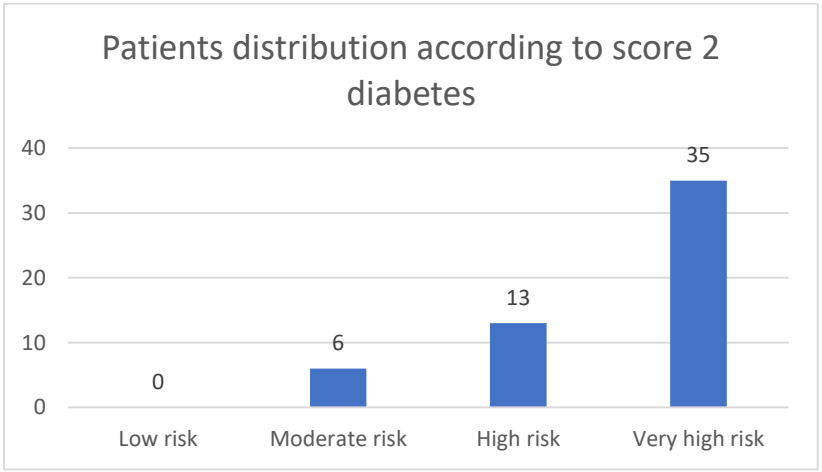

Figure 10: The distribution of the population according to score 02 diabetes

The prevalence of abnormal ECGs is increasing as the risk of having a higher cardiovascular complication rises from low to very high risk according to Score 2 diabetes.

The very high-risk category shows the highest percentage of abnormal ECGs.

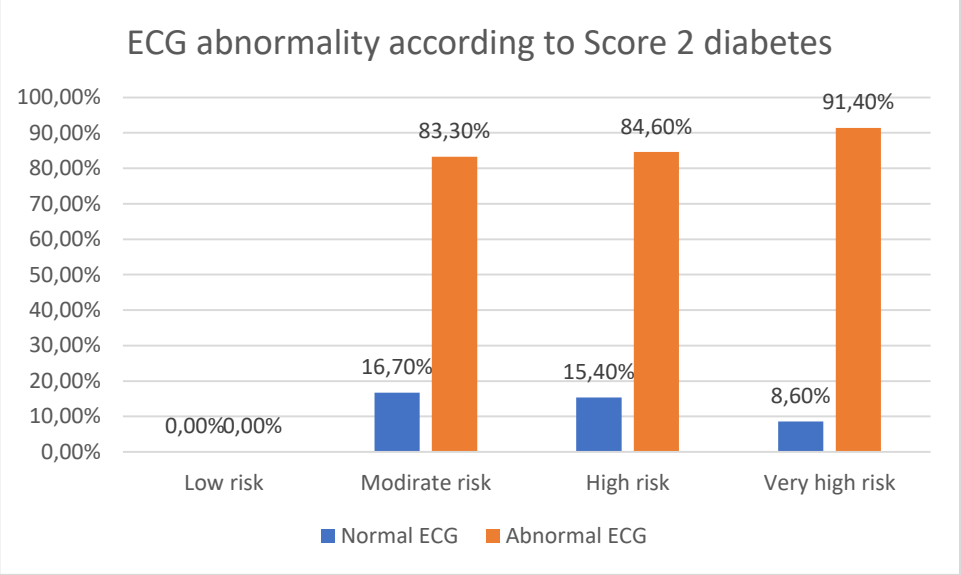

Figure 11: The distribution of ECG abnormalities according to score 02 diabetes

10. The distribution of ECG abnormalities according to the score old person:

In this small group of 5 patients, four of them presented a high risk compared to a single one with a moderate risk, and there are no patients classified as low risk.

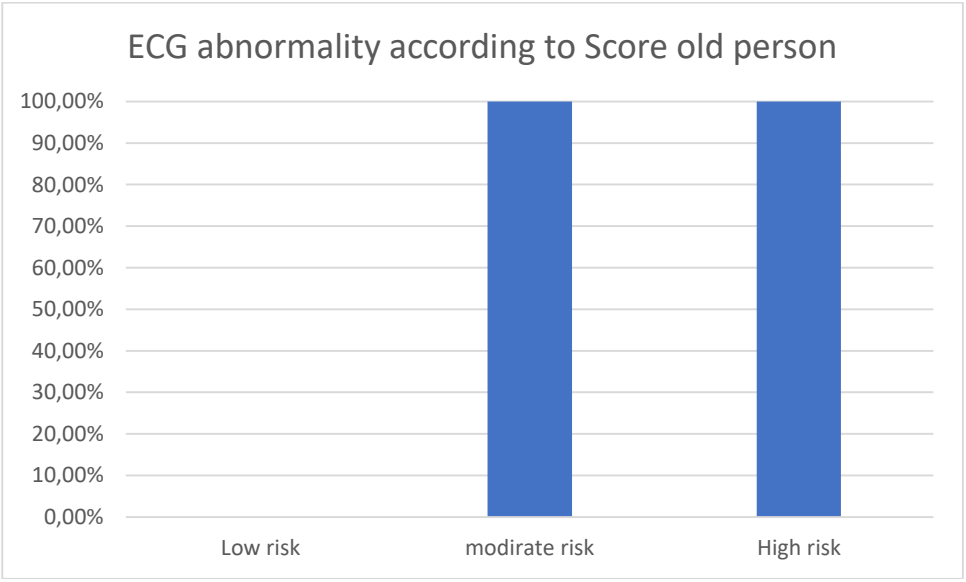

Figure 12: The distribution of ECG abnormalities according to the score old person

11. The distribution of ECG abnormalities according to their hypertensive profile:

The graph below shows the distribution of ECG abnormalities according to their hypertension profile: the overall distribution of normal and abnormal ECGs remains relatively equal across both hypertension groups.

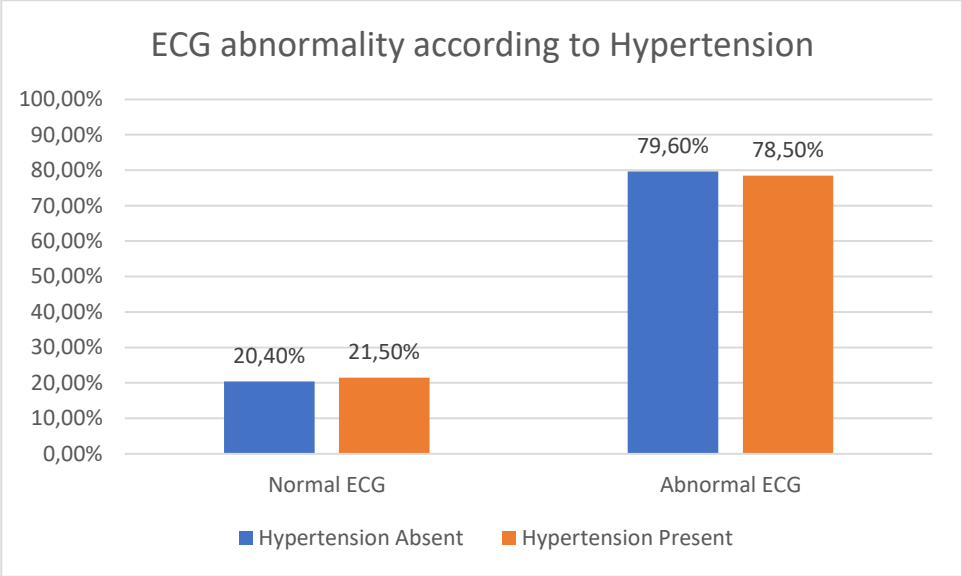

Figure 13: The distribution of ECG abnormalities according to their hypertensive profile

12. The distribution of ECG abnormalities according to their pathological history with diabetic retinopathy:

The bar chart below shows that patients with diabetic retinopathy have a higher prevalence of ECG abnormality. The prevalence of ECG abnormality in patients with diabetic retinopathy is 92.3% while in patients non presenting diabetic retinopathy was 78.1%

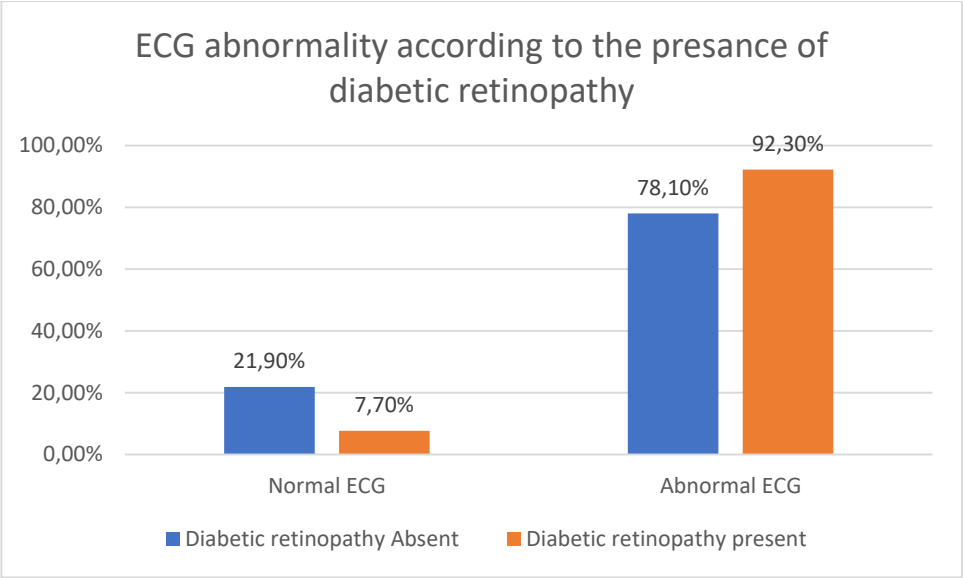

Figure 14: The distribution of ECG abnormalities according to their pathological history with diabetic retinopathy

13. The distribution of ECG abnormalities according to the cardiac symptoms:

A. Dyspnea:

In our population, 73.7 % of patients who presented dyspnea showed abnormal ECG while in the group that didn't have dyspnea 84.8% of them showed an abnormal ECG.

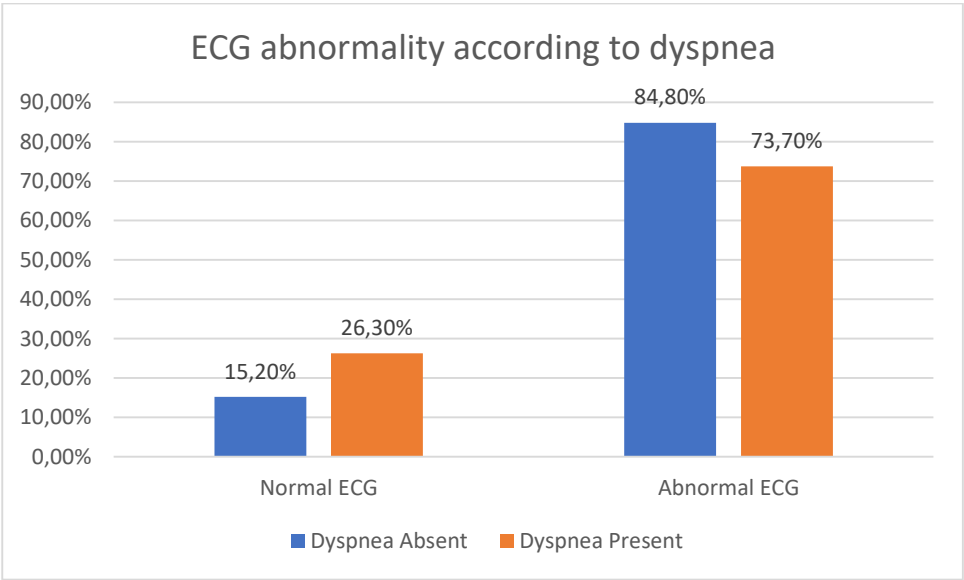

Figure 15: ECG abnormality according to dyspnea

B. NYHA classification:

The bar chart below presents the prevalence of ECG abnormality in patients presenting dyspnea according to the NIHA classification. The results show that the prevalence of ECG

abnormality increases with the patient's NIHA class. In class 04 100% of patients have an abnormal ECG

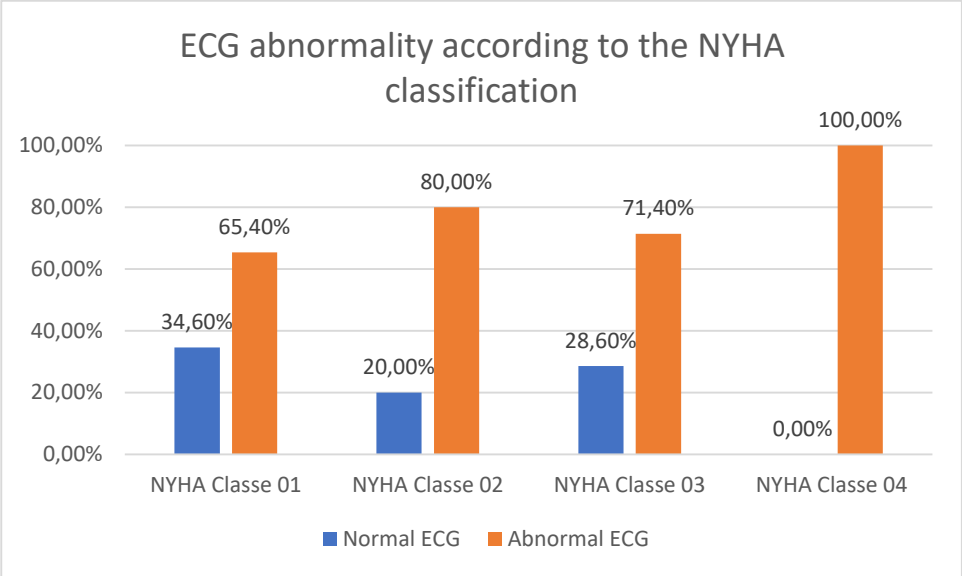

Figure 16: ECG abnormality according to the NYHA classification

C. Chest pain:

The bar chart below presents the prevalence of ECG abnormality according to the symptoms of chest pain. The results show that 81.6% of patients non complaining of chest pain have an abnormal ECG. While only 66.7% of patients presenting characteristic chest pain have an abnormal ECG.

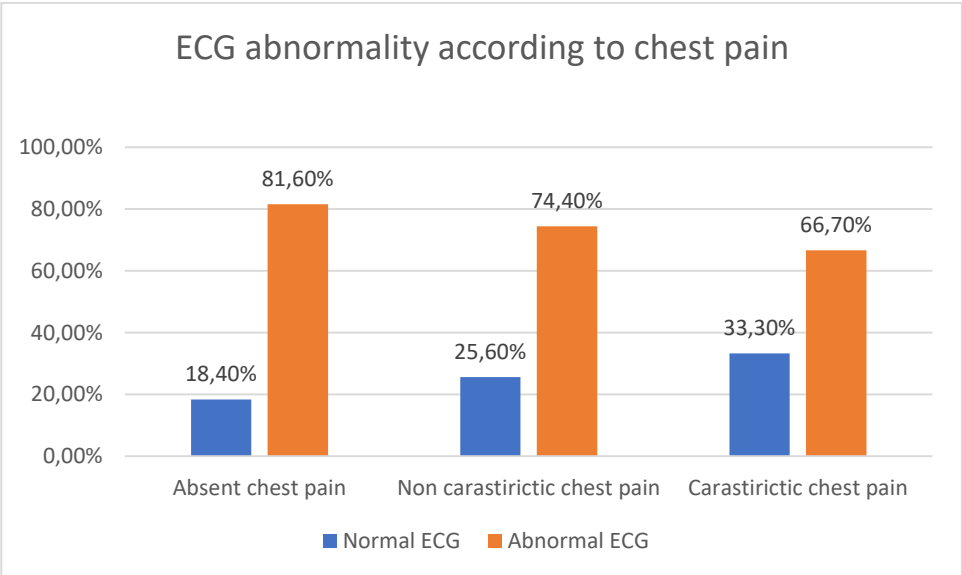

Figure 17: ECG abnormality according to chest pain

Palpitation:

In our population, 74.0 % of patients who presented palpitation showed abnormal ECG while in the group that didn't have palpitation 84.2% of them showed an abnormal ECG.

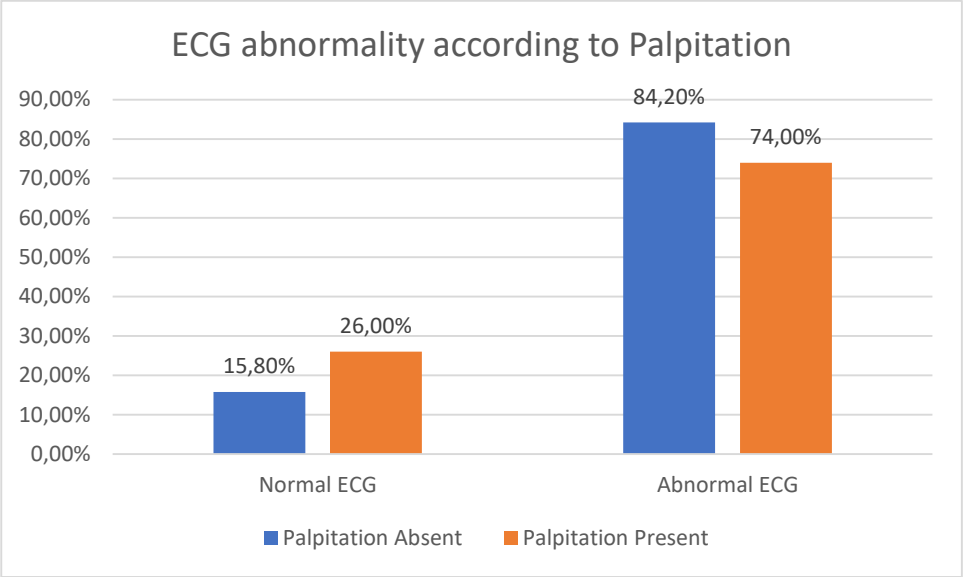

Figure 18: ECG abnormality according to Palpitation

Syncope or fainting:

The bar chart below presents the patients who reported having syncope or fainting as a symptom and its relation to ECG abnormalities:

57.1% of patients who had this symptom showed an abnormal ECG while about 79.9% of the group that didn't have it presented an abnormal ECG.

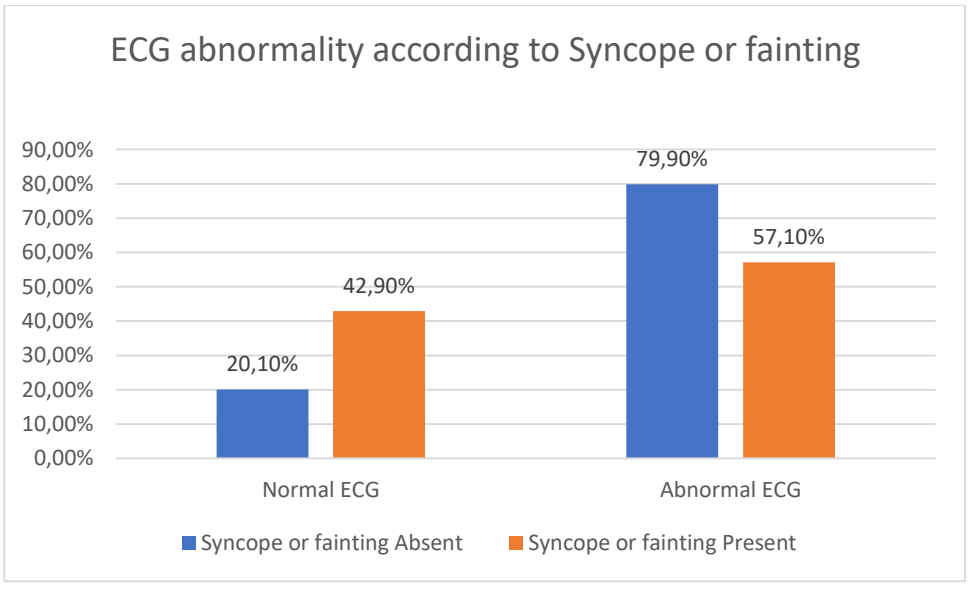

Figure 19: ECG abnormality according to Syncope or fainting

14. The distribution of ECG abnormalities according to the body mass index BMI value:

The bar chart below presents the prevalence of ECG abnormality according to the body mass index. The results show that all the different groups have aprroximaly the same prevalence of ECG abnormality (between 69.2% and 76.3) Except the obesity classe 3 the prevalence was 100%

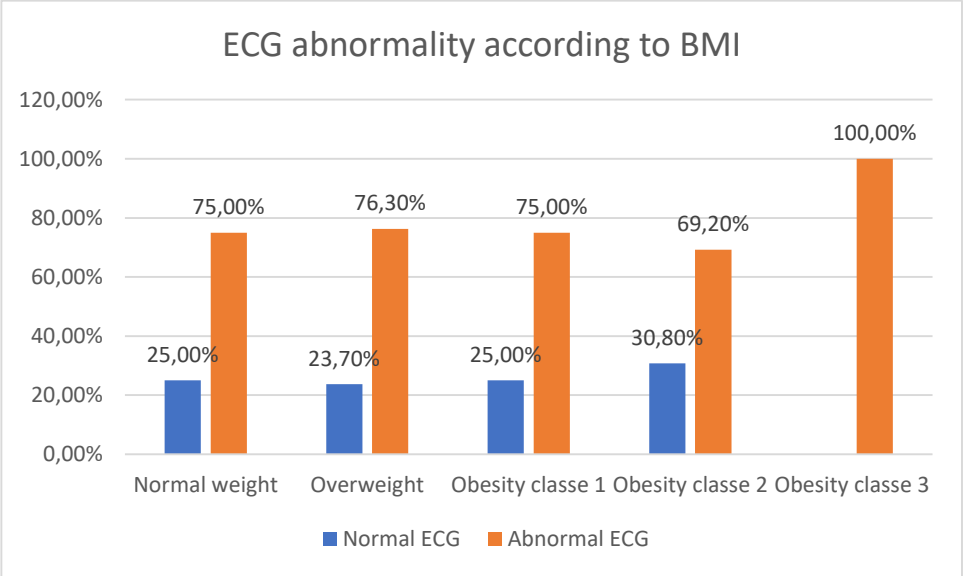

Figure 20: The distribution of ECG abnormalities according to BMI value

15. The distribution of ECG abnormalities according to the glycated hemoglobin (Hb1ac) value:

The bar chart below presents the prevalence of ECG abnormality according to Hb1c. The results show that the group with the highest prevalence was the Hb1c over 15 with 100%. The lowest prevalence was in the group of 7.6 - 9 with 74.6%.

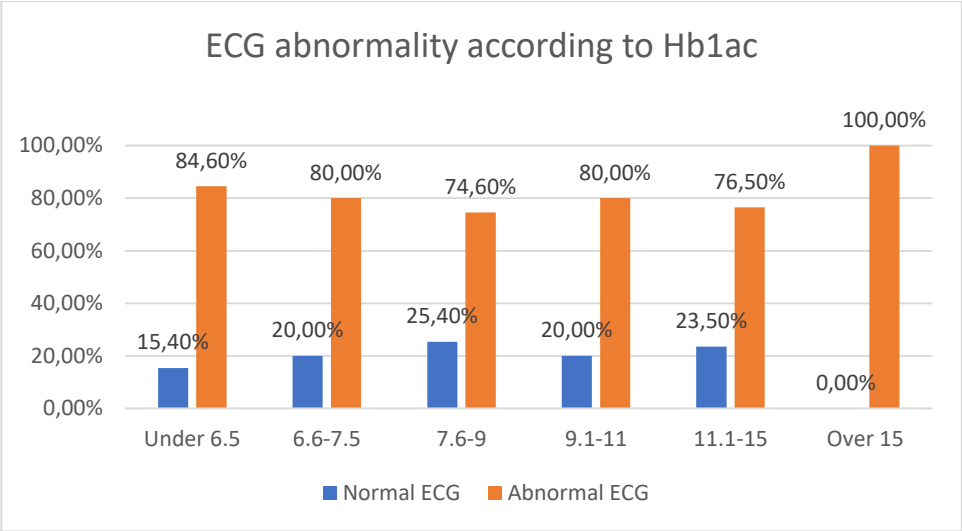

Figure 21: The distribution of ECG abnormalities according to the glycated hemoglobin (Hb1aC) value

16. The distribution of ECG abnormalities according to the fasting glucose level:

The graph shows the distribution of ECG abnormalities according to the fasting glucose level.

Under 1.1g/l: the majority of patients in this category 78.3% had an ECG abnormality.

The fasting glucose level (1.1 – 1.25) g/l: 68.8% of patients in this category had an ECG abnormality. The fasting glucose level (1.26 – 2) g/l: 50.8% of patients in this category had an ECG abnormality. For fasting glucose level (2 – 2.5) g/l: 45 % of patients in this category had an ECG abnormality. The fasting glucose level Over 2.5 g/l: 61.5 % of patients in this category had an ECG abnormality.

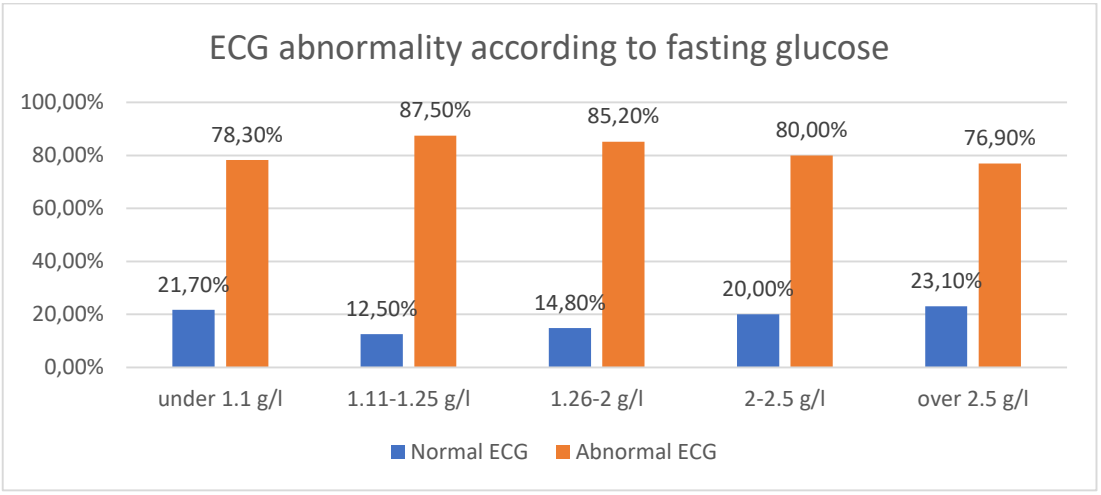

Figure 22: The distribution of ECG abnormalities according to the fasting glucose level

17. The distribution of ECG abnormalities according to their estimated glomerular filtration rate (eGFR) level:

The bar chart shows the distribution of ECG abnormality according to the estimated glomerular filtration rate (eGFR) level:

The prevalence of ECG abnormalities increases with decreasing eGFR.

The highest prevalence of EGC abnormalities is observed in patients with an eGFR of less than 60 ungloving two groups of patients.

In patients with eGFR confined between 61 and 90: half of patients (84.4% %) in this category had an ECG abnormality.

In patients with eGFR confined between 91and 120: 57.1% of patients in this category had an ECG abnormality.

eGFR Over 120: 57.1 % of patients in this category had an ECG abnormality.

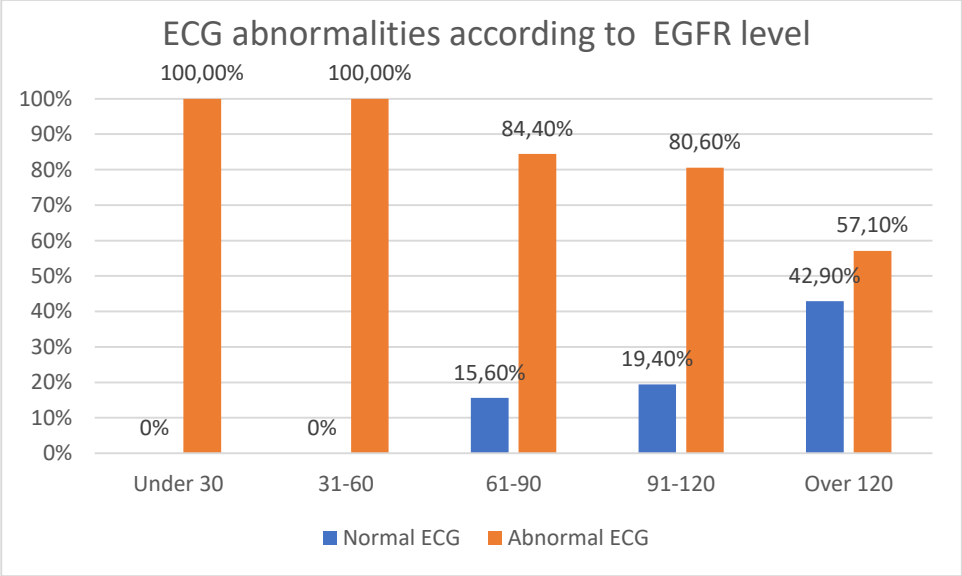

Figure 23: The distribution of ECG abnormalities according to their estimated glomerular filtration rate (eGFR) level

18. The distribution of ECG abnormalities according to the albumin creatinine ratio (ACR) level:

The graph presents data on the relationship between albumin-creatinine ratio (ACR) levels and the prevalence of ECG abnormalities :

In our population, no patients showed an ACR above 30 mg/mmol

As ACR levels increase, the percentage of individuals with abnormal ECGs also increases.

The most significant increase in abnormal ECGs occurs in the 3.1-30 mg/mmol ACR range, where 100% of individuals have abnormal ECGs.

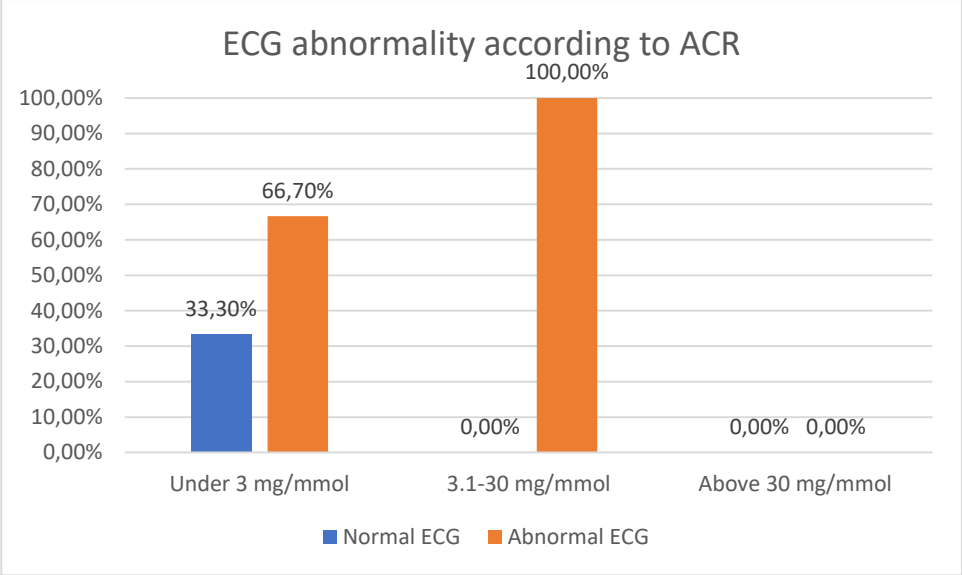

Figure 24: The distribution of ECG abnormalities according to the albumin creatinine ratio (ACR) level

19. The distribution of ECG abnormalities according to the number of diabetes medications they take:

The graph below presents the prevalence of ECG abnormality according to the number of diabetes medications patients take. The results show that patients not taking any diabetes medication have an abnormal ECG prevalence of 100%. The results show that with the greater number of medication patients take the prevalence of ECG abnormality decreases from 79.7% with one medication to 65.0% with three medications. In the group of four medications, the prevalence of ECG abnormality was 100%

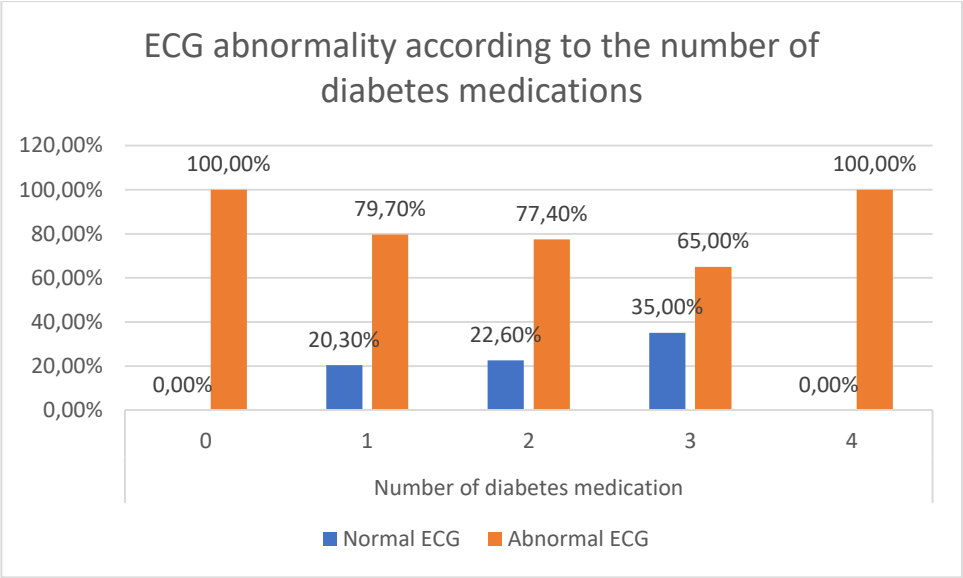

Figure 25: The distribution of ECG abnormalities according to the number of diabetes medications they take

20. The distribution of ECG abnormalities according to the type of diabetes medication (insulin/ oral medication/association oral–insulin medication):

The bar chart below presents the prevalence of ECG abnormality according to the type of diabetes medication. The results show that the highest prevalence of ECG abnormality was in the group of patients taking insulin only (85.7%). The lowest prevalence was in the group of patients taking oral diabetes medication only (74.1%). In the group of patients taking both oral diabetes medications and insulin, the prevalence was 82.9%.

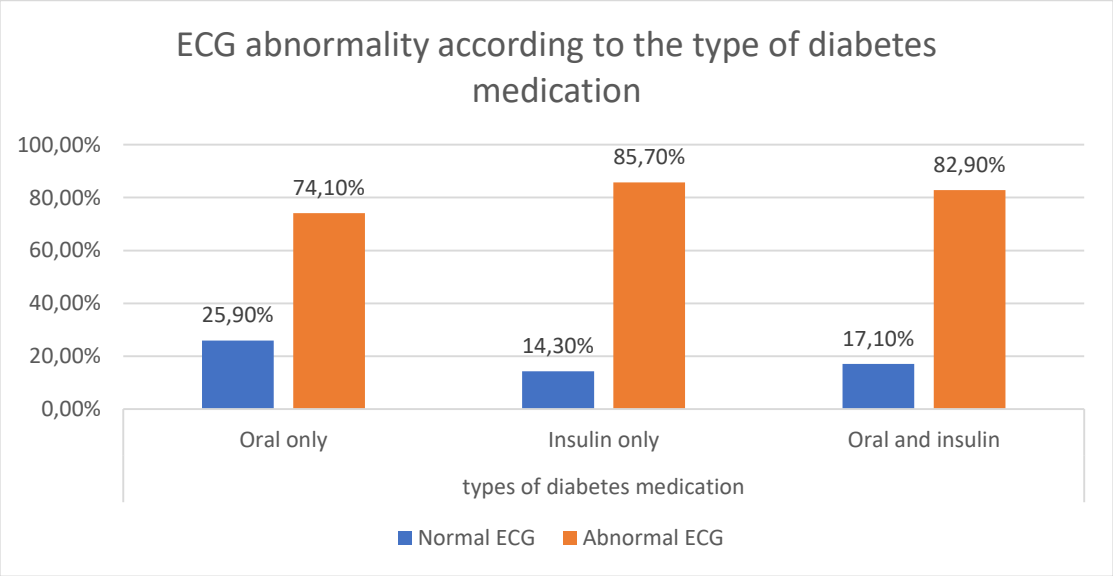

Figure 26: The distribution of ECG abnormalities according to the type of diabetes medication

21. The distribution of ECG abnormalities according to the use of statin:

The bar chart below presents the prevalence of ECG abnormality according to the use of statins. The results show that 87.5% of patients using statins had an abnormal ECG while 73.5% of patients who weren't taking statins had an abnormal ECG.

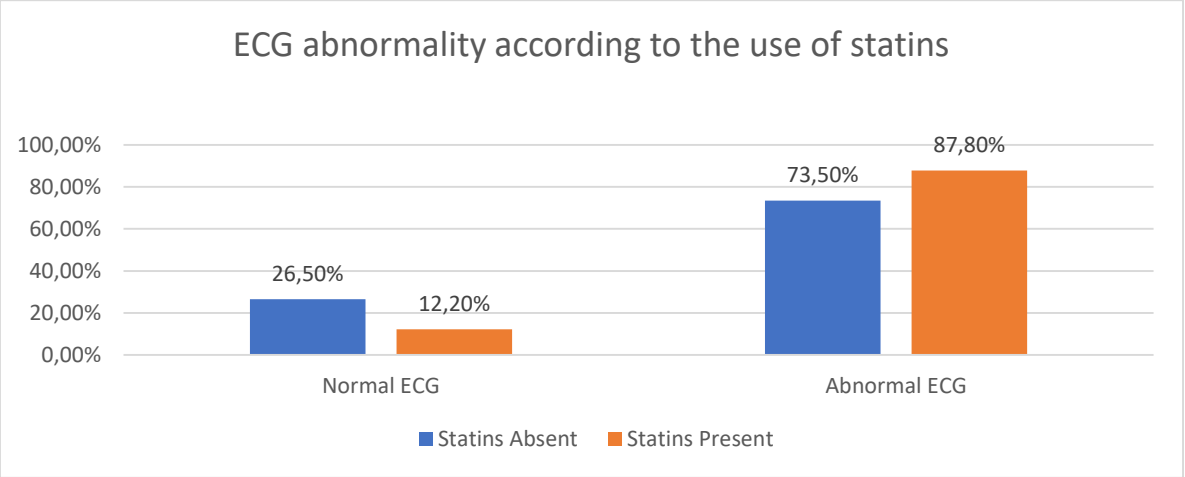

Figure 27: The distribution of ECG abnormalities according to the use of statin

22. The distribution of ECG abnormalities according to the use of antiplatelet:

The bar chart below presents the prevalence of ECG abnormality according to the use of antiplatelets. The results show that 81.8% of patients using antiplatelets had an abnormal ECG while 78.5% of patients who weren't taking antiplatelets had an abnormal ECG

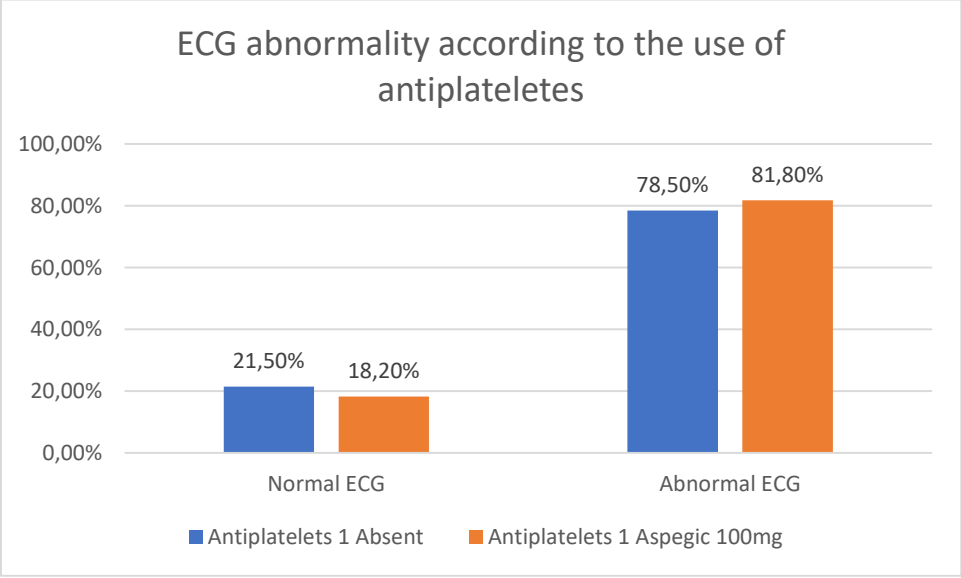

Figure 28: The distribution of ECG abnormalities according to the use of antiplatelet

III. FRAGMENTED QRS ABNORMALITY DISTRIBUTION IN T2DM PATIENTS:

01. The prevalence of fragmented QRS abnormality in the population:

The bar chart shows the prevalence of fragmented QRS abnormality in our population of patients with type 2 diabetes mellitus.

The bar chart shows that out of 191 patients, 50.3% (95 patients) had an abnormal fragmented QRS complex.

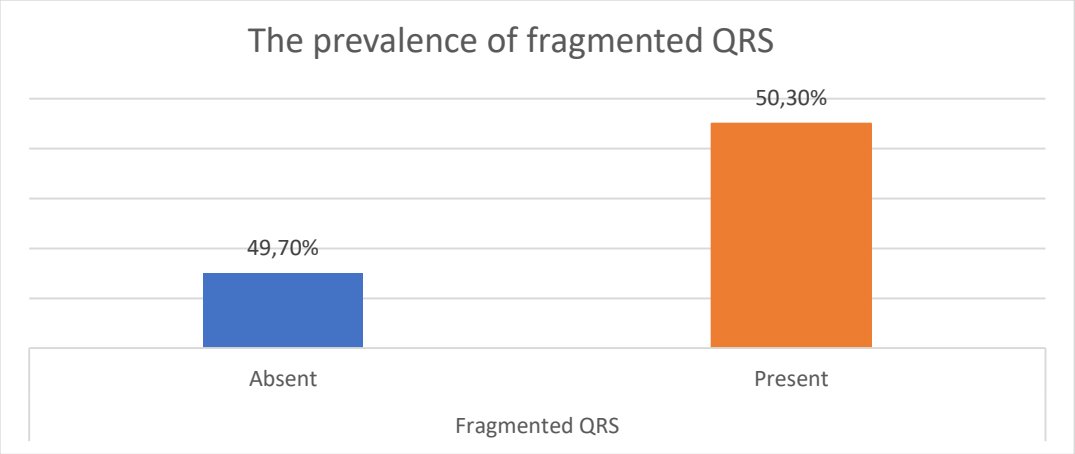

Figure 29: The prevalence of fragmented QRS

02. The distribution of fragmented QRS according to the smoking habit:

The bar chart shows the distribution of fragmented QRS according to smoking habits.

In the table, smoking behaviour is categorized into smoker and non-smoker. For each category, the table shows the percentage of patients with and without fragmented QRS.

the results suggest that there is no significant difference in the prevalence of fragmented QRS between smokers (50%) and non-smokers (55.6%). Both smokers and non-smokers have an almost equal prevalence of fragmented QRS.

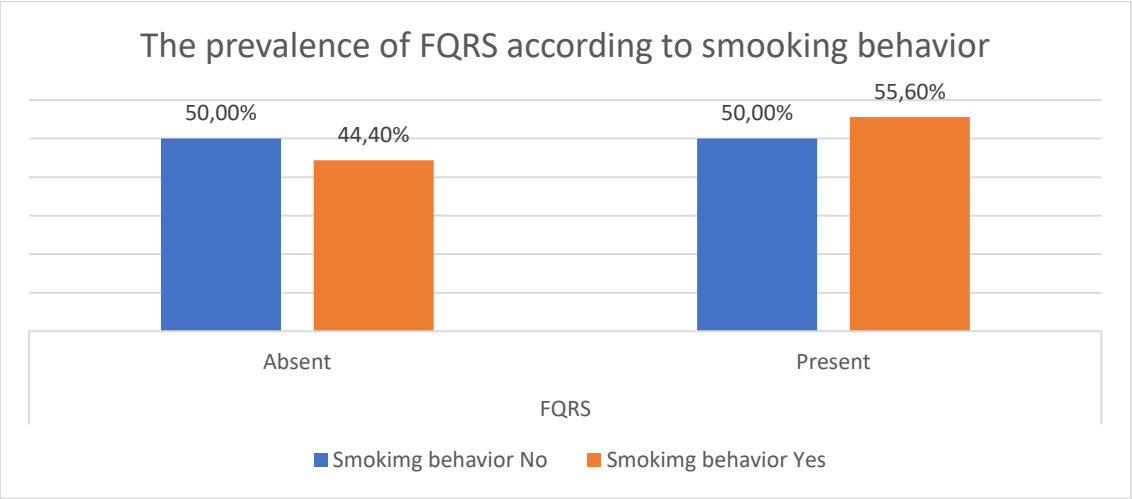

Figure 30: The distribution of fragmented QRS according to the smoking habit

03. The distribution of fragmented QRS according to age:

The bar chart below presents the distribution of FQRS according to patients' age groups. The results show that the group aged between 81– 90 years had the highest prevalence of FQRS (100.0%). In the rest of the groups, we found that almost half of the patients had an FQRS abnormality with an average of 48.7%.

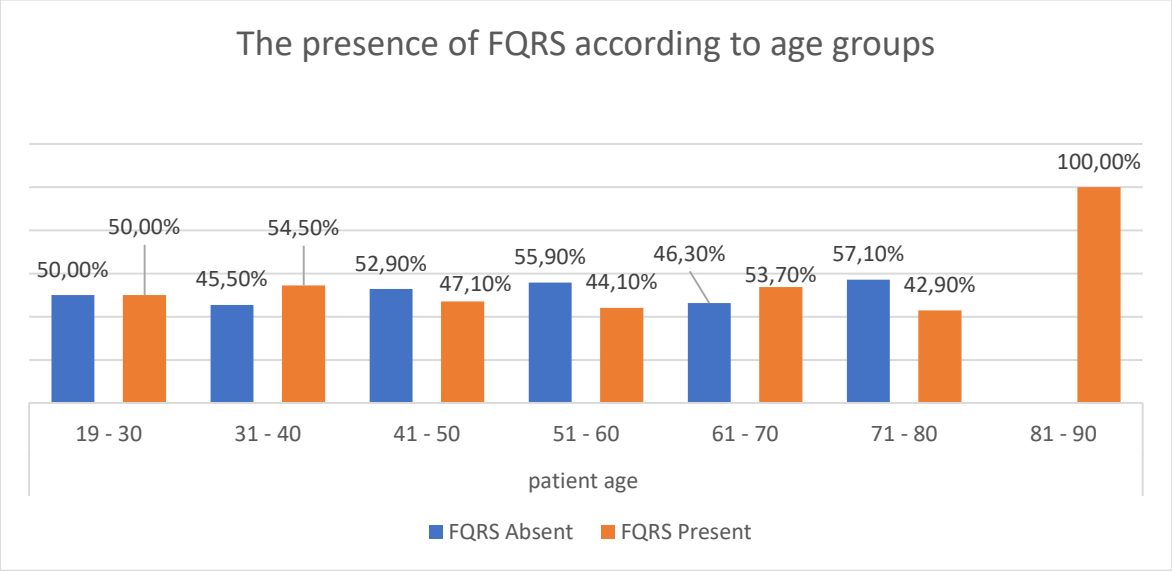

Figure 31: The distribution of fragmented QRS according to age

04. The distribution of fragmented QRS according to gender:

In our population, about half of the patients showed the FQRS abnormality with a higher prevalence in males (53.2%) compared to females (48.8%).

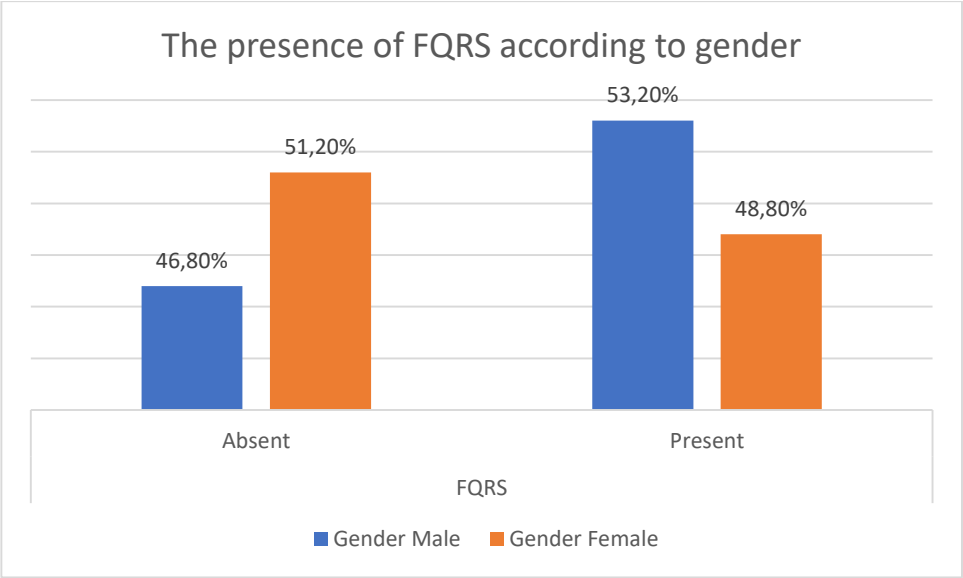

Figure 32: The distribution of fragmented QRS according to gender

05. The distribution of fragmented QRS according to age and gender:

The bar chart below presents the distribution of FQRS according to age and gender. The results show that the highest FQRS prevalence was showed in the group age between 61 – 70 years for the male patients and in the group age between 51 – 60 years for the female patients with 36.4% and 32.7% respectively. The lowest FQRS prevalence was in the group aged between 19 – 30 for both male and female patients with 0.0% for men and 3.6% for women

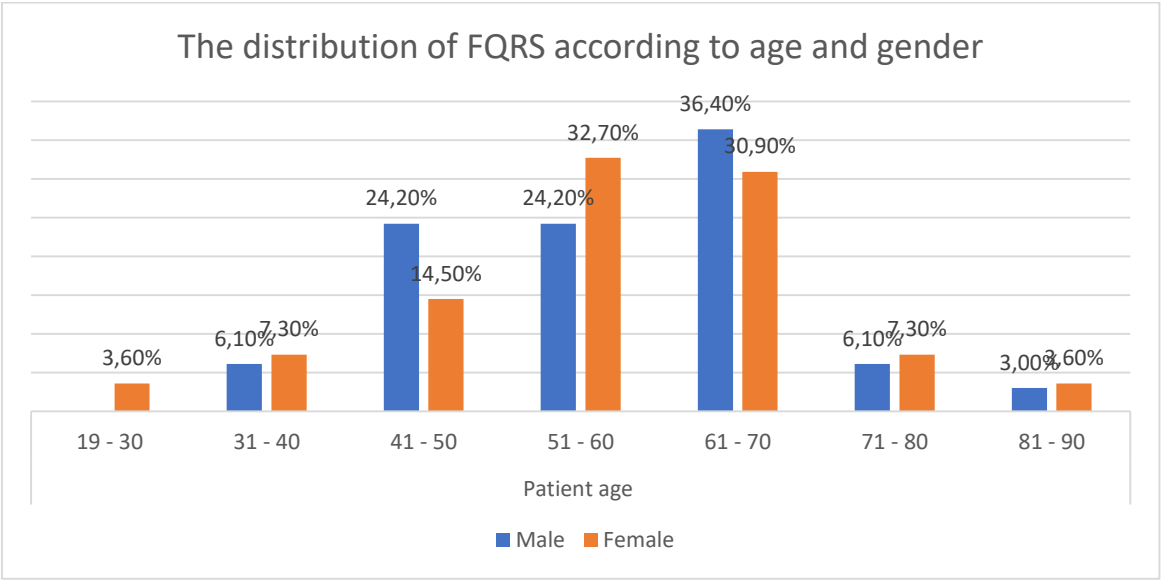

Figure 33: The distribution of fragmented QRS according to age and gender

06. The distribution of fragmented QRS according to the age of diabetes:

The bar chart below presents the distribution of FQRS according to the duration of type 2 diabetes. The results show that the prevalence in the group of less than one year of diabetes was a percentage of 48.4%. The highest prevalence marked was in the group with more than 20 years of diabetes with a percentage of 56.3%.

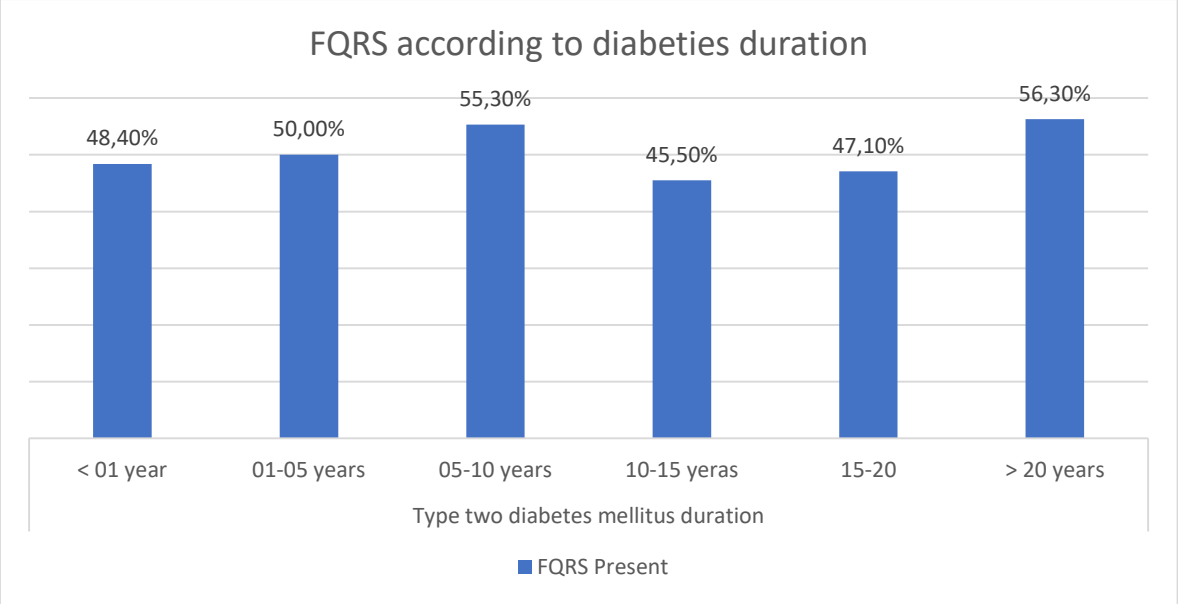

Figure 34: The distribution of fragmented QRS according to the age of diabetes

07. The distribution of fragmented QRS according to score 02 diabetes:

The bar chart below presents the distribution of FQRS according to Score 2 diabetes. The results show that in our population there are 0 patients in the group of Low risk, the prevalence of FQRS in the two groups of moderate and high risk is approximatively equal with a percentage of 14.8% and 11.1% respectively, and the highest prevalence was marked in the group of very high risk with a percentage of 74.1%

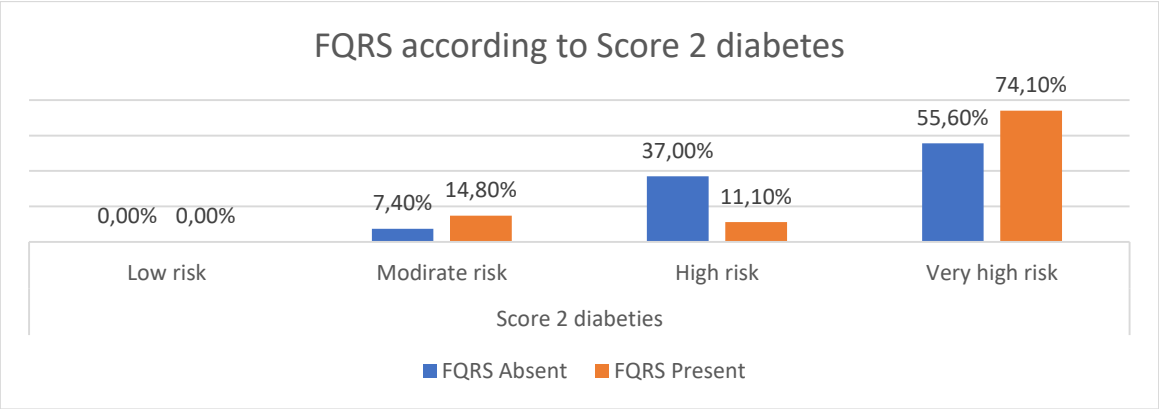

Figure 35: The distribution of fragmented QRS according to score 02 diabetes

08. The distribution of fragmented QRS according to score old person:

The bar chart below presents the distribution of FQRS abnormality according to the Score old person. The results show that 100% of patients with moderate risk had an FQRS while only 25% of patients in the high-risk group presented a FQRS.

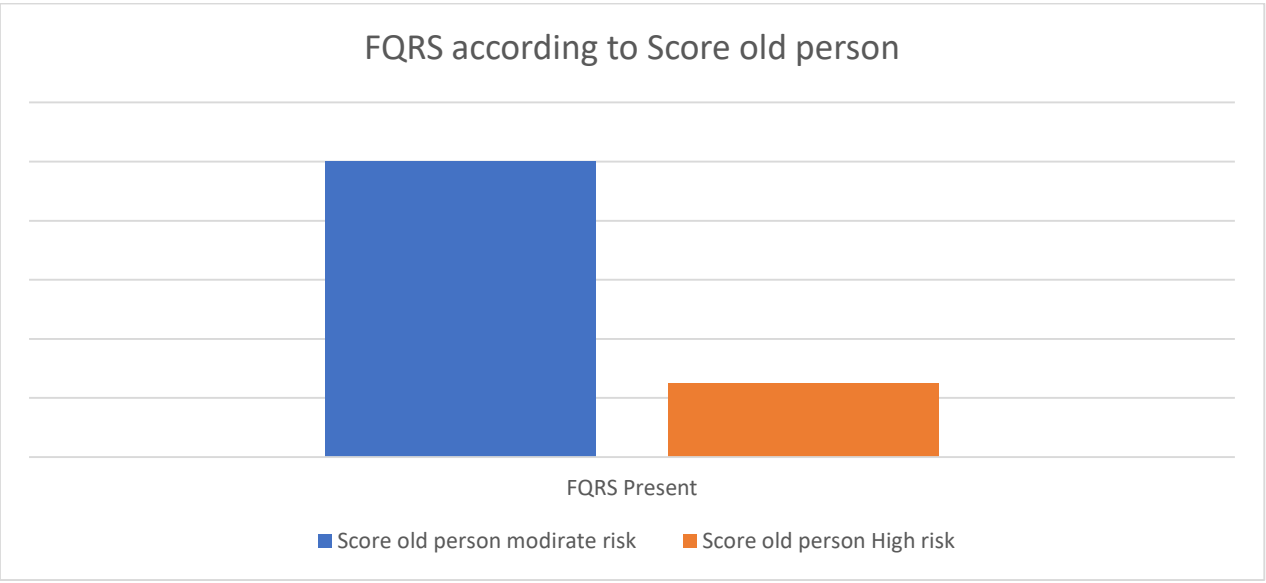

Figure 36: The distribution of fragmented QRS according to the score old person

09. The distribution of fragmented QRS according to patients' hypertensive profile:

The bar chart below presents the distribution of fragmented QRS according to the hypertensive profile of our population, 46.2 %of the patients that presented hypertension showed the FQRS abnormality while in the group that didn't have hypertension 54.1% of them showed it.

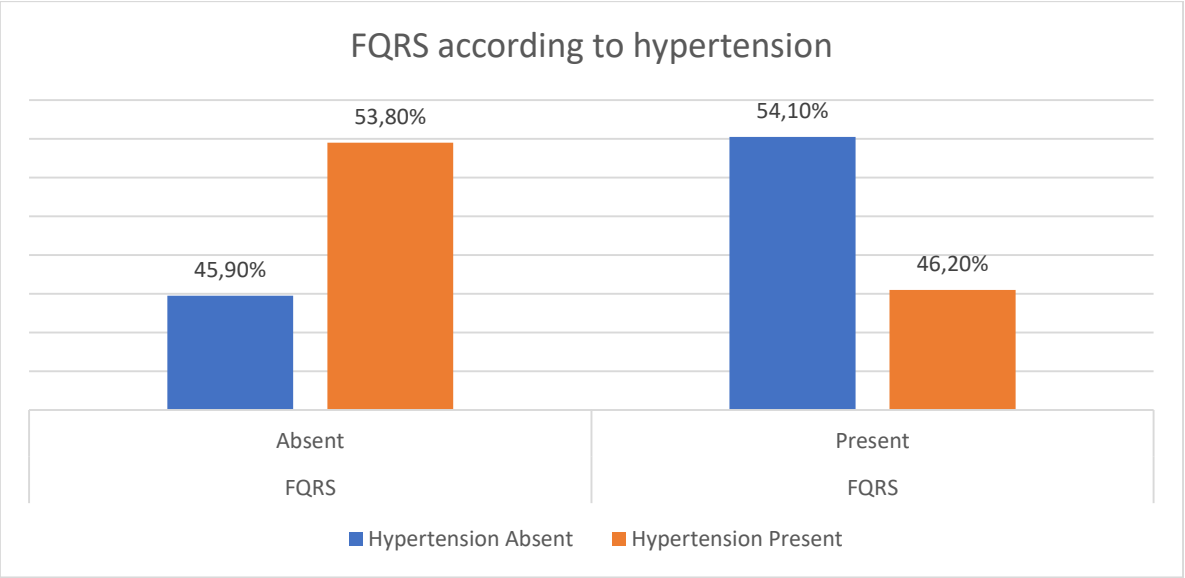

Figure 37: The distribution of fragmented QRS according to patients' hypertensive profile

10. The distribution of fragmented QRS according to patients pathological history with diabetic retinopathy:

The bar chart presents the distribution of FQRS according to diabetic retinopathy, the results show that 8,3% of patients having diabetic retinopathy had an FQRS, while 5,3% of patients who didn't have diabetic retinopathy had an FQRS.

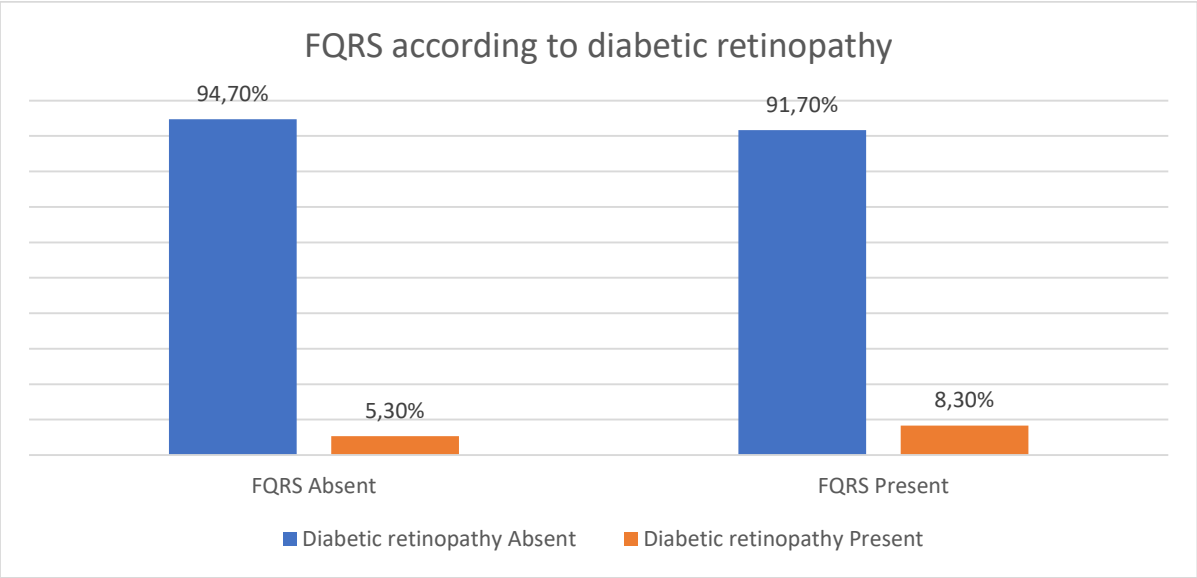

Figure 38: The distribution of fragmented QRS according to diabetic retinopathy

11. The distribution of fragmented QRS according to the cardiac symptoms:

A. Dyspnea:

In our population, 49.5 %of the patients that presented dyspnea showed the FQRS abnormality while in the group that didn't have dyspnea 51.1% of them showed it.

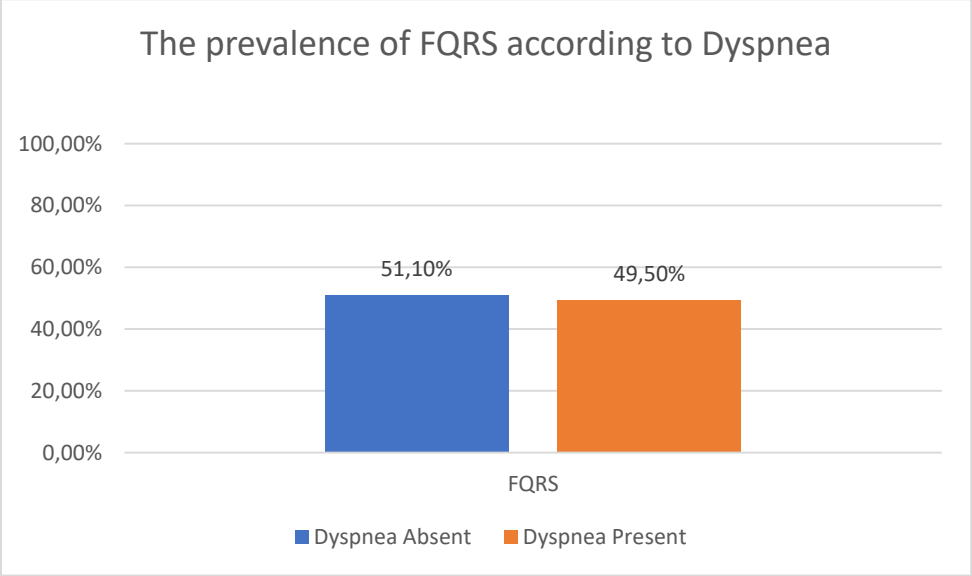

Figure 39: The prevalence of FQRS according to Dyspnea

B. NYHA classification:

The bar chart under presents the distribution of FQRS according to the NYHA classification. The results show that the prevalence of FQRS increases with the class of NIHA. The lowest prevalence was marked in class one with 38.5%. The highest prevalence was in class four with 100%

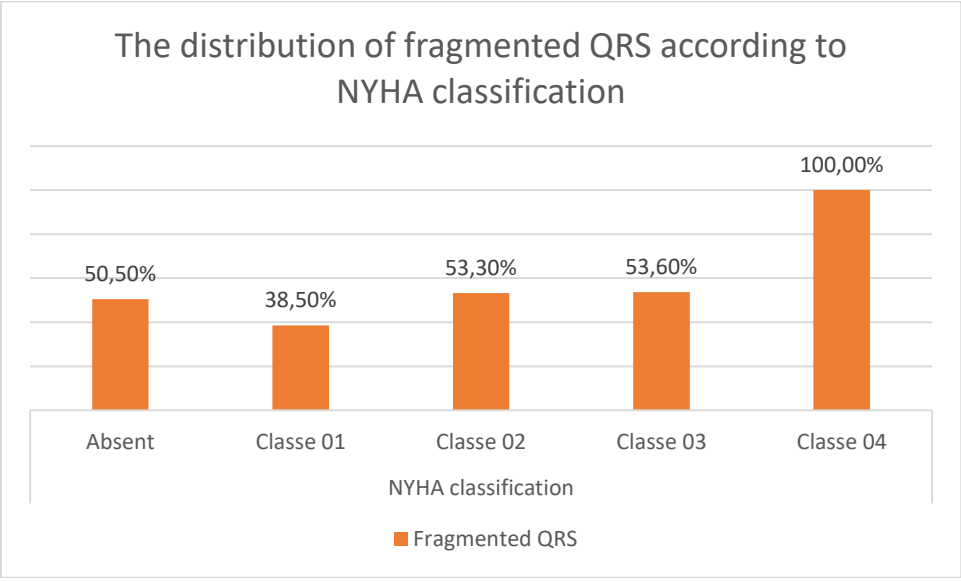

Figure 40: The distribution of fragmented QRS according to NYHA classification

C. Chest pain:

The bar chart under presents the distribution of FQRS according to the symptom of chest pain. The results show that in the group of patients who didn't present chest pain half of them had a FQRS (50.0%). The group with non-characteristic chest pain presented more FQRS abnormality compared to the group of patients complaining of characteristic chest pain. The prevalence of FQRS was 53.5% and 41.7% respectively in the two groups.

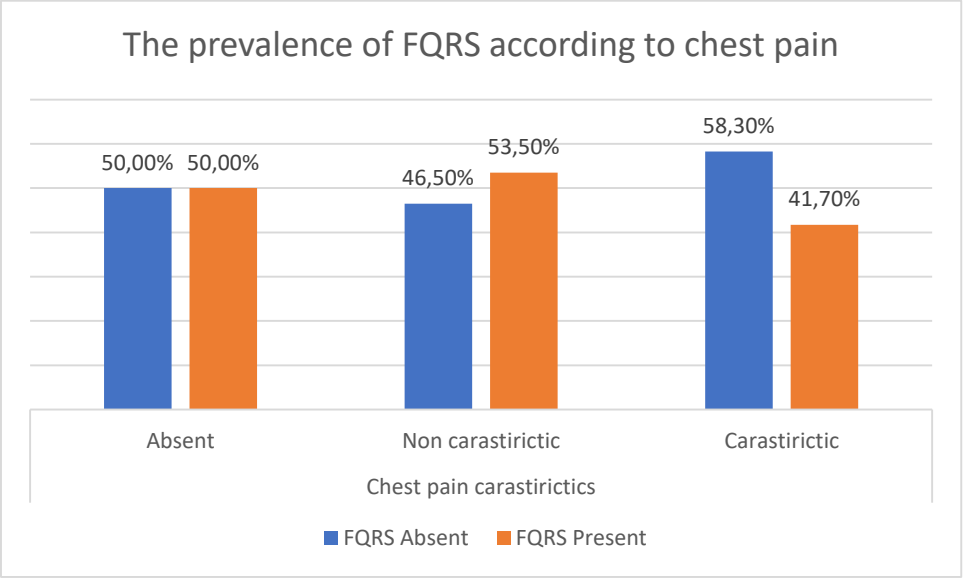

Figure 41: The prevalence of FQRS according to chest pain

D. Syncope and fainting:

The bar chart below presents the patients who reported having syncope or fainting as a symptom and its relation with FQRS abnormality:

28.6 % of patients who had this symptom showed the FQRS abnormality while about 51.1 % of the group that didn't have it presented the FQRS abnormality.

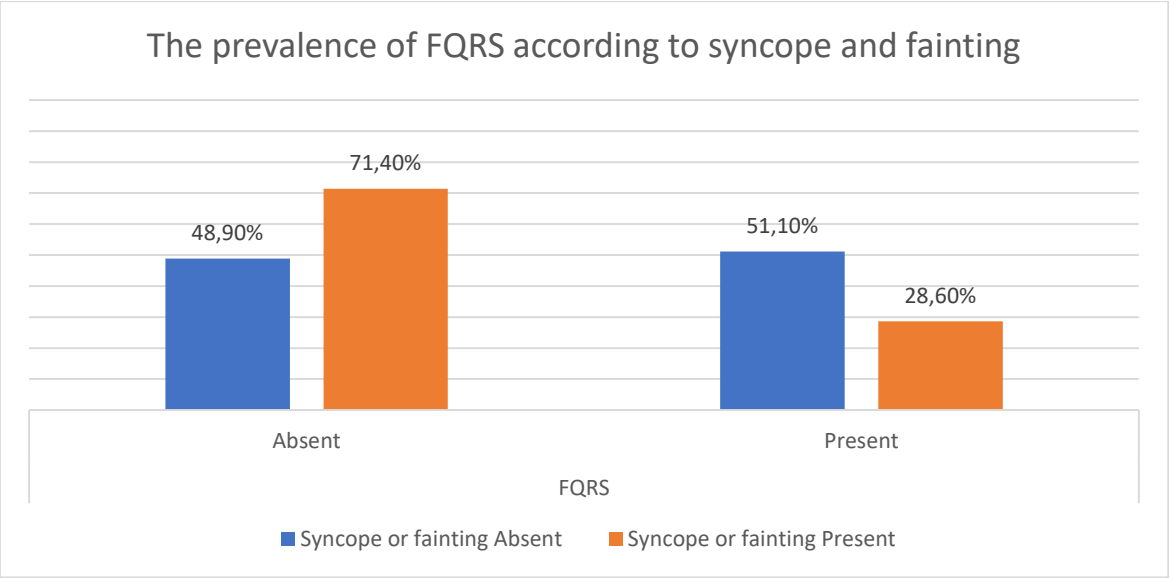

Figure 42: The prevalence of FQRS according to syncope and fainting

E. Palpitation:

In our population, 47.9 % of patients who presented palpitation showed a fragmented QRS abnormality in their ECGs, while in the group that didn't have palpitation 52.6% of them showed an abnormal ECG.

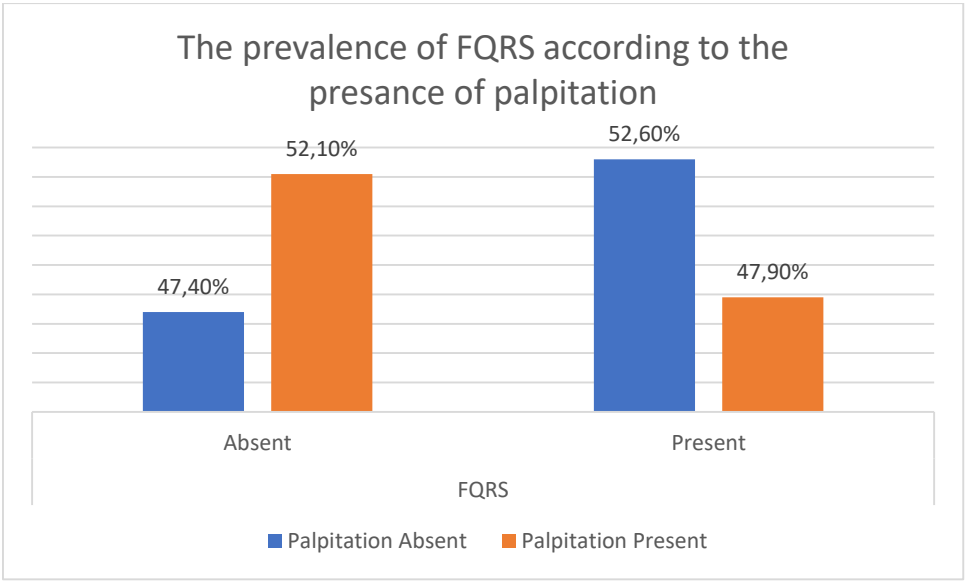

Figure 43: The prevalence of FQRS according to the presence of palpitation

12. The distribution of fragmented QRS according to the body mass index BMI value:

The bar chart below presents the distribution of FQRS according to the body mass index. The results show that the highest FQRS prevalence was marked in the group of obesity class

III with 100.0%. The lowest prevalence of FQRS was shown in the Normal group with a percentage of 37.5%. The overweight and the obesity class II marked an approximal equal prevalence with 45.9% and 46.2% respectively. The obesity class I group marked a higher FQRS prevalence than the last two groups with a percentage of 56.3%

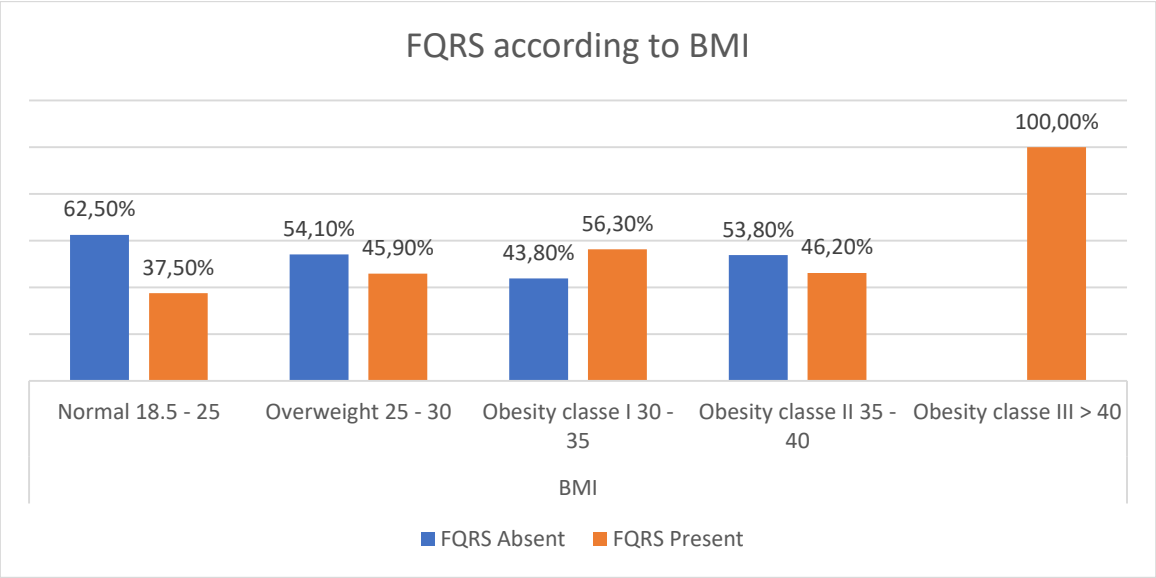

Figure 44: The distribution of fragmented QRS according to BMI value

13. The distribution of fragmented QRS according to the glycated hemoglobin (Hb1ac) value:

The bar chart below presents the distribution of FQRS according to the Hb1c. The results show that the highest FQRS prevalence was marked in the group of Hb1c under 6.5 with a percentage of 61.5%. The lowest prevalence was marked in the group Hb1c between 7.5 – 9 with a percentage of 42.4%. While no patient presenting an FQRS had a Hb1c over 15.

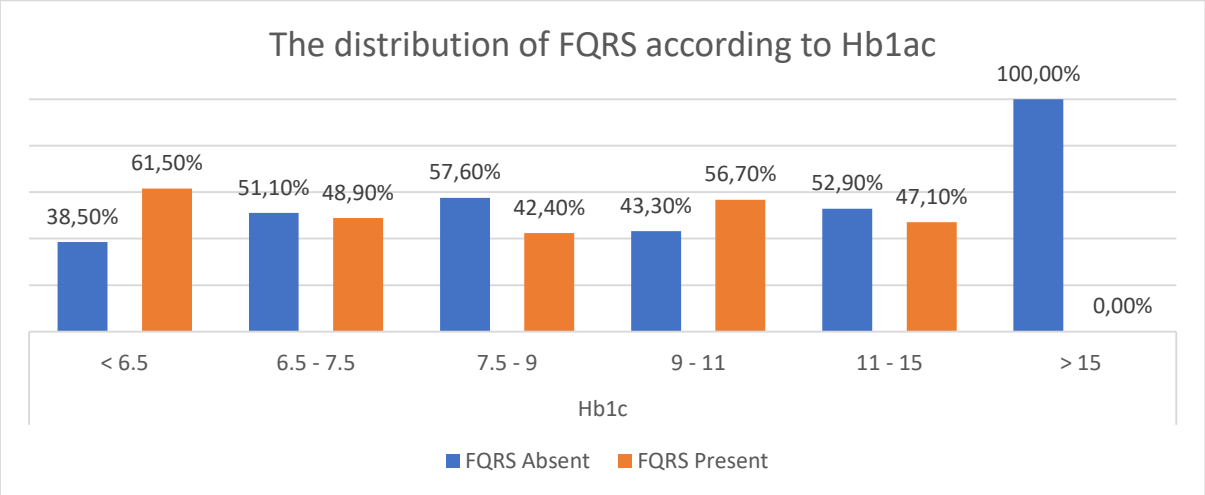

Figure 45: The distribution of fragmented QRS according to the glycated hemoglobin (Hb1ac) value

14. The distribution of fragmented QRS according to the fasting glucose level:

The bar chart under shows the distribution of fragmented QRS abnormality according to the fasting glucose level Under 1.1 g/l: 43.5% in this category had an FQRS abnormality.

The fasting glucose level (1.1 – 1.25) g/l: 68.8% of patients in this category had a FQRS abnormality.

The fasting glucose level (1.26 – 2) g/l: 50.8% of patients in this category had a FQRS abnormality.

The fasting glucose level (2 – 2.5) g/l: 45 % of patients in this category had a FQRS abnormality.

The fasting glucose level Over 2.5 g/l: 61.5 % of patients in this category had an FQRS abnormality.

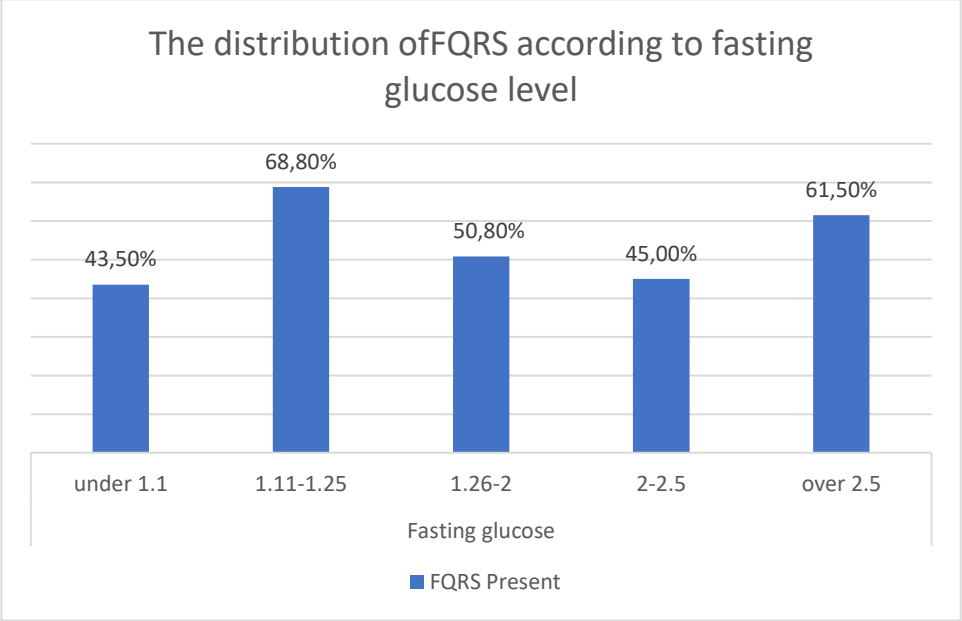

Figure 46: The distribution of fragmented QRS according to the fasting glucose level

15. The distribution of fragmented QRS according to their estimated glomerular filtration rate (eGFR) level:

The bar chart below shows the distribution of fragmented QRS (FQRS) abnormality according to the estimated glomerular filtration rate (eGFR) level:

The prevalence of FQRS increases with decreasing eGFR.

The highest prevalence of FQRS (85.7%) is observed in patients with an eGFR of less than 30.

In eGFR Under 30 All patients (100%) had a FQRS abnormality.

In patients with eGFR between 31 and 60 about 60% of them had a FQRS abnormality.

In patients with eGFR confined between 61 and 90: half of patients (51.1%) in this category had an FQRS abnormality.

In patients with eGFR confined between 91 and 120: 49.3% of patients in this category had an FQRS abnormality.

eGFR Over 120: only 14.3% of patients in this category had an FQRS abnormality.

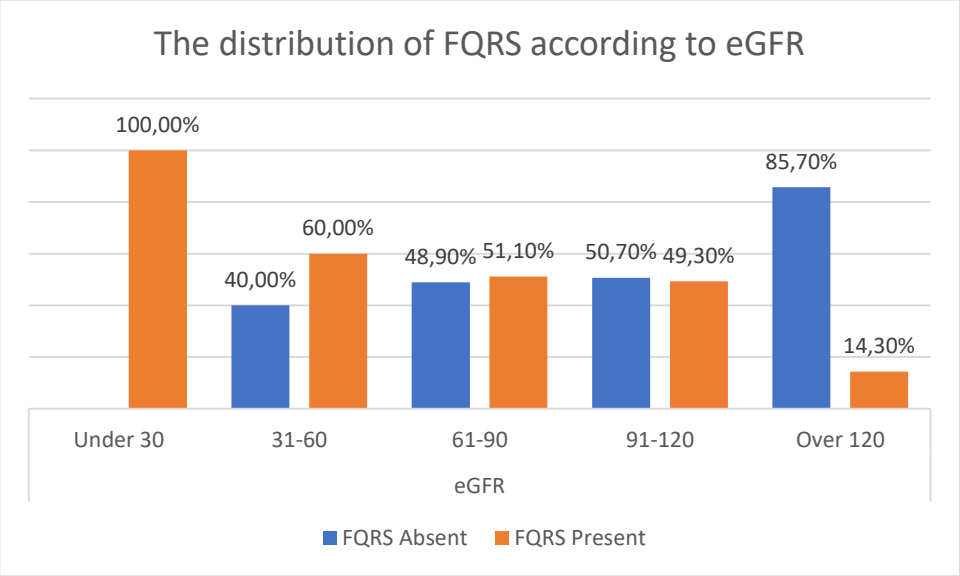

Figure 47: The distribution of fragmented QRS according to their estimated glomerular filtration rate (eGFR) level

16. The distribution of fragmented QRS according to the albumin creatinine ratio (ACR) level:

The bar chart shows the distribution of fragmented QRS (FQRS) according to the albumin-to-creatinine ratio (ACR) level:

- The prevalence of FQRS increases with increasing ACR.
- In patients with an ACR less than 3 mg/mmol, 34.5% of them have FQRS.

- In patients with an ACR of 3.1-30 mg/mmol, 65.5%of them have FQRS.

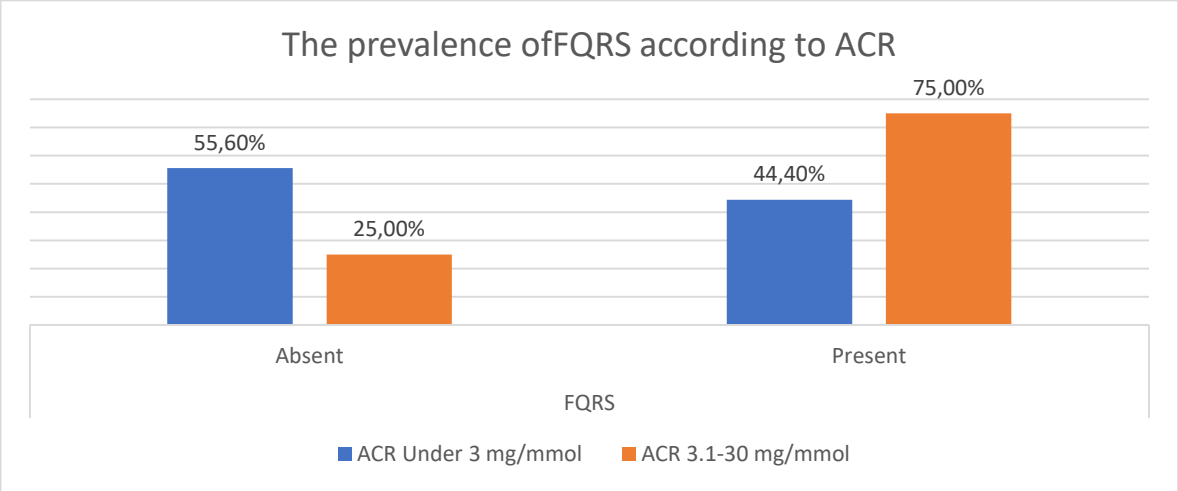

Figure 48: The distribution of fragmented QRS according to the albumin creatinine ratio (ACR) level

17. The distribution of fragmented QRS according to the number of diabetes medications they take:

As shown in the bar chart below:

ABOUT 4/5 of the patients who weren't taking diabetes treatment showed FQRS in their ECGs.

The percentages are approximately equal for the patients whether taking only one medication (50.7%) and (49.3%), or two medications (51.2%); (48.8%) to show an f QRS in their ECGs.

The patients who were taking three medications, only 30% of them showed an FQRS abnormality.

Contrarily, people who were already taking four medications were all (100%) presenting the FQRS in their ECGs.

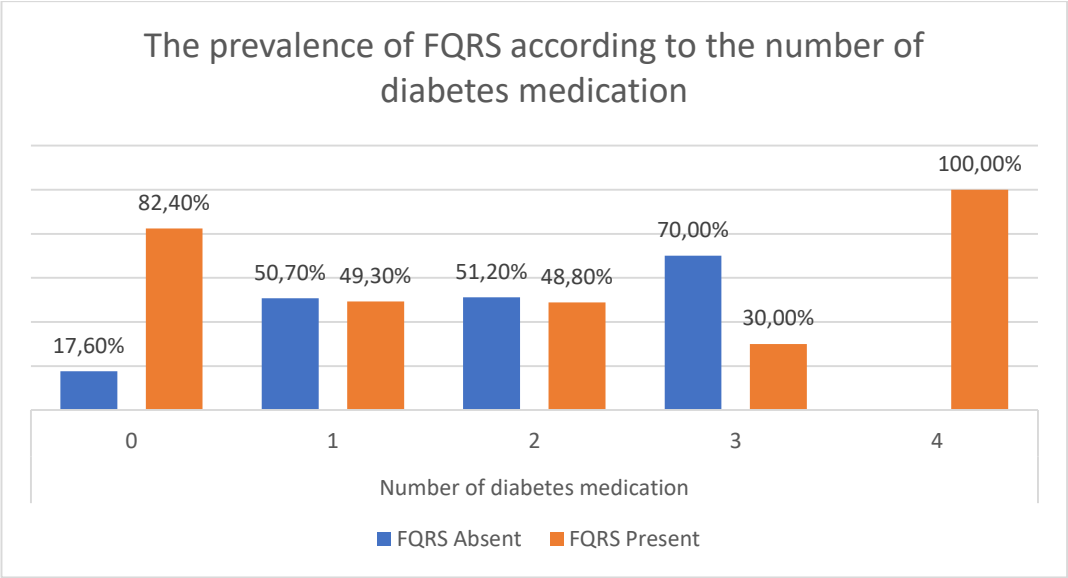

Figure 49: The distribution of fragmented QRS according to the number of diabetes medications they take

18. The distribution of fragmented QRS according to the type of diabetes medication (insulin/ oral medication/association oral–insulin medication:

. The chart below shows the relation between the presence of fragmented QRS and the type of diabetes medication:

Compared to the sample of patients who were taking only one type of medication either insulin only or oral medication (47.6%),(45.7%) respectively, the patients who were taking them together presented a lot more susceptibility to having FQRS abnormality.

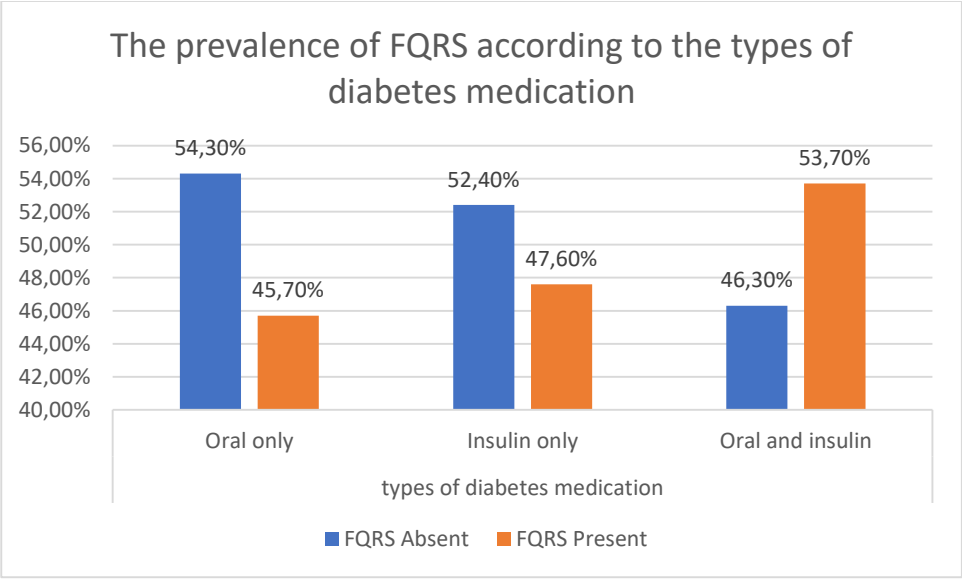

Figure 50: The distribution of fragmented QRS according to the type of diabetes medication

Notifying that there is a slight elevation in the patients who take insulin compared to those who take oral medication only.

19. The distribution of fragmented QRS abnormality according to the use of statin:

The bar chart below shows the distribution of fragmented QRS according to the use of statins: 50.3% of the patients had FQRS abnormality.

Compared to those who take statins and have an FQRS abnormality (56.8%), the percentage of patients who didn't take appear to be less presenting this abnormality (46.2%).

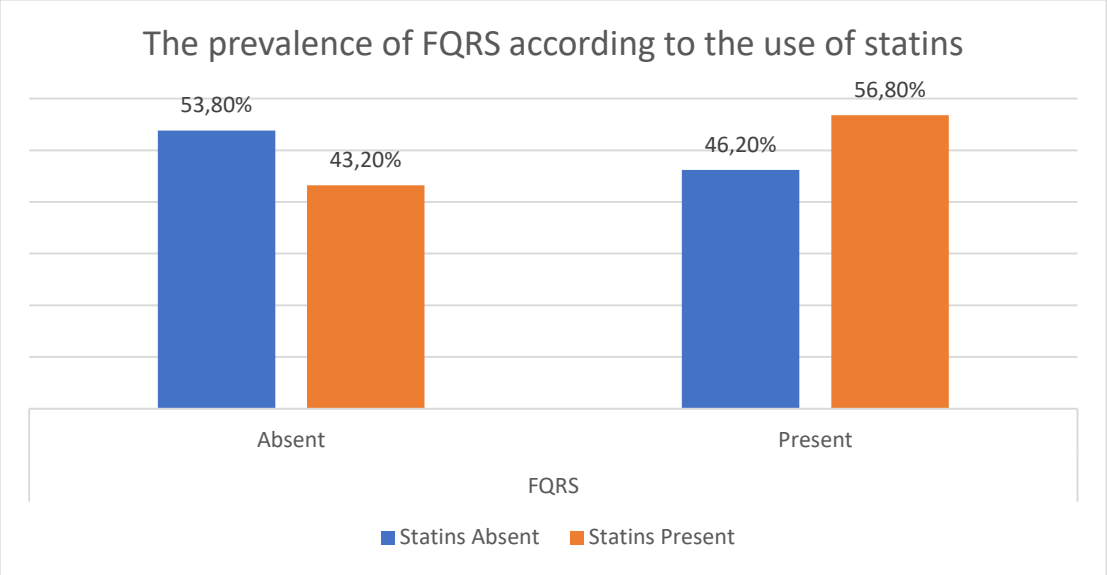

Figure 51: The distribution of fragmented QRS abnormality according to the use of statin

20. The distribution of fragmented QRS abnormality according to the use of antiplatelet (ASP/ PLAVIX/ association ASP-PLAVIX):

The bar chart below shows the distribution of fragmented QRS according to the use of antiplatelet medications: about half of the patients had FQRS abnormality (50.3%).

There is a slightly higher percentage of FQRS abnormality in the patients who do not take antiplatelets (51.9%) compared to those who take it.

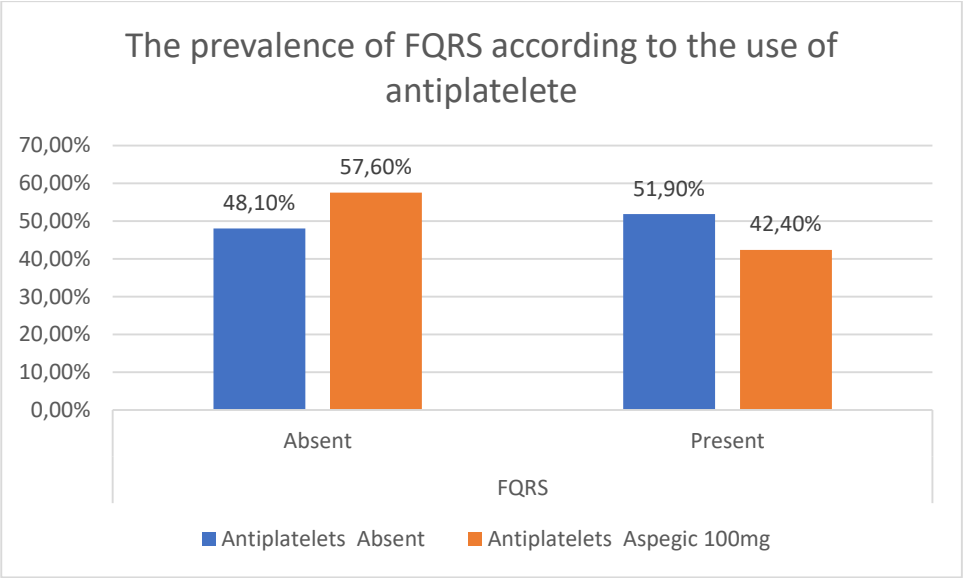

Figure 52: The distribution of fragmented QRS abnormality according to the use of antiplatelet

DISCUSSION

I. The discussion of abnormal ECG:

01- The Prevalence of abnormal ECG:

During the period of our research, among many patients consulting the diabetic care center doing their follow-up, 215 cases were randomly chosen as a sample that benefited from an ECG and consulted by us interns, 191 of them were included as a population of our research respecting the inclusion criteria.

Our study included 191 patients with T2DM followed-up in the diabetic care center in Ouargla in the period between 20/12/2023 and 29/02/2024 (about 02 months and 10 days), which is less than the study of ETHIOPIA.(160) That was done in 02 months and included 344 T2DM patients and the study of CAMEROON.(161) Which included 420 T2DM patients over 02 years. In other words, it was more than the population of the study of BAMAKO.(162), which included 140 patients and persisted for 10 months. Overall, this can be explained by a variety of reasons such as the difference in the studied populations, the period of each study, the inclusion and exclusion criteria, and the small size of our team composed of three members.

In our population, the majority of patients 151 (79.1%) had at least one electrocardiogram abnormality. The high prevalence of ECG abnormalities in our population can be due to a variety of reasons such as the higher risk of developing cardiovascular complications in T2DM patients compared to the general population.

Compared to a prevalence of (61%) in the Ethiopian(160) study, and (55%) in the study of Bamako(162). Our population showed a prevalence of 79.1% of abnormal ECGs. The difference between the prevalence in our population and other studies can be explained by the difference in the socio-economic conditions, health care system in each country, other co-morbidities, patients' history, our study plan, selection criteria, the presence or absence of other risk factors, environmental and genetic variations in each population.

Table 6: Comparison of the abnormal ECG prevalence with Bamako and the Ethiopian study

Study	Our study	Ethiopian study (160)	Bamako study (162)
The prevalence of abnormal ECG	**79,1%**	**61%**	**55%**

02- The distribution of ECG abnormalities according to the type of abnormality in T2DM:

The most present type of abnormality in our population is ischemic and repolarization abnormalities (n=121. 57,1%) which can be explained by the association between type 02 DM with microvascular complications that can affect blood vessels including those supplying the heart. This can lead to reduced blood flow resulting in ischemia. ECG abnormalities serve as a valuable marker for assessing those complications.

The last type of abnormality is arrhythmias with a percentage of (4.7%) and that might be because arrhythmias often manifest later in the progression of T2DM when other complications are more prevalent. It can also be a consequence of the inclusion criteria for the patients in our study that excluded patients with advanced heart complications.

A. The prevalence of LVH in our study was 8.51% which is similar to Bamako(162) study (9.3%) and lower than the study of Dzudie and al (161) Who found the prevalence of LVH at 16.4% and 16%, In another study in South Africa pillay and al (163) Found an even higher prevalence of LVH of 36%, interestingly blood pressure variable was the main determinant of LVH in all the studies, the difference between prevalence in each study can be explained by the different sizes of the samples.
B. The prevalence of atrial fibrillation in our study was 0.43% after excluding patients that were already diagnosed with this pathology, which is similar to Bamako(162) study (0.7%) and lower than Dzudie(161) Who found approximately 5%, this difference in prevalence can be explained by the difference in the number of patients in each study.
C. In our study the prevalence of conduction defects was 16,7% which is higher than the studies of Bamako(162) and Sellers(164) Who found 0,7% and 7% respectively. And almost similar to the study of Pillay(163) That found 17,7% of these outcomes can be explained by the higher prevalence of LVH and signs of ischemic cardiopathy in our study and Pillay's(163) a study comparing Bamako(162) and sellers(164)
D. The prevalence of ischemic cardiopathy in our study was 30,21% which is similar to the study of tougouma(165) (31%). And was higher than the studies of Bamako.(162) Dzudie(161) and Pillay(163) Who found a prevalence of 15% 13,6% and 21,7% respectively, this could be a result of the variation in the sample sizes.
E. In our study the percentage of FQRS between all the ECG abnormalities was 40,85%, this abnormality hasn't been studied in other studies like ours, the high percentage of this

abnormality can be explained by that FQRS is an electrocardigrammic reflection of fibrosis and scar in the myocardium tissue conditions that highly accurate in the diabetes Mellitus

Table 7: Comparison of the prevalence of ECG abnormalities with the other studies

Study	Our study	Bamako (162)	Dzudie and al (161)	Pillay and al (163)	Sellers and al (164)	Tougouma (165)
LVH	8,51%	9,3%	16,4%	36%	/	/
AF	0,43%	0,7%	5%	/	/	/
Conduction defects	16,7%	0,7%		17,7%	7%	/
Ischemic cardiopathy	30,21%	15%	13,6%	21,7%	/	31%
Fragmented QRS	40,85%	/	/	/	/	/

03- The distribution of ECG abnormalities according to the smoking behavior in patients with T2DM:

In our population, the results show that smokers have more abnormal ECGs (88.90 %) compared to non-smokers(78.6%) which was also shown in other studies such as Harms PP(166) And the conclusion was not the same in the study of Bamako.(162) That didn't show a link between smoking behavior and ECG abnormalities in people with T2DM.

Another study by Irfan A(167) That concerned the ECG abnormalities in a normal population showed also a higher prevalence of ECG abnormalities in smokers than the non-smoker participants which confirms that smoking is a risk factor for having an ECG abnormality.

In our population, it was clear that there's a synergetic effect of T2DM and smoking on the cardiovascular system. and it was notable that smoking behavior amplifies the risk of developing ECG abnormalities in T2DM patient this could be explained by their contribution to the development of atherosclerosis, that can lead essentially to a higher risk of ischemia and microvascular damage.

04- The distribution of ECG abnormalities according to age:

In our population, the highest prevalence is found in the older age group (80 – 90) with 100 % abnormal ECG while the least prevalence is found in the age group between (31 – 40) with 54.55% abnormal ECG. If we excluded the youngest age group we observe an increase in the prevalence of ECG abnormality with aging. Our study is similar in results to those concerning the normal population when it comes to age.

A study in Tehran(168) That concerned the ECG abnormalities according to age and gender and found that the prevalence of abnormalities increases with aging. That might mean the increase in ECG abnormalities prevalence with age could be attributed to the natural deterioration of the cardiovascular system.

05- The distribution of ECG abnormalities according to gender:

In our population, a feminine predominance in abnormal ECG with a percentage of (65%) is shown which was similar to Bamako's study(162), and this result could be due to the higher prevalence of women in the population, but comparing the overall results between genders, the prevalence of abnormal EGCs is higher in males (85.5% in males vs 76.0% in females), this could be a result of that the male gender is a risk factor of CVD. It can be also a consequence of the difference in lifestyle between males and females since females are more likely to engage in preventive health behaviors such as regular checkups and screening and to exhibit higher adherence to medication regimens for chronic conditions compared to men.

06- The distribution of ECG abnormalities according to the duration of diabetes:

The prevalence of ECG abnormalities in our population increases as the duration of T2DM increases. The same results were found in the study of Ethiopia.(160) and the study of Cameroon(161). It was different from the Bamako study.(162) That didn't find a relation between the duration of T2DM and the ECG abnormalities.

07- The distribution of ECG abnormalities according to score 02 diabetes:

The prevalence of abnormal ECGs is increasing as the risk of having a higher cardiovascular complication rises from low to very high risk according to Score 2 diabetes.

This score that was recently published in the ESC guidelines proves its efficiency in our population as a predictor of ECG abnormalities and consequently the CV health in patients with T2DM.

The very high-risk category shows the highest percentage of abnormal ECGs.

This might lead to proving the importance of calculating and considering this score in T2DM patients' follow-up and the possibility of its association with the appearance of EGC abnormalities and the CVD risk in the diabetes mellitus population.

It could also to a certain degree replace the need to use each factor mentioned in this score separately since it combines them in a significant way.

08- The distribution of ECG abnormalities according to the score of old persons:

Because of the small sample of our population, we were able to calculate this score, and it is improbable to generalize the usefulness of this score among patients.

09- The distribution of ECG abnormalities according to the patient's hypertensive profile:

In our population, the distribution of normal and abnormal ECGs remains relatively equal across both groups of patients whether they have or do not have hypertension, which indicates the least possibility of finding a correlation between the hypertension profile and a higher risk of ECG abnormality in T2DM patients, same as the study of Bamako that didn't find statistically a link between them in their population conversely to the study of Cameroon were high blood pressure was a common predictor of ECG abnormalities in T2DM.

10- The distribution of ECG abnormalities according to their pathological history with diabetic retinopathy:

In our population, we found a relation between having diabetic retinopathy and ECG abnormalities, and this might be reasonable considering the microvascular damage caused due to diabetes including multiple mechanisms such as oxidative stress, endothelial dysfunction, and vascular inflammation causing target organ damage (microalbuminuria along with retinopathy and neuropathy) associated to the ASCVD.

11- The distribution of ECG abnormalities according to the cardiac symptoms:

In our population, great attention was dedicated during the data collection and analyses to search for a relation between the cardiac symptoms and the ECG abnormalities whether it would be a synergic relation or not. Each symptom was studied separately with its characteristics.

As shown in the results, there wasn't any significant correlation between any of the cardiac symptoms and ECG abnormalities.

The insidious nature of diabetes and its physiopathology allows the development of CVD and TOD which amplifies and increases the risk of having a silent death among the patient or at least a notable progression of its complications and deterioration in the patient's health.

12- The distribution of ECG abnormalities according to the body mass index (BMI) value

The results show that the prevalence of ECG abnormality was approximately the same (between 69.2% and 76.3) in normal and overweight and also in obesity class 01 and 02. Conversely, in body mass index greater than 40 kg/m2, the prevalence reached 100% abnormal ECG. This may suggest that extreme obesity has a profoundly negative impact on cardiac health, another explanation might be that for obesity class 03 the sample size is significantly smaller than the other groups, so 100% might not be representative of the entire population. All, it is essential to consider our population size which might be non-representative to study such an indicator.

13- The distribution of ECG abnormalities according to the glycated hemoglobin (HbA1c) value and fasting glucose level:

In our population, HbA1c and fasting glucose levels were approximately equal in all categories, whether the normal or abnormal ranges and didn't show any significant effect on the presence of ECG abnormalities. Conversely, other studies such as the Netherlands(166) A study showed that higher Hba1c levels and lower fasting glucose levels were predictors of major and minor ECG abnormalities.

This might be explained by the small sample of our population and the limited duration of our study.

In HbA1c greater than 15% the prevalence reached 100% abnormal ECG. The explanation might be that in this category the sample size was significantly smaller than the other categories, so 100% could not be representative of the entire population.

14- The distribution of ECG abnormalities according to the patient's estimated glomerular filtration rate (EGFR) level and the albumin creatinine ratio (ACR) level.

The results of our research show that there appears to be a strong correlation between lower eGFR levels and a higher likelihood of ECG abnormalities. As eGFR decreases, the percentage of abnormal ECGs increases.

These results were similar to those shown in the study of the Netherlands.(166) and Ethiopia(160).

And this may lead us to think that.

Lower eGFR levels directly can present a predictor of the development of cardiac abnormalities as reflected by ECG changes.

This can be explained by a variety of mechanisms such as Autonomic Dysfunction, Oxidative Stress, Electrolyte Imbalance, and systemic and chronic inflammation caused by diabetes same mechanisms that lead to TOD and CVDs.

The same results were observed according to the ACR levels:

A clear correlation indicates a strong association between the two variables. As ACR levels increase, there's a consistent upward trend in the rate of ECG abnormalities.

This can lead us to conclude that this renal indicator can be a strong predictor of cardiovascular events among individuals with type 2 diabetes mellitus.

15- The distribution of ECG abnormalities according to the number and type of diabetes medication they take:

Patients without any diabetes medication had a 100% prevalence of abnormal ECGs. Patients in this group might have very advanced, poorly controlled diabetes or a late diabetes diagnosis that could already create CV complications.

A decreasing trend in ECG abnormalities was observed with an increasing number of medications, from 79.7% with one medication to 65.0% in patients taking three medications. However, patients on four medications surprisingly showed a 100% prevalence of ECG abnormalities. This might be because Patients with a higher number of diabetes medications represent more severe cases of the disease, which is associated with a higher risk of cardiovascular complications, including ECG abnormalities.

Also, the results show the prevalence of ECG abnormalities among patients with different diabetes medication regimens. Patients solely on insulin exhibited the highest rate of ECG abnormalities (85.7%), while those exclusively on oral medications showed the lowest (74.1%). The combined use of oral medications and insulin resulted in an 82.9% prevalence. Oral medication-only patients might have milder diabetes, better controlled with oral agents, and consequently, a lower risk of ECG abnormalities. While Insulin-only patients might represent a more severe form of diabetes, often already an advanced type 2 DM, which is associated with a higher risk of complications, including cardiovascular issues also, Insulin therapy can influence electrolyte balance, particularly potassium levels, which can affect heart rhythm and lead to ECG abnormalities.

16- The distribution of ECG abnormalities according to the use of statin:

The results show that 87.5% of patients using statins had an abnormal ECG while 73.5% of patients who weren't taking statins had an abnormal ECG. Our results suggest a potential association between statin use and a higher prevalence of abnormal ECG findings. However, this does not necessarily imply that statins directly cause these abnormalities. Other Factors might be included. For example, patients on statins might have underlying cardiovascular conditions or at least another condition that needs statin prescription and predisposes them to ECG abnormalities, Jun JE.(169) Found that Statin has a protective effect against CVD and all-cause death in type 2 diabetes, this effect was reduced beyond the age of 75 years and disappeared in young patients aged <40 years.

17- The distribution of ECG abnormalities according to the use of antiplatelet:

The results show that the patients using antiplatelets had more abnormal ECG than patients who weren't taking antiplatelet medication. Among our patients, there was only aspirin as an antiplatelet. Other such as clopidogrel was found during collection but it was eliminated according to exclusion criteria. The PPP trial(170) was a study to see if aspirin or vitamin E

could help people with a high risk of heart problems Aspirin helped people without diabetes a lot. It reduces their risk of heart problems, heart attacks, and death from heart problems. But Aspirin didn't seem to help people with diabetes as much. There was no clear difference between those who took aspirin and those who didn't.

We could explain this by that People with diabetes may be more exposed to blood clots due to increased platelet activity and inflammation. Aspirin might not be as effective in preventing these clots because alternative pathways for clot formation might be reasonable. Normally, aspirin blocks the production of TXA2, but in people with diabetes, another enzyme called COX-2 might take over and continue to produce TXA2.COX-2 is often activated in situations of inflammation, which is common in diabetes(171–173).

II. The discussion of fragmented QRS:

01- The prevalence of fragmented QRS abnormality in the population of patients with type 2 diabetes mellitus:

The results of our research show that out of 191 patients, 50.3% (95 patients) had an abnormal fragmented QRS complex. Which represent approximately half of our patients.

In this study we found that half (50,3%) of our population presented an FQRS abnormality in their 12 leads rest ECG, Kunimasa Yagi(174) found a prevalence of 37% in Japanese patients with diabetes Mellitus and metabolic syndrome and a prevalence of 35% in diabetic subjects without metabolic syndrome, Bayramoglu et al (175) reported a prevalence of FQRS of 28%, Eren et al(155) reported 37.5% among diabetes mellitus patients in a Turkish population, another study in Egypt done by Mahfouz and al (176) detected a prevalence of 62% of FQRS in their population of diabetic patients the difference in prevalence is most likely because of the differences in the studied population numbers and race, the high prevalence of FQRS in diabetes mellitus populations compared to the general population can be explained by the cardiac fibrosis that can touch myocardium tissue, Hyperglycemia induces a profibrotic cascade, characterized by the accumulation of advanced glycation end products (AGEs). These glycated proteins crosslink extracellular matrix components, thereby promoting fibrosis. Mechanistically, AGEs exert their effects through the generation of reactive oxygen species and activation of the receptor for advanced glycation end products (RAGE). Concurrently, pro-inflammatory cytokines and chemokines orchestrate the recruitment of inflammatory cells into the cardiac interstitium, fostering a fibrotic

microenvironment. The activation of the transforming growth factor-beta (TGF-β)/Smad signaling pathway stimulates fibroblast differentiation and extracellular matrix deposition. Moreover, adipokines, endothelin-1, and the renin-angiotensin-aldosterone system are implicated in the pathogenesis of diabetic cardiomyopathy(177).

Table 8: Comparison of the FQRS prevalence with the other studies.

Study	Our study	Kunimasa Yagi(174)	Bayramoglu and al (175)	Eren and al(155)	Mahfouz and al (176)
The prevalence of FQRS	50,3%	37% D+,Mets+ 35% D+,Mets-	28%	37.5%	62%

02- 02. The distribution of fragmented QRS according to the smoking habit:

The results suggest that there is no difference in the prevalence of fragmented QRS between smokers and non-smokers. Both smokers and non-smokers have an almost equal prevalence of fragmented QRS, the prevalence of FQRS in smokers was 55,65% vs 50,0% in non-smoker patients. Bayramoğlu and al(178) Found a difference between the smokers and the non-smokers (18,5% vs 6%) where smokers presented more abnormalities. This could be because of the small size of our subpopulation of smokers (n=9).

Table 9: Comparison of the distribution of FQRS according to smoking habit with Bayramoğlu and al(178)

Study	Our study	Bayramoğlu and al(178)
The prevalence of FQRS in non-smokers	50,0%	6%
The prevalence of FQRS in smokers	55,65%	18,5%

03- The distribution of fragmented QRS according to age:

The distribution of FQRS according to age didn't show a significant difference between age groups except for the elder group which presented a prevalence of 100.0% this could be of the variety of age group sizes the elder age group had only three patient while the group age between 51-60 had a 59 patient, while numerous studies have explored the relationship

between FQRS and various cardiovascular conditions, specific research focusing solely on FQRS and age is relatively limited. However, several studies have shown that older populations with cardiovascular diseases often exhibit a higher prevalence of FQRS compared to younger patients. FQRS in elderly patients is associated with increased mortality and morbidity.

04- The distribution of fragmented QRS according to gender:

The distribution of FQRS according to gender showed that male patients slightly presented more FQRS abnormality than female patients with a difference of 4.40%, the reasons behind this could be attributed to the masculine sex being a risk factor for cardiovascular diseases and the fact that female patients are more discipline in respecting diabetes plans of treatment and regular follow-ups if we considered the fact that only the third of our population is male patients (32,5%. N=62) we could expect a higher prevalence of FQRS abnormality if we had a population divided equally according to patients gender, Haukilahti and al.(179) Found that in the general population, FQRS was more commonly found among men in comparison to women (20.5% vs. 14.8%, $p < 0.001$). The prevalence of FQRS rose gradually along with the severity of prior cardiac disease in both genders, yet remained significantly higher in the male population: subjects with suspected or known cardiac disease (25.4% vs. 15.8% $p < 0.001$), CAD patients without prior MI (39.9% vs. 26.4%, $p < 0.001$), CAD patients with prior MI (42.9% vs. 31.2%, $p < 0.001$), and victims of SCD (56.4% vs. 44.4%, $p < 0.001$).

Table 10: Comparison of the FQRS prevalence according to patients' gender with Haukilahti and al(179)

Study	Our study	Haukilahti and al(179)
The prevalence of FQRS in males	**53,2%**	**20.5%**
The prevalence of FQRS in females	**48,8%**	**14.8%**

05- The distribution of fragmented QRS according to the age of diabetes:

The table below presents the distribution of FQRS according to the duration of type 2 diabetes. The results show that the prevalence in the group of less than one year of diabetes had a percentage of 48.4%. The highest prevalence marked was in the group with more than 20 years of diabetes with a percentage of 56.3%.

The prevalence of FQRS was shown to be variable in the different group durations, we couldn't find a significant relation between the two variables. However, the highest prevalence of FQRS was observed in the longest duration of T2DM above 20 years.

06- The distribution of fragmented QRS according to score 02 diabetes:

The results show that in our population there is 0 patient in the group of Low risk, the prevalence of FQRS in the two groups of moderate and high risk is approximately equal with a percentage of 14.8% and 11.1% respectively, and the highest prevalence was marked in the group of very high risk with a percentage of 74.1%.

In our population, the risk of having this abnormality increases when this score increases,

This can lead to the conclusion that this score can be useful as a predictor of CVD and in detecting this abnormality, To our knowledge, there weren't any recent studies that have used this score and studied it after being published in the ESC guidelines.

07- The distribution of fragmented QRS according to score old person:

In our population, the subpopulation where it was possible to calculate this score was very small the reason why we couldn't build any hypothesis on its statistics results.

08- The distribution of fragmented QRS according to their hypertensive profile:

In our population, there wasn't any significant relation between the first abnormality and hypertension. Other studies that are concerned with FQRS and hypertension have shown that FQRS may be a sign of increased hypertension and may predict a higher fibrotic burden in people with hypertension independently of diabetes.(180).

09- The distribution of fragmented QRS according to their pathological history with diabetic retinopathy:

In a small subpopulation where the patients presented diabetic retinopathy, 8.3% of them presented FQRS while 5.3% of them didn't have an FQRS, although this sample can't be that representative, we could notice a correlation since both of these abnormalities (DR and FQRS) might be a consequence of the diabetes CV complication and its damage on the microvascular circulation.

10- The distribution of fragmented QRS according to the cardiac symptoms:

A. Dyspnea:

The results suggest that there is no significant difference in the prevalence of fragmented QRS patients who presented dyspnea and those who didn't. Both of the groups have an almost equal prevalence of fragmented QRS.

It seems that when speaking about diabetic patients, the correlations between clinical symptoms and their significance, should not be always present since the complication can be present whether the patient has the symptom or not.

It might also be explained that dyspnea is not the major symptom that can refer to finding an FQRS in a diabetic patient.

B. Chest pain:

In our population, in the group of patients who didn't present chest pain half of them had an FQRS (50.0%). The group with non-characteristic chest pain presented more FQRS abnormality compared to the group of patients complaining of characteristic chest pain, with a higher one in patients with non-characteristic pain.

According to these results, the FQRS abnormality is not related to the presence of chest pain as a symptom. And apparently, patients can have this abnormality.

C. Syncope /fainting and palpitation:

As seen before, syncope fainting and palpitation as cardiac symptoms weren't related to FQRS complications and both apparently healthy people and patients who reported having those symptoms presented this abnormality in their ECG.

Overall, there wasn't any correlation between cardiac symptoms and the presence of FQRS abnormality. This might be explained by the fact that Diabetic patients often exhibit atypical or absent symptoms of cardiac disease due to diabetic neuropathy, a nerve damage caused by chronically high blood sugar levels. This condition can impair the nerves responsible for transmitting pain signals from the heart, leading to a phenomenon known as "silent ischemia." Studies like those published in the New England Journal of Medicine have shown a correlation between the severity of diabetic neuropathy and the likelihood of silent

myocardial ischemia, where heart damage occurs without the typical chest pain or discomfort. Consequently, diabetic individuals are at increased risk of heart attacks and other cardiac complications that go undetected until they reach critical stages.

11- The distribution of fragmented QRS according to the body mass index (BMI) value:

Among the study population, overweight and obese patients had more FQRS than weight patients, significantly obese patients presented the highest FQRS prevalence at 53.3% these results are similar to the results of Eyuboglu and al(181) Who found that obese patients had a significantly higher frequency of FQRS on ECG compared to non-obese patients ($p < 0,001$). And revealed that BMI is an independent predictor of the presence of FQRS on ECG (OR:1,220, 95% CI: 1,177-1,266, $p < 0.0001$). Several mechanisms may explain the association between BMI, obesity, and FQRS:

Increased cardiac workload: Obesity can increase the heart's workload, leading to hypertrophy and potential fibrosis.

Metabolic disturbances: Obesity is often associated with metabolic abnormalities like insulin resistance and dyslipidemia, which can contribute to cardiac damage.

Inflammatory processes: Chronic low-grade inflammation, common in obesity, can promote fibrosis and other cardiac complications(182,183).

12- The distribution of fragmented QRS according to the glycated hemoglobin (HbA1C) value:

The results show that there is no significant relation between FQRS and the patient's HbA1c we observed that the group of hb1c <6.5 marked the highest prevalence of FQRS abnormality 61.5%, this could be explained by the different size of HbA1c divided groups and the fact that less level of HbA1c could be found in patients who had a long history of non-controlled diabetes then after years they managed to decrease their HbA1c level when the cardiac tissue damage is already installed, furthermore there is no specific research that studied the relationship between HbA1c and FQRS. More research is needed to fully understand the complex relationship between HbA1c and FQRS.

13- The distribution of fragmented QRS according to the fasting glucose level:

Among our population patients who had an above 1.10 g/l glucose level presented more FQRS abnormality than patients who had an under 1.10 g/l glucose level this suggests that there is a significant relationship between FQRS and fasting glucose level, elevated fasting glucose levels are often associated with insulin resistance increased oxidative stress and inflammation additionally to the formation of advanced glycation end products (AGEs), these factors contribute to myocardial fibrosis

14- The distribution of fragmented QRS according to their estimated glomerular filtration rate (EGFR) level:

In our population, FQRS abnormality showed an increase in prevalence with decreasing in eGFR level which suggests a significant relationship between these two variants, the patient group of eGFR over 120 presented only 14,30% of FQRS among the group subjects while all the patients who had eGFR under 30 presented an FQRS, diabetes is a leading cause of CKD. High blood sugar levels damage the kidneys over time, leading to decreased eGFR. Both CKD and diabetic cardiomyopathy share common pathophysiological mechanisms, including inflammation, oxidative stress, and endothelial dysfunction. Which can explain the relationship between eGFR level and FQRS in diabetic patients

15- The distribution of fragmented QRS according to the albumin creatinine ratio (ACR) level:

In our population, we found that patients who had an ACR between 3-30 mg/l presented more FQRS abnormality compared to patients who had a normal ACR under 3 mg/mmol (75,0% vs 44.4%), Cetin et al(184) Found the prevalence of FQRS was 59.2% in the presence of microalbuminuria in patients with T2DM vs 26,0% in patients without microalbuminuria, Ozkan et al(185) Investigated the association between FQRS and proteinuria in nephrotic syndrome patients who are under treatment. They found higher proteinuria and TEI index in those whose ECG had FQRS. Adar et al(186) Found that the prevalence of an FQRS was 60% in chronic renal failure patients with a preserved left ventricular ejection fraction, Both ACR and FQRS represent early signs of organ damage, with ACR reflecting kidney involvement and FQRS indicating cardiac abnormalities. The fact that diabetes is a major risk factor for these two pathologies can explain the reason behind the relationship between ACR and FQRS in T2DM patients.

Table 11: Comparison of the FQRS prevalence according to ACR with Cetin and al(184)

Study	Our study	Cetin and al(184)
The prevalence of FQRS without microalbuminuria	44.4%	26,0%
The prevalence of FQRS with microalbuminuria	75,0%	59,2%

16- The distribution of fragmented QRS according to the number of diabetes medications they take:

The results showed that the prevalence of FQRS according to the number of diabetes medications patients take is drawing a U-shaped graph which means that the highest rates are found in the extremes of the population this could be explained by that the patients who don't take any treatment are more threatened to have cardiovascular complications as results of uncontrolled diabetes while the patients who take four treatments had even a higher prevalence of FQRS 100.0% the use of multiple medications often suggests a higher overall cardiovascular risk, we observed also a decreasing in FQRS from the patients that use only one medication 49.30% to the category of three types of diabetes medication 30,0% this results could mean that multiple medications help better in preventing cardiovascular complications in diabetes patients.

17- The distribution of fragmented QRS according to the type of diabetes medication (insulin/ oral medication/association oral–insulin medication:

The patients who were taking only one type of medication insulin or oral only presented similar prevalences of FQRS. It may be inferred that this category of patients has similar lab results and clinical symptoms so they need only one type of medication regardless of other factors, or it is possible to hypothesize that insulin only has the same results in controlling diabetes as oral medication, the patients who take insulin and oral medication in the same time presented a higher prevalence of FQRS this could be attributed to that this category of patients is in advanced stages of diabetes complications, especially cardiovascular ones.

18- The distribution of fragmented QRS abnormality according to the use of statin:

The distribution of FQRS according to the use of statins didn't show any significant relationship, the results show that patients who didn't have statins presented less FQRS

abnormality 43,20% compared to those who did use statins 56,80%, statins are often indicated in patients with cardiovascular risk factors like hypertension, diabetes, and dyslipidemia. They have anti-inflammatory properties, which can potentially reduce inflammation-mediated myocardial damage and fibrosis, factors contributing to FQRS, Statins have been shown to reduce the risk of heart attacks and strokes, which can indirectly impact the development or progression of FQRS, so we expected to see a reducing in FQRS prevalence by the use of statins but the results were the opposite this outcome might be a consequence of that the two samples size are different (statins n= 74. No statins n=117) additionally our study is not a follow-up study so this results with time could be inversed

19- The distribution of fragmented QRS abnormality according to the use of antiplatelets (ASPIRIN/ CLOPIDOGREL/ association ASPIRINE-CLOPIDOGREL):

The patients who were taking antiplatelet had less prevalence of FQRS at 42,40% compared to the patients who didn't take it at 51,90%, Diabetes patients may experience altered platelet function due to various factors such as metabolic changes, oxidative stress, and endothelial dysfunction(187,188), Diabetic platelets are more sensitive to agonists and respond differently to antiplatelet drugs compared to non-diabetics due to these anomalies. Aspirin is the first antiplatelet agent of choice for secondary prevention of ischemic events in patients with atherothrombotic disease, including in patients with diabetes mellitus. Aspirin may also be used for primary prevention of ischemic complications. Although its use in the latter scenario in the general population remains somewhat controversial, there is an overall expert consensus on the appropriateness of using aspirin for primary prevention in patients with diabetes mellitus, which can explain the role of antiplatelet in reducing FQRS.(189).

III. Forces and limitations in the study:

A. Limitations:

From the beginning and throughout this work, we encountered several obstacles and biases, including:

1. A limitation of the study was the lack of full cooperation from some patients, which may have impacted the completeness and accuracy of the collected data.
2. We did not calculate statistical indicators such as the p-value and chi-square. Instead, the presentation of results was limited to percentages and simple comparisons, which may limit the depth of statistical analysis and the ability to draw more robust inferences from the data.
3. Lack of a computerized system: The absence of a computerized system facilitating access to patients' medical data can lead to data entry errors, data loss, and difficulties in research.
4. Cross-Sectional Design: Our study employed a cross-sectional design, which provides a snapshot of the prevalence of ECG abnormalities in Type 2 Diabetes Mellitus patients at a single point in time. This design limits our ability to conduct long-term assessments or track changes in patients' cardiovascular health over time. Consequently, we were unable to observe the progression of ECG abnormalities or their impact on long-term clinical outcomes. Future longitudinal studies are needed to provide insights into the temporal dynamics of ECG abnormalities and their long-term implications for patients with Type 2 Diabetes Mellitus.

B. Forces:

Despite the challenges encountered during this study, it has several notable strengths:

1. Our study could serve as a starting point for several other research efforts. By investigating the prevalence of electrocardiographic abnormalities in patients with Type 2 Diabetes Mellitus and their relationship to clinical features and cardiac symptoms in the Ouargla region, this research lays the groundwork for future studies. Subsequent research could delve deeper into the specific causes and consequences of ECG abnormalities in diabetic patients, explore their prognostic value, and assess the impact of various management strategies. This foundational work can also prompt further exploration in different geographic areas or among diverse populations, potentially leading to a broader understanding of cardiovascular

complications in diabetes and informing more effective clinical practices and public health policies.

2. Our study contributes to highlighting the importance of continued research into the cardiovascular health of diabetic patients. By emphasizing the need for further investigation, this study aims to encourage additional research initiatives that could address unresolved questions, refine diagnostic and treatment approaches, and ultimately improve patient outcomes in the management of Type 2 Diabetes Mellitus.
3. Our study brings attention to previously neglected ECG abnormalities that were common but not well recognized within our population and among clinicians in the region. These findings underscore the originality of our research and its alignment with the latest information and recommendations concerning diabetes and ECG abnormalities. By identifying and highlighting these overlooked abnormalities, our study helps to fill critical gaps in knowledge, emphasizing the need for clinicians to be aware of and address these issues to enhance diagnostic accuracy and patient care.

IV. Recommendations and perspectives:

General Recommendations:

A. Managing Diabetes:

Diabetes is a major risk factor for cardiovascular disease, and our study aimed to draw attention to how important it is to prevent the appearance of cardiovascular complications in this population, or at least be capable of controlling it and detecting it when it happens. This disease is a major health problem so we recommend:

01- Raise Awareness and Educate:

Regional health authorities should implement awareness campaigns highlighting the dangers of diabetes and the importance of maintaining a healthy diet and regular physical activity. Regular educational sessions should be held for diabetic patients and their families to guide managing the condition, it is important to notify diabetic patients about the importance of ECG screening to detect early cardiac abnormalities.

02- Promote Early Detection:

Establish screening centers across various communities to facilitate the early diagnosis of diabetes. Regular blood glucose testing should be offered to those at high risk, particularly older adults, individuals with excess weight, and those with a family history of diabetes.

03- Ensure Access to Care:

Diabetic patients should have easy access to medical care and necessary medications. Local healthcare facilities should be established, and healthcare professionals trained to provide proper diabetes management.

04- Regular chick up:

Implement Regular Check-ups and Preventive Examinations for Patients, to effectively manage Type 2 Diabetes Mellitus (T2DM) and reduce the risk of complications, it is crucial to schedule regular check-ups and preventive examinations for patients. Consistent monitoring allows healthcare providers to assess blood sugar levels, adjust medications, and track any emerging health issues. Preventive care, including screenings for cardiovascular health, kidney function, eye health, and foot care, can detect complications early, enabling timely interventions. By prioritizing these routine evaluations, you can help ensure better disease management, improve patient outcomes and enhance the overall quality of life for those living with T2DM.

05- Utilize Complementary Check-ups, Including Blood Tests and ECGs, to Enhance Patient Care:

To provide comprehensive care for patients, it is essential to incorporate complementary check-ups such as blood tests and electrocardiograms (ECGs). Blood tests can offer critical insights into various health markers, including blood sugar levels, cholesterol, and kidney function, which are vital for managing chronic conditions like Type 2 Diabetes Mellitus (T2DM). Additionally, ECGs can help monitor heart health, identifying any early signs of cardiovascular issues. By integrating these diagnostic tools into regular care routines, you can gain a more complete understanding of your patients' health, allowing for more informed treatment decisions and better long-term outcomes.

B. Managing Other risk factors that amplify the risk of CVD in T2DM and prevention methods:

01- Hypertension:

It is important to screen for hypertension early in life. Screening initiatives could be conducted in schools, health centers, and other public venues to enable the early detection of high blood pressure.it is also important to Continuous monitoring of individuals with hypertension is essential.

02- Smoking:

Educate the general public about the dangers of smoking and the benefits of quitting through media campaigns and educational programs.it is needed to Create centers to help smokers quit by providing medical, and psychological support, and counseling. The government should Prohibit smoking in public spaces such as restaurants, healthcare facilities, and workplaces and raise taxes on tobacco products to make them less accessible and less appealing, especially to young people.

03- Dyslipidemia lipidic and metabolic disorders:

Inform the public about dyslipidemia, its health consequences, and prevention strategies. Also, offer regular lipid profiles for individuals at risk (based on age, family history, obesity, diabetes, hypertension, and smoking).

Ensuring optimal medical management of individuals with dyslipidemia, with personalized treatment depending on the type and severity of dyslipidemia is a necessity to manage.

Finally, establish regular monitoring and evaluation systems to measure the program's impact and adjust actions accordingly.

04- Sedentary Lifestyle:

We have to Raise Awareness and educate the public about the dangers of a sedentary lifestyle and the benefits of staying active.

It is also important to Encourage regular physical activities that are culturally appropriate, such as walking, swimming, or cycling, and promote the use of public spaces for exercise.

05- Lifestyle Interventions:

- Healthy Eating: Advocate for a diet rich in fresh fruits and vegetables, whole grains, and lean proteins, while reducing the intake of saturated fats and added sugars.
- Stress Management: Promote stress management techniques such as meditation, deep breathing, yoga, and muscle relaxation exercises.
- Maintain a Healthy Weight: Encourage individuals to maintain a healthy body weight through balanced eating and regular physical activity.

C. Development of Therapeutic Education Programs:

1. Create Educational Materials: Develop informational resources for patients, such as brochures, educational videos, and health guides.
2. Organize Regular Educational Sessions: Conduct regular therapeutic education sessions for patients to help them manage their conditions effectively.
3. Provide Ongoing Support: Offer regular follow-up to assess patients' health status and their progress in managing their condition.
4. Form a Multidisciplinary Team: Establish a working group of healthcare professionals, including endocrinologists, nurses, dietitians, and psychologists, to design and implement the program.

To the Hospital Administration:

Provide ECG machines in all healthcare services and regional clinics to ensure early detection and management of cardiac abnormalities in patients particularly those with diabetes. These measures would help improve patient outcomes by facilitating timely diagnosis and appropriate treatments.

Establish a Regional Registry: Implement a regional registry to document the epidemiological and clinical characteristics of the population affected by diabetes.

Digitize Health Systems: Introduce computerized health systems and patient management software to facilitate the collection, analysis, and management of medical data. Utilizing these digital tools will improve care coordination and enable faster, more efficient patient management.

Ongoing Training for Physicians:

- In-Person Training: Organize in-person training sessions through recognized medical institutions to enhance physician's knowledge in diabetes management.
- Offer Online Courses: Provide online training options that allow physicians to learn at their own pace and according to their availability.
- Encourage Conference Participation: Promote participation in conferences and seminars to keep physicians updated on the latest advancements in diabetes care.

To the Ministry of Health:

Establishing and Enhancing Diabetes Centers:

- Create New Specialized Diabetes Centers in our region: Develop new centers focused on comprehensive diabetes management to provide specialized care and support for patients and that would Increase accessibility to specialized diabetes care for underserved populations and ensure equitable treatment across different regions.
- Develop Existing Centers: Upgrade and expand current diabetes centers to enhance their service offerings, including advanced treatment options, patient education, and research facilities.
- Strengthen studies and research on this pathology by:
- Encouraging collaboration between different research stakeholders, whether from the academic or industrial sectors, to promote the sharing of knowledge and resources.
- Increasing funding allocated to research on this pathology to support ongoing research projects and encourage new initiatives.
- Stimulating patient participation in studies and research by providing better access to information and involving them more in the research process

CONCLUSION

Conclusion:

Type 2 Diabetes Mellitus (T2DM) is not merely a disorder of glucose metabolism but a systemic disease with widespread effects, particularly on the cardiovascular system. As the global prevalence of T2DM continues to rise, so too does the burden of its complications, with cardiovascular disease (CVD) being the most significant contributor to morbidity and mortality in this population.

Our study, which assessed the prevalence of electrocardiogram (ECG) abnormalities in 191 T2DM patients, revealed that an alarming 79% exhibited abnormal ECG findings. This high prevalence highlights the covert nature of cardiovascular pathology in diabetic individuals, many of whom remain unaware of their cardiovascular risk due to the often asymptomatic progression of such conditions.

The most commonly detected type of abnormalities in our study were ischemic and repolarization disturbances, among them fragmented QRS complexes were the most frequent. These findings are particularly noteworthy as they suggest underlying myocardial ischemia, scarring, cardiac fibrosis, or other forms of cardiac stress, which are frequently silent in T2DM patients. The fragmented QRS, for example, is indicative of myocardial fibrosis, which may be a result of prior silent myocardial infarctions – a phenomenon not uncommon in diabetics due to their altered pain perception caused by autonomic neuropathy.

One of the most striking findings of our study was the lack of correlation between clinical symptoms and ECG abnormalities. Many patients with significant ECG findings did not report any cardiac symptoms, a fact that poses a substantial challenge for clinicians. This disconnect underscores the need for proactive cardiovascular screening in T2DM patients, irrespective of symptomatology, to prevent the development of more severe, symptomatic disease stages that could lead to catastrophic outcomes.

The role of ECG in the management of T2DM patients thus emerges as critical. ECG is a readily available, non-invasive tool that provides valuable insight into the cardiac status of these patients. Given the high prevalence of subclinical cardiovascular disease in T2DM, routine ECG screening should be integrated into standard care protocols. Early detection of ECG abnormalities can facilitate timely interventions, such as further diagnostic testing, risk factor modification, and the initiation of cardioprotective therapies.

Furthermore, the predictive value of specific ECG findings in T2DM patients cannot be overlooked. For instance, the presence of fragmented QRS complexes and ischemic changes has been linked to an increased risk of major adverse cardiovascular events, including heart failure and sudden cardiac death. Identifying these high-risk patients through routine ECG screening could allow for more personalized and aggressive management strategies, potentially improving long-term outcomes.

Finally, our study highlights the pervasive nature of cardiovascular abnormalities in T2DM patients and the essential role that ECG screening can play in mitigating this risk. The lack of symptom correlation with ECG findings suggests that reliance on clinical symptoms alone is insufficient in managing cardiovascular risk in this population. Therefore, incorporating regular ECG assessments into the care of T2DM patients could significantly enhance early detection and intervention, ultimately reducing cardiovascular morbidity and mortality.

Looking forward, further research is needed to explore the mechanisms linking T2DM with specific ECG abnormalities and to evaluate the long-term benefits of routine ECG screening. As the global burden of T2DM continues to grow, so too does the need for comprehensive, evidence-based strategies to manage its cardiovascular complications effectively. Routine ECG screening represents a valuable, underutilized tool in this effort, offering a pathway to better cardiovascular outcomes for millions of T2DM patients worldwide.

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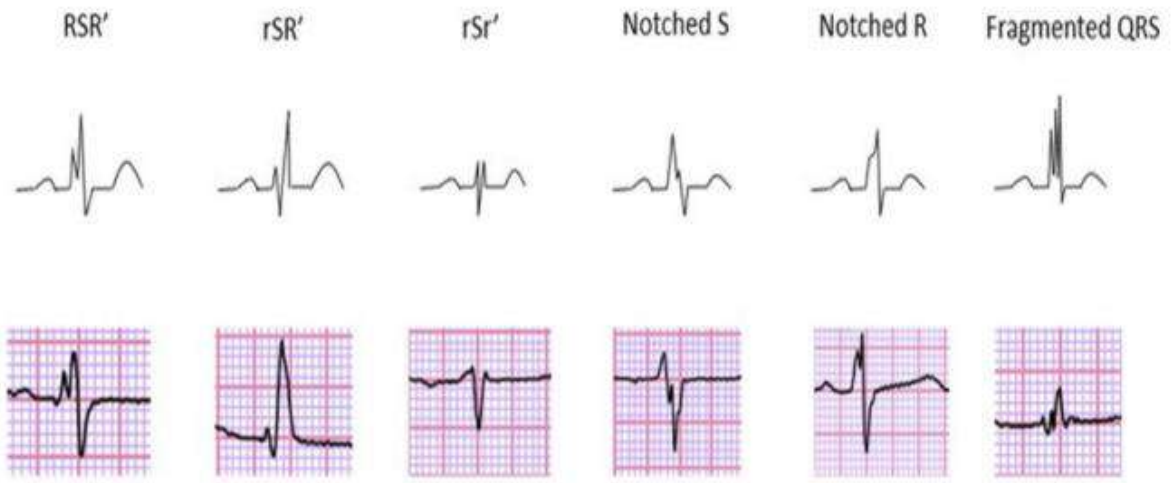
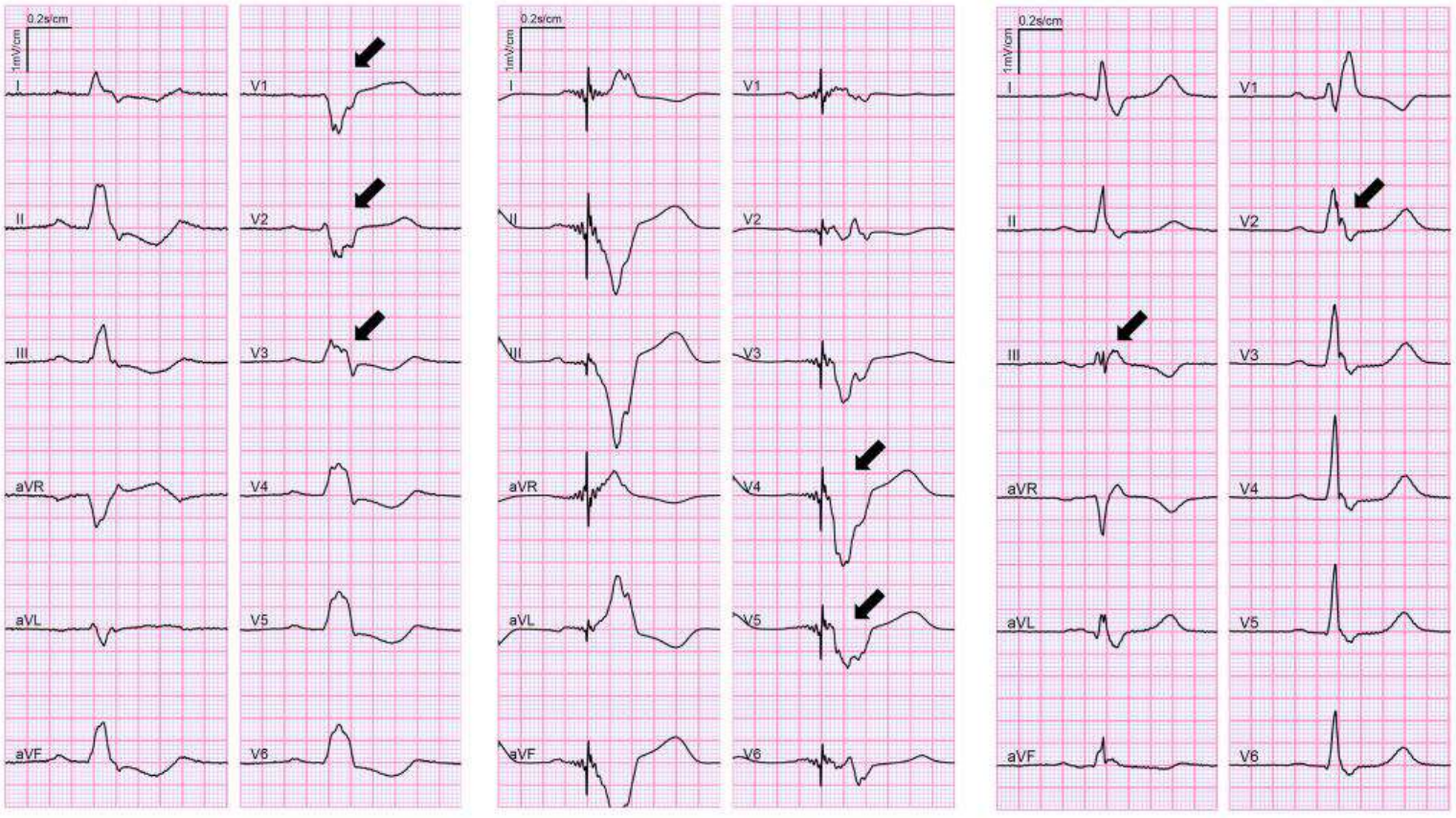
ANNEXES

Annexe 1



- An illustration of various fQRS morphologies on 12-lead ECG(190)

LBBB PACED PATIENT RBBB



- Examples of fQRS in prolonged QRS complexes(179).

Annexe 2

Arrythmias (excitability disordres) :	conduction disorders :	ischemic and repolarisation abnormalities:	Axis deviation:	Hypertrophie:
1. Tachycardia 2. AF 3. Atrial flutter 4. Premature atrial contraction 5. Premature ventricular contraction 6. supraventricular tachycardia 7. Short QT	1. Bradycardia 2. BSA 3. 1st degree AV block 4. 2nd degree AV block 5. 3rd degree AV block 6. Left bundle branche block 7. Right bundle branche block 8. Incomlete left bundle branche block 9. Incomplete right bundle branche block 10. Left anterior fascicular block 11. Left posterior fascicular block	1. ST segment abnormalities (elevation/depression) 2. T wave abnormalities (inversion ....) 3. Long QT 4. fQRS 5. Pathologic Q wave	1. LAD (Left axis deviation) 2. RAD (Right axis deviation)	1. Left ventricular hypertrophy 2. Right ventricular hypertrophy

- EGC abnormalities classification (used to summarize the abnormalities).

Annexe 3

Technical file

Research title : Prevalence of ECG abnormalities in patients with type 02 diabetes in OUARGLA : cross-sectional study

Patient's information:

Name :

Age : years old.

Adresse /Num :

Sex : ☐ Male ☐ Female

T2DM Duration :……

☐ ≤ 01 year ☐ 01-05 years

☐ 05-10 years ☐ 10- 15 years

☐ 15- 20 years ☐ ≥ 20 years

Educational level : ……

☐ Primary ☐ Secondary

☐ Universary ☐ Non education

Smoking behaviour : ……pack/year

☐ yes ☐ No

Alcohol consommation :……bottle/day

☐ yes ☐ No

Patient's history:

HYPERTENSION : ☐ Present ☐ Absent

FA : ☐ Present ☐ Absent

Pre-exsistant CVD or Complications :

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Familly history of coronary artery disease :

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Known lung disease :

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Other diseases :

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……

Clinical Cardiac signs :

Weight : kg Height : m

BMI : kg/m^2

BP : Systolic :

Diastolic :

Abdominal perimeter : cm

Dyspnea : ☐ yes ☐ No

NIHA : ☐ CLASS 01

☐ CLASS 02

☐ CLASS 03

☐ CLASS 04

Chest pain : ☐ Present ☐ Absent

☐ Carastirictic ☐ Non carastirictic

Syncope & Fainting : ☐ yes ☐ No

Palpitation : ☐ yes ☐ No

Other symptoms :

……
……
……
……

Biological tests :

Hb1C : …… %

☐ ≤ 07 % ☐ 07 – 08 %

☐ 08 – 09 % ☐ 09 – 10 %

☐ 10 – 11 % ☐ ≥ 11 %

Fasting glucose : ……g/dl

……mmol/L

Total cholesterol : ……

LDL colesterol : ……

HDL colesterol : ……

TG : ……

Urea : ……

Creatinine :……

Albuminuria : ……

Creat/Albumin urine ratio : ……

eGFR : ……(CDKEPI)

Medications :

Diabetes medicines :

☐ Oral only

☐ Insulin only

☐ Oral and insulin

Medicines	Present	Absent	Dose	Times/day
Mitformine				
DPP4-I				
iSGLT				
GLP-1				
Sulfonylurea				

Types of insulin	Dose	Times/day
Slow (24h)		
Rapid (02 – 04 h)		
Mixte (12 – 16 h)		

Lipid-lowering medication :

Medicines	Present	Absent	Dose	Times/day
statins				
……				

Antiplatelets :

Medicines	Present	Absent	Dose	Times/day
B-bloker				
ACE-I				
ARA2				
Ca^{2+}-I				
DIURETICS				
……				

Medicines	Present	Absent	Dose	Times/day
……				

AntiHTA medication :

ECG interpretation :

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ECG abnormalities :

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Conclusion :

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LAKHDARI Mohammed El-Fadhil

SANDALI Fatma Zohra

Prevalence of electrocardiographic abnormalities and their relation to clinical features and cardiac symptoms in patients with type 2 diabetes in Ouargla: a cross-sectional study during the period 20/12/2023 - 29/02/2024 in Ouargla.

ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2DM) is a pervasive and increasingly prevalent chronic condition, significantly elevating the risk of cardiovascular complications. T2DM is recognized as a cardiovascular disease risk equivalent, with patients facing a markedly increased risk of premature atherosclerotic cardiovascular disease (CVD). Despite the high incidence of cardiovascular involvement among diabetics, many remain asymptomatic. Electrocardiogram (ECG) abnormalities are critical in identifying hidden ischemic changes that may not present with symptoms but indicate a higher risk of cardiac mortality and morbidity. **Aim:** This study aims to investigate the prevalence and types of ECG abnormalities in patients with Type 2 DM and to explore the relationship between these abnormalities and clinical features, and cardiac symptoms. **Materials and Methods:** A cross-sectional study was conducted involving 191 T2DM patients from Ouargla. All participants were assessed for ECG abnormalities and clinical features such as age, gender, smoking status, physical activity, Body Mass Index, and blood pressure. The study focused on identifying the prevalence and types of ECG abnormalities and their association with cardiac symptoms and diabetes-related clinical features. **Results:** Among the 191 T2DM patients, 151 exhibited abnormal ECG findings (79,1%). The most prevalent abnormalities were ischemic changes and repolarization abnormalities (57.1%), with fragmented QRS complexes being the most common abnormality observed between all abnormalities (40,85%). The study found no significant correlation between the presence of ECG abnormalities and the reported cardiac symptoms in the patients. The prevalence of these ECG abnormalities underscores the hidden risk posed by T2DM, highlighting the importance of routine ECG screening in this population, Patients with mild, high, and very high risk according to the SCORE2-Diabetes were more likely to present ECG abnormalities. Biological findings, such as ACR and eGFR, were correlated with the presence of abnormalities; however, HbA1c and fasting glucose were not. The highest prevalence of abnormalities was found in the older age group, between 80 and 90 years old. **Conclusion:** The high prevalence of ECG abnormalities among Type 2 DM patients, particularly the frequent occurrence of fragmented QRS complexes, underscores the significant cardiovascular risk inherent in this condition. Despite the lack of a direct correlation between ECG abnormalities and cardiac symptoms, the findings emphasize the critical role of ECG in identifying subclinical cardiac issues in diabetic patients. Regular ECG monitoring is essential for early detection and management of potential cardiovascular complications in individuals with T2DM.

Key words: ECG abnormalities, Type 2 diabetes mellitus, Fragmented QRS, FQRS

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