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# Thèse

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Diplôme d'État

par


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Prévalence et incidence des troubles de la conduction chez les diabétiques de type 1 et de type 2 en comparaison à la population non diabétique : une double étude observationnelle à partir de 2 bases de données indépendantes à l'échelle nationale et internationale

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**RESUME**

**Introduction**. Le diabète de type 1 (DT1) ou 2 (DT2) augmentent le risque d'évènements cardiovasculaires athéromateux, d'insuffisance cardiaque et d'arythmies par rapport aux populations non diabétiques. En revanche, peu d'études ont évalué le risque de troubles de la conduction chez les patients diabétiques.

**Méthodes**. Pour le recueil de données, deux bases ont été utilisées : PMSI et TriNetX. Tous les patients âgés d'au moins 18 ans, vus dans les hôpitaux français en 2016, avec un suivi ultérieur minimal de 5 ans (sauf si décédés dans l'intervalle) ont été identifiés et catégorisés selon leur statut diabétique à partir de la base PMSI. La réseau international TriNetX recrutait des patients suivis depuis 20 ans jusqu'au 1er août 2024. Au total, plus de 20 000 patients atteints de DT1 (TriNetX) et plus de 900 000 patients atteints de DT2 (TriNetX) et 440 895 patients atteints de DT2 (PMSI) ont été identifiés. Les taux d'événements pour tous les types de troubles de la conduction et la nécessité d'implanter un dispositif électrique de stimulation ou défibrillation cardiaque définitif ont été comparés entre les populations diabétiques et non diabétiques avec réalisation d'analyses matchées prenant en compte l'ensemble des comorbidités pouvant être des facteurs favorisants directement ou indirectement la survenue de troubles de la conduction, ou qui pourraient causer un décès prématuré avant la survenue d'un trouble de la conduction. L'incidence d'infarctus du myocarde (IDM) au cours du suivi a aussi été étudiée au sein des deux bases, ainsi que l'influence du taux d'HbA1c.

**Résultats**. Au cours du suivi, un surrisque de troubles conductifs a été retrouvé chez les patients avec DT2 par rapport aux patients non diabétiques : BAV III (HR 1,22 [1,19-1,25]) ; BBG (HR 1,12 [1,08-1,17]) ; BBD (HR 1,14 [1,09-1,18]) dans la base PMSI et dysfonction sinusale (HR 1,28 [1,21-1,34]) ; BAV III (HR 1,50 [1,45-1,55]) ; BBG (HR 1,50 [1,47-1,54]) ; BBD (HR 1,38 [1,34-1,43]) pour les patients du réseau TriNetX. Une incidence plus élevée d'IDM a aussi été mise en évidence au cours de suivi pour les patients avec DT2 comparés aux patients sans diabète (HR 1,29 [1,25-1,32]) dans la base PMSI et dans le réseau TriNetX (HR 2,14 [2,08-2,19]), ce qui n'était pas le cas chez les patients avec DT1 (HR 1,11 [0,94-1,31]). En outre, un taux élevé d'HbA1c n'était pas associé de manière significative à la survenue de troubles conductifs chez les patients avec DT2 du réseau TrinetX.

**Conclusion**. Dans cette double étude observationnelle à partir de deux bases de données indépendantes à l'échelle nationale et internationale, le DT2 était associé à un taux plus élevé de troubles de la conduction et d'implantation de dispositif intra-cardiaque par rapport aux patients sans diabète après analyses matchées tenant compte des comorbidités associées, le DT2 étant parallèlement associé à une incidence significativement plus élevée d'IDM au cours du suivi. Ces observations n'étaient pas retrouvées dans la population avec DT1. Ils concerneraient ainsi possiblement une atteinte macro vasculaire associée au syndrome métabolique et à l'évolution sous-jacente d'une cardiopathie ischémique pour les DT2, ce qui ne serait pas le cas dans l'atteinte plutôt microvasculaire s'intégrant habituellement au sein de l'évolution pour les patients avec DT1.

**Mots clés :** diabète de type 1, diabète de type 2, bloc atrio-ventriculaire, dysfonction sinusale, bloc de branche, pacemaker, cardiomyopathie.

# Prevalence and incidence of cardiovascular conduction disturbances in type 1 and type 2 Diabetes compared to Diabetes-free population: a dual observational analysis in 2 large independent administrative databases at a nationwide and international level

**ABSTRACT**

**Background**. Type 1 diabetes (T1DM) and type 2 diabetes (T2DM) increase the risk of atheromatous cardiovascular events, heart failure and arrhythmias compared with non-diabetic populations. However, few studies have assessed the risk of conduction disorders in patients with diabetes.

**Methods**. We used two large databases: PMSI and TriNetX. All patients aged at least 18 years, seen in French hospitals in 2016, with a minimum subsequent follow-up of 5 years (unless they died in the meantime), were identified and categorized according to their diabetic status from the PMSI database. The international TriNetX network recruited patients who had been followed for 20 years until the 1st of August in 2024. A total of more than 20,000 patients with T1DM (TriNetX) and more than 900,000 patients with T2DM (TriNetX) and 440,895 patients with T2DM (PMSI) were identified. The event rates for all types of conduction disorders and the need to implant a definitive electrical cardiac stimulation or defibrillation device were compared between diabetic and non-diabetic populations, with matched analysis considering all the comorbidities which, on their own, may be factors favoring the onset of conduction disorders, or which may cause premature death before the onset of a conduction disorder. The incidence of ischemic heart disease during follow-up was also studied in the two databases, as was the influence of HbA1c levels.

**Results**. During follow-up, a higher risk of conductive disorders was found in patients with T2DM than in patients with no diabetes: AV block (HR 1.22 [1.19-1.25]) ; left BBB (HR 1.12 [1.08-1.17]) ; right BBB (HR 1.14 [1.09-1.18]) based on PMSI and sinus node dysfunction (HR 1.28 [1.21-1.34]) ; AV block (HR 1.50 [1.45-1.55]) ; left BBB (HR 1.50 [1.47-1.54]) ; right BBB (HR 1.38 [1.34-1.43]) according to TriNetX. A significant incidence of de novo or recurrent myocardial infarction during follow-up was also found for T2DM (HR 1.29 [1.25-1.32]) in PMSI and for TriNetX (HR 2.14 [2.08-2.19]) compared with T1DM (HR 1.11 [0.94-1.31]). However, HbA1c levels were not significantly associated with the occurrence of conductive disorders.

**Conclusion**. In this double study based on two independent national and international database and network, T2DM was associated with a higher rate of conduction disorders and cardiac device implantations compared with control patients after matched analysis considering associated comorbidities and was associated with a significant incidence of ischemic heart disease during follow-up. These observations were not found in T1DM populations. It is therefore possible that they concern macrovascular damage associated with the metabolic syndrome and the underlying course of ischemic heart disease in T2DM, which would not be the case in the more microvascular damage that is usually part of the course in patients with T1DM.

**Key words:** type 1 diabetes, type 2 diabetes, atrio-ventricular block, sinus dysfunction, bundle branch block, pacemaker, cardiomyopathy.

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# SERMENT D'HIPPOCRATE

En présence des enseignants et enseignantes
de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits aux indigents,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis(e) dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

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je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs parents.

Que les hommes et les femmes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert(e) d'opprobre
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si j'y manque.

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**ABBREVIATIONS**

T1DM: type 1 diabetes

T2DM: type 2 diabetes

SND: sinus node disease

AV: atrioventricular

BBB: bundle branch block

ICD: implantable cardioverter defibrillator

MI: myocardial infarction

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# I) Introduction

Type 1 diabetes (T1DM) and type 2 diabetes (T2DM) increase risks of atheromatous cardiovascular events, heart failure and arrhythmias compared with non-diabetic populations[1–6]. There are only few studies comparing T1DM and T2DM vs diabetes-free population for the risk of conduction disturbances and many did not analyse separately the different types of clinical events. The study of cardiac conduction disorders in patients with diabetes has been a focus of research interest in recent years, particularly in Scandinavian populations. In 2020, a Swedish study assessed the prevalence of complete atrioventricular block in T2DM[7]. The populations included relatively large numbers of subjects (25,995 cases and 130,004 controls) and were made comparable by matching for confounding factors linked to diabetes. This enabled the impact of T2DM to be assessed independently of the other criteria. On the other hand, data concerning T1DM were missing. Another Swedish study had a large database with hundreds of thousands of patients (416,247 patients with T2DM and 2,081,253 patients with no diabetes) but, this time, the lack of information on cardiovascular risk in the control group limited the possibility of making the two populations comparable on these factors, and therefore limited the evaluation of the impact of the cardiovascular co-morbidities in patients with diabetes in the occurrence of significant conduction abnormalities[8]. The same applies to another Swedish study[6] which showed that patients with T2DM had an increased risk of conduction and rhythm disorders, but one of the limitations of their study was that they did not have data on the risk factors of the control group, and a confounding bias between the two populations could not be fully ruled out. Another difficulty in this type of study is to avoid classification bias within the populations with diabetes themselves, which could lead to misinterpretation of the results in the event of errors in distribution between the groups.

Overall, uncertainties remain about diabetes mellitus and the incidences of conduction disturbances regarding:

- Their different types and locations: sinus node disease (SND), atrio-ventricular (AV) block located above the His bundle or of infra-Hissian location, left bundle branch block (left BBB) or right bundle branch block (right BBB).
- Their possible relation to the type of diabetes.

We investigated whether diabetes confers higher relative rates of conduction disturbances, and whether this may depend on T1DM or T2DM. We examined these issues in a nationwide database in France which provides exhaustive anonymous data for all patients hospitalized in public and private health centres. We then used another international network, in parallel in order, firstly, to validate the reliability of our results on a large scale and ensuring that the results could be compared with an international database beyond findings at the French level and, secondly, to reduce a potential classification bias that could be induced by incorrect recording of patient information, including for patients T1DM who were rarely evaluated in previous analysis.[9]

# II) Methods

## A) Data sources and analysis

Retrospective studies were performed in two independent cohorts of patients from 1) the French PMSI database and 2) the international TriNetX network.

The national administrative PMSI (Programme de Médicalisation des Systèmes d'Information) database recovered the data for all patients admitted in French hospitals in France from January to December 2016 with at least 5 years of subsequent follow-up (or dead earlier). Through this program, medical activity is recorded in a database, computed, and rendered anonymous. It includes more than 98% of the French population (67 million people) from birth (or immigration) to death (or emigration), even if a person changes occupation or retires. This process allows the determination of each hospital's budget, in more than 1,500 French healthcare facilities for both public and private hospitals. Each hospitalization is encoded in a standardized dataset, which includes information about the patient (age during first hospitalization in 2016 and sex), hospital, stay (date of admission, date of discharge, and modes of discharge), pathologies, and procedures. Routinely collected medical information includes the principal diagnosis and secondary diagnoses. In the PMSI system, identified diagnoses are coded according to the International Classification of Diseases, Tenth Revision (ICD-10). All medical procedures are recorded according to the national nomenclature, Classification Commune des Actes Medicaux (CCAM). The PMSI contains individual anonymized information on each hospitalization that are linked to create a longitudinal record of hospital stays and diagnoses for each patient. The reliability of PMSI data has already been assessed and this database has previously been used to study patients with diabetes or cardiovascular conditions [10–12].

TriNetX is a healthcare data network with real-time access to anonymized electronic healthcare records from over 120 healthcare organizations internationally, predominantly within North America. Data within the platform include demographics, International Classification of Diseases, 10th Revision (ICD-10) disease codes, procedures (ICD-10 Procedure Coding system), medication details (using Anatomical Therapeutic Chemical Classification System ATC codes) and laboratory measurements (coded as Logical Observation Identifiers Names and Codes (LOINC)). This database thus makes it possible to search for patients presenting specific criteria in a de-identified database and may increase the amount of information available.

We identified patients with DM, or no DM based on ICD-10 codes from the PMSI database and the TriNetX network. T2DM was defined with ICD code E11 (non-insulin-dependent diabetes mellitus). When testing an algorithm for identifying T1DM in the PMSI database based on ICD-10 code E10 (insulin-dependent diabetes mellitus) and no diagnosis of T2DM to patients from the TriNetX network, it appeared that this was not sufficiently reliable since more than 50% of the patients were treated with oral glucose lowering drugs and only 40% were treated with long-term insulin. Thus, this constatation of a classification bias within T1DM population in PMSI data, due to a lack of information on patients' anti-diabetic treatments, could lead to misinterpretation of some of the results, and prompted us to omit the analysis of patients with T1DM in the PMSI database, limiting the identification and analysis of patients with T1DM to the international TriNetX network. In these patients, T1DM was identified as code E10 with no coding of E11, use of insulin and no use or oral glucose-lowering drugs. A detailed description of the ICD-10 codes used to identify the cohorts, as well as details on the item and outcomes definitions, are available in Supplement (Table S1).

## B) Study population

Adults (⩾18 years old) with T1DM and T2DM as defined above were included for analysis in both datasets. In the PMSI registry, we identified from 1 January 2016 to 31 December 2016, 440,895 patients with T2DM (age 68.2 ± 14.9, 56% male) who were hospitalized for any reason and then had at least 5 years of follow-up (or suffered in-hospital death earlier). In TriNetX, all adults with a hospital (inpatient or outpatient) encounter for the last 20 years until the 1st of August 2024 were included for analysis. Comparisons between T1DM and non-diabetic population was only possible in TriNetX and not in the PMSI registry. There were more than 900,000 patients with T2DM (age 58±13.6, 50.5% male) and more than 20,000 patients with T1DM (age 37.4±17.5, 53.4% male) identified in the TriNetX network. Data regarding 'treatments' and 'laboratory tests' were only available in the TriNetX network. Patient information (demographics, comorbidities, medical history, and events during hospitalization or follow-up) was described using data collected in the hospital records. For each hospital stay, combined diagnoses at discharge were obtained. Each diagnosis was identified using ICD-10 codes and because the information was based on these codes (present or absent), there were no missing values.

The study was conducted retrospectively for both the PMSI database and the TriNetX network. As patients were not involved in its conduct, there was no impact on their care. Ethical approval was not required, as all data were anonymized. The French Data Protection Authority granted access to the PMSI data. Procedures for data collection and management were approved by the Commission Nationale de l'Informatique et des Libertés (CNIL), the independent National Ethical Committee protecting human rights in France, which ensures that all information is kept confidential and anonymous, in compliance with the Declaration of Helsinki (authorization number 1897139). As far as the TriNetX network is concerned, the de-

identification of information means that prior approval by the Institutional Review Board (IRB) is not required.

## C) Statistical analysis

In PMSI registry, qualitative variables were described as frequency and percentages and quantitative variable as means (standard deviations [SDs]). The analysis for clinical outcomes during the whole follow-up in the groups of interests was performed using a Cox model in the different strata, and reporting hazard ratios. We report hazard ratios (HR) with 95% confidence intervals (CIs). All comparisons with $p<0.05$ were considered statistically significant. All analysis were performed using Enterprise Guide 7.1, (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina), USA and STATA version 16.0 (Stata Corp, College Station, TX).

The database used in the second analysis came from the TriNetX Global Research Network, which provides access to electronic health records (EHRs) for approximately 151 million de-identified patients from 126 healthcare organizations in 17 countries worldwide. This federal research network has previously been used to study patients with diabetes[13]. The outcomes of interest were all-cause death, acute myocardial infarction, pacemaker implantation or implanted cardiac defibrillator (ICD), SND, AV block, left BBB, right BBB. Baseline characteristics were compared using Chi $\chi 2$ tests for categorical variables and independent-sample t tests for continuous variables. To control for baseline differences in the patient cohorts, propensity score matching (PSM) with greedy nearest-neighbor matching was used. Main covariates for matching included age, hypertension, ischemic heart disease, valve disorders, hyperlipidemia, kidney disease, lung disease, use of cardiovascular medications, estimated glomerular filtration rate (eGFR), blood pressure (BP) and body mass index. These variables were chosen because of their potential impact on exposure and on overall and cardiovascular outcomes. Balance was assessed with standardized differences with <0.1 (10%) defining similarity. Following PSM, outcomes were compared between cohorts at 60 months. Hazard

ratios and log-rank tests were used for survival analysis. Statistical analyses were performed using integrated R-for statistical computing on the TriNetX platform.

Patients and controls with no DM were matched 1:1 on age and sex with patients with no diabetes (Figure 1). We calculated incidence rates, incidence rate ratios and adjusted hazard ratios in patients with T1DM and T2DM (vs patients with no DM) after a complete matching on all comorbidities for the different types of conduction disturbances and for the need of treatment with cardiac implantable electronic device (CIED) such as pacemakers or ICD. Hazard ratios were calculated after matching for comorbidities known or suggested to be directly or indirectly associated with conduction disturbances and for those associated with a high mortality rate and less likely to reach high age with development of conduction disturbances or the need of CIED during follow-up by using propensity score. In addition to the variables regarding cardiovascular risk factors and comorbidities, use of cardiovascular and glucose-lowering drugs at baseline and some biologic parameters (including estimated GFR and glycated haemoglobin at baseline) were available in the TriNetX network. Cardiovascular drugs (not including glucose-lowering drugs) were included among the variables for matching.

## D) Outcomes

Patients were followed until 31 December 2021 for the occurrence of all-cause death and outcomes of interest for the analysis concerning PMSI database and data was collected over a 20-year period until the 1st of August 2024 for patients from TriNetX. We evaluated separately the incidence of the different types of conduction disturbances: SND, AV block, intraventricular block (LBBB and RBBB, allowing to identify conduction disorders with a more specifically infra-Hissian location), and the need of treatment with CIED such as pacemakers or ICD. We calculated incidence rates and hazard ratios in patients with T1DM and T2DM compared to matched populations with no diabetes. We also monitored the incidence of de novo or recurrent myocardial infarction during the follow-up.

# III) Results

## A) Prevalence and incidence of cardiac conduction disorders in T2DM

Baseline characteristics of patients with T2DM and patients with no DM before and after age and sex-matching are presented in Table S2 for T2DM in the PMSI database and Table S3 for T2DM in the TriNetX network. Characteristics of patients with T2DM and patients with no DM before and after a complete matching are presented in Table 1 for T2DM in the PMSI database and Table 2 for T2DM in the TriNetX network. Patients with T2DM were older and had higher prevalence for many comorbidities than patients with no DM. After matching, patients with T2DM and patients with no DM were well matched (standard difference of all parameters between the 2 groups <10%) for baseline characteristics included in the propensity score calculation. There was a marginally higher prevalence for some conduction disorders at baseline in the matched patients with T2DM (including SND or previous pacemaker/ICD)

In the age and sex-matched analysis from the PMSI database, duration of follow-up was 4.6±2.2 years (median 5.6, IQR 2.9). We found a higher risk for all types of conductive disorders in patients with T2DM than in those with no DM (Table S4). After the full matching analysis, patients with T2DM still had a statistically significant higher risk for AV block (HR 1.22 [1.19-1.25]), left BBB (HR 1.12 [1.08-1.17]), right BBB (HR 1.14 [1.09-1.18]) and pacemaker or ICD implantation (HR 1.13 [1.11-1.16]) than patients with no DM (Table 3 and Figure 2).

Duration of follow-up was 4.6±2.0 years (median 6.0, IQR 2.7) in the TriNetX analysis for patients with T2DM (vs no DM), TriNetX patients with T2DM as well had a higher incidence of conduction disorders of all types than those with no DM in the age and sex-matched analysis (Table S5). After a complete matching on the same cardiovascular risk factors and comorbidities than in the PMSI database, with the addition of the cardiovascular treatments, we also found a higher incidence of conduction disorders of all types and/or need for implantation of CIED in patients with T2DM than in patients with no DM: SND (HR 1.28

[1.21-1.34]) ; AV block (HR 1.50 [1.45-1.55]) ; left BBB (HR 1.50 [1.47-1.54]) ; right BBB (HR 1.38 [1.34-1.43]) and ICD implantation (HR 1.77 [1.68-1.86]) . Results are presented in Table 4 and Figure 3.

Concomitantly, there was a significantly higher number of de novo or recurrent myocardial infarction during follow-up in the matched patients with T2DM (vs those with no DM) in both databases: PMSI (HR 1.29 [1.25-1.32]) and TriNetX (HR 2.14 [2.08-2.19]) (respectively Table 3 and Table 4).

Since the TriNetX network gave access to some laboratory parameters, we compared the occurrence of conductive disorders in relation to HbA1c level at baseline (Table S6 and Table S7). We found no significant differences for the incidence of conduction disorders in patients with T2DM with HbA1c below or above 8% at baseline: HR 0.84 [0.79-0.90] for SND when comparing patients with HbA1c ≥8 % to those with HbA1c <8 % ; HR 0.92 [0.88-0.95] for AV block; HR 0.99 [0.96-1.02] for left BBB and HR 1.00 [0.96-1.04] for right BBB. These results indicated that there was no increased risk of conduction disorders in T2DM patients with higher HbA1c at baseline.

Regarding the location of the conductive disorders after the extensive matching for confounding factors, the highest incidence in patients with T2DM was found for AV block (13,225 events, 0.71%/yr) in the PMSI analysis and left BBB in the TriNetX analysis (14,249 events 1.06%/yr). Conversely, the least frequent conductive disorder was sinus node disease with 4,650 (0.25/yr) and 3,318 events (0.25%/yr) respectively in the PMSI and TriNetX analysis.

## B) Prevalence and incidence of cardiac conduction disorders in T1DM

For the analysis regarding T1DM, whose statistics were based exclusively on the TriNetX network, baseline characteristics of patients with T1DM and patients with no DM before and after age and sex-matching are presented in Table S8. Characteristics of patients with T1DM and patients with no DM before and after a complete matching are presented in Table 5. At baseline, we found that patients with T1DM were younger than those with no DM but nevertheless had higher prevalence for many comorbidities. After matching, patients with T1DM and patients with no DM were well matched for baseline characteristics used for propensity score matching. There was a marginally higher prevalence of conduction disorders at baseline in patients with T1DM.

Duration of follow-up was 3.7±2.2 years (median 4.3, IQR 4.2) for the matched populations of TriNetX patients with T1DM or no DM. We did not find any excess risk of conductive disorders during follow-up neither after matching analysis on sex and age (Table S9) nor full matching analysis (Table 6). Indeed, in the matched analysis, there was not a higher risk of conductive disorders in the population with T1DM compared with the population with no diabetes for any type of conduction disorder: SND (HR 0.48 [0.34-0.68]) ; AV block (HR 0.79 [0.64-0.97]) ; left BBB (HR 0.80 [0.67-0.96]) ; right BBB (HR 0.69 [0.55-0.86]). In this population with T1DM, there was neither a significantly higher risk of de novo or recurrent myocardial infarction during follow-up in the propensity-matched analysis (HR 1.11 [0.94-1.31]).

# IV) Discussion

First of all, strengths of the current study include the large population-based cohorts from modern healthcare covering essentially all patients with T2DM in France for the PMSI analysis and on an international level for patients with T1DM and T2DM in healthcare centres from the TriNetX network. These representative populations constitute a real-world data set and include patients of a wide age range. To our knowledge, this is one of the largest and most comprehensive studies analysing cardiac conductions complications in T1DM and T2DM.

The main points observed in our study are: 1) there were more conduction disturbances in patients with T2DM than in those with no DM 2) there were not more conduction disorders in patients with T1DM compared to those with no DM 3) there was a significantly higher incidence of coronary events during follow-up in T2DM patients and this was not seen for patients with T1DM 4) there was no correlation between HbA1c levels and incidence of conduction disorders. The results for the need of pacemaker, ICD and CRT-D implantation are consistent with the results mentioned above but should be treated with caution. The indications leading to their implantation may be various and may not relate solely to conductive disorders. This may also include primary or secondary prevention of ventricular tachyarrhythmia in the case of ICD implantation for patients with reduced ejection fraction, or may be part of treatment of heart failure with cardiac resynchronisation therapy[14].

For patients with T2DM, the higher incidence of conductive disorders in the infra-Hissian region (reflected by the higher risk of both right BBB and left BBB) may suggest myocardial damage partly related to the concomitant development of coronary artery disease since a higher incidence of myocardial infarction was also seen during follow-up for these patients (while the patients were properly matched for history of coronary artery disease or myocardial infarction at baseline). T2DM might be more closely associated with an atheromatous risk with macrovascular damage, inherent to the metabolic syndrome, and leading

to conduction disturbances. Our results would suggest that diabetes per se may not result in conduction disorders since patients with T1DM did not have a higher risk of these events during follow-up. T1DM might be more closely associated with the development of cardiac disease through microvascular damage leading to renal or neurological complications, or directly through glucotoxicity causing complex metabolic disorders, which may be associated with tissue remodelling that may serve as a substrate for the development of cardiac pathology. This observation is supported by the fact that cross-sectional images with evaluation of the calcium score (obtained by injection-free scans and reflecting the rate of coronary calcification that may predict the cardiac macrovascular risk) may show higher numerical values in T2DM patients than in T1DM patients[15].

For patients with T2DM, the lack of higher risk of conduction disorders associated with poor glycemic control, as assessed by higher HbA1c levels, may contradict a simple direct dose effect of hyperglycemia directly worsening cardiac conduction. This was a further indirect argument in favor of the involvement of coronary artery disease in the development of conductive disorders. Caution must however be exercised with these results, since HbA1c was only estimated once at baseline. This may not prejudge the quality of subsequent diabetes control: a long-standing and chronic imbalance could contribute to the occurrence of cardiac complications despite an HbA1c that was initially low (or transiently improved) or the opposite when HbA1c was initially high at diagnosis of diabetes and then adequately controlled.

A Japanese study aimed to evaluate the indirect markers of myocardial fibrosis and myocardial scarring, which may themselves be the cause of conductive disorders, in diabetic patients after matching on metabolic syndrome items[16]. This study reported the occurrence of intra-ventricular conductive disorders in patients with diabetes and the authors suggested that QRS could be a biomarker for diabetic cardiomyopathy with increased myocardial fibrosis,

since fragmented QRS was observed more frequently in diabetes mellitus patients than in patients with metabolic syndrome alone and control individuals.

Only few studies have directly compared the hazards of cardiovascular outcomes and premature death among people with T1DM to those among people with T2DM[12,17–20]. They generally showed higher mortality during follow-up among people with T1DM than among those with T2DM, although this was not a constant finding in studies with lower number of patients. Some studies have reported risks of cardiovascular disease and death but have focused on only one outcome or performed indirect comparisons through populations without diabetes[21]. Since the higher risk of conduction disorders for patients with T2DM vs those with no DM was not seen for patients with T1DM in our analysis, a direct comparison of patients with T2DM and T1DM was in our opinion not needed.

Finally, the location of the conductive disorders, in which a substantial part may be infra-Hissian after matching for confounding factors (including drugs acting by slowering atrioventricular node conduction) is also an argument in favour of ventricular myocardial damage mediated by coronary artery disease. The independent association of diabetes with a higher risk of incident infra-Hisian disease has also been reported in the smaller Cardiovascular Health Study but the authors did not distinguish T2DM and T1DM in their analysis.[22] If dysautonomia alone was the only mechanism involved in the appearance of conductive disorders in patients with T2DM, this would theoretically not explain the significantly higher incidence in infra-Hissian conductive disorders and BBB that was seen in our results for both the PMSI and TriNetX analysis of these patients.

To continue this line of thoughts, a recent study showed that cardiac autonomic neuropathy, diagnosed on a simple resting ECG (based on R-R interval variability) was an independent predictor of rapid decline in kidney function in both T1DM and T2DM[23]. Autonomic dysfunction therefore plays a role, at different levels, in the complications of

diabetic disease, both directly in complications such as conductance disorders, and indirectly in the deterioration of renal function, via an increase in renal sympathetic activity, which in turn increases cardiovascular risk. This third component, inherent to diabetic pathology, may directly worsen conductive disorders and may moreover interact with cardiovascular conditions, possibly worsening indirectly the risk of rhythm abnormalities for patients with diabetes. Screening for dysfunction of the autonomic nervous system by means of a regular resting ECG therefore might be helpful for identifying and preventing the progression of such diabetic complications. This is a further argument in favour of a multifactorial origin for the occurrence of conduction disorders in patients with diabetes, with cardiovascular disease playing a central role and being a favourable environment for the occurrence of this type of complication.

# V) Limitations

Our study has a number of limitations. A main limitation is inherent to the retrospective, observational nature of the study and its potential biases. Further, the study was based on administrative data, with limitations related to such methodology. The PMSI database and TriNetX network contain diagnoses coded using ICD-10, which are obtained at hospital discharge and are the physician's responsibility. Data were not (and could not be) systematically externally checked, and this could have caused information bias. However, as coding of complications is linked to reimbursement (in France and in many other countries) and is regularly controlled, it is expected to be of good quality.[24,25] Events included were only those diagnosed in-hospital and we were not able to analyse data for out-of-hospital deaths, but most of the major cardiovascular events analysed in our study are not managed out of hospitals. Our large population of patients likely represents a heterogeneous group of patients seen with various kinds of illnesses and severities, which may have affected prognosis. Another limitation in the PMSI database is the lack of information in terms of therapies recommended for diabetes or cardiovascular conditions. We have tried to compensate for this information bias by validating our results using the TriNetX network.

Because of the structure of the analysis, it was not possible to accurately determine diabetes duration for patients in the study. Longer duration of T2DM has been linked with a greater risk of cardiovascular disease and death, and since we did not have information about diabetes duration, we could not evaluate further or adjust for this. Nor do we have any information on the exact definition of ischemic heart disease or on what criteria patients were recruited.

Our analysis was restricted to the variables present in the database, which means that characteristics such as information on some of the lifestyle factors (physical activity level or diet), or details for cardiac imaging were not available in the PMSI analysis whilst some of

these risk factors may be associated with increased rates of cardiovascular or renal events in diabetes. The TriNetX network enabled us to compensate for the lack of data on the monitoring of risk factors (glucose levels, lipids, body mass index and blood pressure), data not present in the PMSI database, which could have an impact on the results. Such confounding factors and their dynamic changes over time should be evaluated in future studies.

# VI) Conclusion

In these two large analysis both at the nationwide and international levels, the propensity-matched comparisons make it possible to avoid certain biases that can occur when comparing patients with diabetes to those with no diabetes.

Our results suggested that the substrate for the higher risk of conduction disturbances in patients with T2DM may not only be related to the influences of the autonomic nervous system or to the use of bradycardic agents, but possibly to a damage in the His-Purkinje network. This latter may be favored by the underlying evolving coronary artery disease and its inflammatory environment, possibly being part of complications of the metabolic syndrome, in addition to the glycemic abnormalities and their control or the associated dysautonomia.

In the case of T1DM, one may suggest the involvement of other mechanisms for main clinical complications that may be related to microvascular damage and glucotoxicity, not resulting in a higher risk of conduction disturbances.

These observations suggested the involvement of different pathophysiological mechanisms between the two types of diabetes. By investigating the occurrence of conductive disorders in patients with diabetes, this study highlights the complex pathophysiology of diabetes. There is an interest in treating diabetes intensively, as an entity, and guiding the management and monitoring of these patients by insisting on monitoring risk factors and coronary pathology. This should contain cardiac arrhythmia monitoring in patients with T2DM considering the markedly higher risk of conduction disturbances in our matched analysis of these patients. Clinical evaluation should include the tracking of symptoms and not attributing episodes of dizziness, syncope, too quickly to poor adaptation of blood pressure in the context of dysautonomia and move quickly towards the use of Holter monitoring and electrophysiological investigations. This study also suggests treating all the comorbidities associated with diabetes within the metabolic syndrome, as they are jointly involved in the

development of complications, particularly for coronary artery disease. All in all, this comprehensive observational study could suggest that the mechanisms at the origin of conductive disorders in patients with diabetes are intimately linked and interdependent, and that diabetes is a complex pathology, to be considered as part of and interacting with the pathological environment in which it develops.

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## TABLES AND FIGURES

**Table 1.** Baseline characteristics of unmatched and fully matched patients with T2DM or no diabetes in PMSI database

| | Before PS matching | | | | After PS matching | | | |
|---|---|---|---|---|---|---|---|---|
| | **No diabetes mellitus (n=3503588)** | **Type 2 diabetes mellitus (n=440895)** | **p** | **Standardized difference (%)** | **No diabetes mellitus (n=408905)** | **Type 2 diabetes mellitus (n=408905)** | **p** | **Standardized difference (%)** |
| **Age (years), mean±SD** | 59.9±18.9 | 68.2±14.9 | <0.0001 | 45.1 | 68.6±15.2 | 68.6±15.2 | 1 | 0.0 |
| **Sex (male), n (%)** | 1594833 (45.5) | 246989 (56.0) | <0.0001 | 21.1 | 226329 (55.4) | 226329 (55.4) | 1 | 0.0 |
| **Hypertension, n (%)** | 806876 (23.0) | 295091 (66.9) | <0.0001 | 102.8 | 274212 (67.1) | 264153 (64.6) | <0.0001 | -5.2 |
| **Heart failure, n (%)** | 265572 (7.6) | 97129 (22.0) | <0.0001 | 50.6 | 89346 (21.9) | 87669 (21.4) | <0.0001 | -1.0 |
| **History of pulmonary edema, n (%)** | 16852 (0.5) | 5247 (1.2) | <0.0001 | 9.5 | 4866 (1.2) | 4702 (1.2) | 0.1 | -0.4 |
| **Valve disease, n (%)** | 101254 (2.9) | 28305 (6.4) | <0.0001 | 19.8 | 26988 (6.6) | 26415 (6.5) | 0.01 | -0.6 |
| **Aortic stenosis, n (%)** | 42744 (1.2) | 14373 (3.3) | <0.0001 | 17.1 | 12840 (3.1) | 13412 (3.3) | 0.0004 | 0.8 |
| **Aortic regurgitation, n (%)** | 19655 (0.6) | 4409 (1.0) | <0.0001 | 5.6 | 4702 (1.2) | 4212 (1.0) | <0.0001 | -1.2 |
| **Mitral regurgitation, n (%)** | 42043 (1.2) | 11066 (2.5) | <0.0001 | 11.4 | 10672 (2.6) | 10264 (2.5) | 0.005 | -0.6 |
| **Previous endocarditis, n (%)** | 4064 (0.1) | 1217 (0.3) | <0.0001 | 4.4 | 1165 (0.3) | 1108 (0.3) | 0.22 | -0.3 |
| **Dilated cardiomyopathy, n (%)** | 57809 (1.7) | 19532 (4.4) | <0.0001 | 20.1 | 18033 (4.4) | 17665 (4.3) | 0.06 | -0.4 |
| **Coronary artery disease, n (%)** | 285542 (8.2) | 108240 (24.6) | <0.0001 | 55.5 | 99895 (24.4) | 96706 (23.7) | <0.0001 | -1.8 |
| **Previous MI, n (%)** | 52904 (1.5) | 16357 (3.7) | <0.0001 | 16.8 | 15947 (3.9) | 14884 (3.6) | <0.0001 | -1.4 |
| **Previous PCI, n (%)** | 79181 (2.3) | 29055 (6.6) | <0.0001 | 26.6 | 28010 (6.9) | 25884 (6.3) | <0.0001 | -2.1 |
| **Previous CABG, n (%)** | 8374 (0.2) | 4285 (1.0) | <0.0001 | 13.0 | 3819 (0.9) | 3762 (0.9) | 0.5 | -0.1 |
| **Vascular disease, n (%)** | 219675 (6.3) | 81433 (18.5) | <0.0001 | 46.4 | 77324 (18.9) | 73439 (18.0) | <0.0001 | -2.4 |
| **Atrial fibrillation, n (%)** | 276783 (7.9) | 76672 (17.4) | <0.0001 | 33.4 | 74871 (18.3) | 71885 (17.6) | <0.0001 | -1.9 |
| **Sinus node disease, n (%)** | 21302 (0.6) | 5599 (1.3) | <0.0001 | 8.0 | 6420 (1.6) | 5152 (1.3) | <0.0001 | -2.6 |
| **AV block, n (%)** | 46948 (1.3) | 15960 (3.6) | <0.0001 | 18.2 | 14271 (3.5) | 14639 (3.6) | 0.03 | 0.5 |
| **Right BBB, n (%)** | 22003 (0.6) | 7583 (1.7) | <0.0001 | 12.7 | 6665 (1.6) | 6910 (1.7) | 0.03 | 0.5 |
| **Left BBB, n (%)** | 17238 (0.5) | 6084 (1.4) | <0.0001 | 11.6 | 5766 (1.4) | 5438 (1.3) | 0.003 | -0.7 |
| **Previous pacemaker or ICD, n (%)** | 89692 (2.6) | 26718 (6.1) | <0.0001 | 20.7 | 26620 (6.5) | 24739 (6.1) | <0.0001 | -1.9 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Previous pacemaker, n (%)** | 46948 (1.3) | 13535 (3.1) | <0.0001 | 14.1 | 13494 (3.3) | 12676 (3.1) | <0.0001 | -1.1 |
| **Previous ICD, n (%)** | 8584 (0.2) | 2954 (0.7) | <0.0001 | 7.9 | 3472 (0.8) | 2527 (0.6) | <0.0001 | -2.7 |
| **Ischemic stroke, n (%)** | 56057 (1.6) | 16093 (3.7) | <0.0001 | 15.3 | 15866 (3.9) | 15089 (3.7) | <0.0001 | -1.0 |
| **Intracranial bleeding, n (%)** | 33950 (1.0) | 6305 (1.4) | <0.0001 | 4.6 | 6624 (1.6) | 6011 (1.5) | <0.0001 | -1.2 |
| **Smoker, n (%)** | 223529 (6.4) | 42811 (9.7) | <0.0001 | 13.3 | 44775 (11.0) | 38519 (9.4) | <0.0001 | -5.1 |
| **Dyslipidaemia, n (%)** | 302710 (8.6) | 147788 (33.5) | <0.0001 | 80.7 | 127578 (31.2) | 125452 (30.7) | <0.0001 | -1.1 |
| **Obesity, n (%)** | 305863 (8.7) | 144525 (32.8) | <0.0001 | 77.9 | 115107 (28.2) | 118296 (28.9) | <0.0001 | 1.7 |
| **Alcohol related diagnoses, n (%)** | 166771 (4.8) | 30730 (7.0) | <0.0001 | 10.1 | 30259 (7.4) | 27519 (6.7) | <0.0001 | -2.6 |
| **Chronic kidney disease, n (%)** | 92845 (2.7) | 41620 (9.4) | <0.0001 | 37.7 | 34716 (8.5) | 36924 (9.0) | <0.0001 | 1.9 |
| **Lung disease, n (%)** | 279236 (8.0) | 67677 (15.4) | <0.0001 | 26.1 | 69800 (17.1) | 62399 (15.3) | <0.0001 | -4.9 |
| **Sleep apnoea syndrome, n (%)** | 127531 (3.6) | 53040 (12.0) | <0.0001 | 40.5 | 41259 (10.1) | 43630 (10.7) | <0.0001 | 1.9 |
| **COPD, n (%)** | 154508 (4.4) | 41488 (9.4) | <0.0001 | 23.1 | 43139 (10.6) | 38069 (9.3) | <0.0001 | -4.1 |
| **Liver disease, n (%)** | 88290 (2.5) | 34346 (7.8) | <0.0001 | 30.5 | 27560 (6.7) | 27519 (6.7) | 0.81 | 0.0 |
| **Gastroesophageal reflux, n (%)** | 115268 (3.3) | 12433 (2.8) | <0.0001 | -2.7 | 11899 (2.9) | 11736 (2.9) | 0.26 | -0.2 |
| **Thyroid diseases, n (%)** | 166771 (4.8) | 43957 (10.0) | <0.0001 | 23.2 | 40522 (9.9) | 39827 (9.7) | 0.01 | -0.6 |
| **Inflammatory disease, n (%)** | 184289 (5.3) | 29628 (6.7) | <0.0001 | 6.4 | 27928 (6.8) | 27397 (6.7) | 0.02 | -0.5 |
| **Anaemia, n (%)** | 257163 (7.3) | 66884 (15.2) | <0.0001 | 28.6 | 63217 (15.5) | 60927 (14.9) | <0.0001 | -1.6 |
| **Previous cancer, n (%)** | 495057 (14.1) | 71293 (16.2) | <0.0001 | 5.8 | 73235 (17.9) | 68369 (16.7) | <0.0001 | -3.1 |
| **Poor nutrition, n (%)** | 217222 (6.2) | 47661 (10.8) | <0.0001 | 18.5 | 47883 (11.7) | 44816 (11.0) | <0.0001 | -2.4 |
| **Cognitive impairment, n (%)** | 95298 (2.7) | 22750 (5.2) | <0.0001 | 14.3 | 22408 (5.5) | 21999 (5.4) | 0.04 | -0.4 |
| **Frailty index, mean±SD** | 4.3±6.9 | 7.7±8.8 | <0.0001 | 47.5 | 7.8±8.8 | 7.7±8.8 | <0.0001 | -1.7 |

Values are n (%) or mean ± SD. BBB = bundle branch block; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter defibrillator; MI = myocardial infarction; PCI= percutaneous coronary intervention; SD = standard deviation.

**Table 2.** Baseline characteristics of patients with T2DM before and after propensity score matching in TriNetX network

| | Before propensity-score matching | | | | After propensity-score matching | | | |
|---|---|---|---|---|---|---|---|---|
| | **Type 2 DM (n = 981,772)** | **No DM (n = 1,865,584)** | **P-Value** | **Std diff. (%)** | **Type 2 DM (n = 378,132)** | **No DM (n = 378,132)** | **P-Value** | **Std diff. (%)** |
| **Age at Index, n (%)** | 58.0 +/- 13.6 | 44.5 +/- 16.6 | <0.001 | 88.5 | 54.1 +/- 14.7 | 53.4 +/- 15.3 | <0.001 | 4.3 |
| **Men, n (%)** | 495,563 (50.5%) | 758,961 (40.7%) | <0.001 | 19.8 | 183,034 (48.4%) | 189,228 (50%) | <0.001 | 3.3 |
| **Hypertension, n (%)** | 585,637 (59.7%) | 135,707 (7.3%) | <0.001 | 133.4 | 118,422 (31.3%) | 127,751 (33.8%) | <0.001 | 5.3 |
| **Smoker, n (%)** | 96,966 (9.9%) | 12,965 (0.7%) | <0.001 | 41.9 | 10,951 (2.9%) | 10,224 (2.7%) | <0.001 | 1.2 |
| **Overweight or obesity, n (%)** | 273,009 (27.8%) | 72,299 (3.9%) | <0.001 | 69.4 | 44,766 (11.8%) | 46,606 (12.3%) | <0.001 | 1.5 |
| **Dyslipidaemia, n (%)** | 516,077 (52.6%) | 106,527 (5.7%) | <0.001 | 120.3 | 95,709 (25.3%) | 99,314 (26.3%) | <0.001 | 2.2 |
| **Alcohol related diagnoses, n (%)** | 23,785 (2.4%) | 8,571 (0.5%) | <0.001 | 16.5 | 5,330 (1.4%) | 3,999 (1.1%) | <0.001 | 3.2 |
| **Heart failure, n (%)** | 85,347 (8.7%) | 7,696 (0.4%) | <0.001 | 40.5 | 8,481 (2.2%) | 7,316 (1.9%) | <0.001 | 2.2 |
| **Coronary artery disease, n (%)** | 159,036 (16.2%) | 20,270 (1.1%) | <0.001 | 55.8 | 20,470 (5.4%) | 19,267 (5.1%) | <0.001 | 1.4 |
| **Myocardial infarction, n (%)** | 43,536 (4.4%) | 9,037 (0.5%) | <0.001 | 25.7 | 6,862 (1.8%) | 7,197 (1.9%) | 0.004 | 0.7 |
| **Dilated cardiomyopathy, n (%)** | 6,415 (0.7%) | 502 (0%) | <0.001 | 10.8 | 500 (0.1%) | 407 (0.1%) | 0.002 | 0.7 |
| **Ischemic stroke, n (%)** | 43,574 (4.4%) | 12,883 (0.7%) | <0.001 | 23.9 | 8,174 (2.2%) | 9,560 (2.5%) | <0.001 | 2.4 |
| **Intracranial haemorrhage, n (%)** | 6,749 (0.7%) | 2,236 (0.1%) | <0.001 | 9 | 1,040 (0.3%) | 1,813 (0.5%) | <0.001 | 3.3 |
| **Valve disease, n (%)** | 32,846 (3.3%) | 4,248 (0.2%) | <0.001 | 23.7 | 3,672 (1%) | 2,825 (0.7%) | <0.001 | 2.4 |
| **Mitral regurgitation, n (%)** | 29,961 (3.1%) | 3,503 (0.2%) | <0.001 | 22.8 | 3,325 (0.9%) | 2,385 (0.6%) | <0.001 | 2.9 |
| **Mitral stenosis, n (%)** | 4,722 (0.5%) | 621 (0%) | <0.001 | 8.8 | 567 (0.1%) | 375 (0.1%) | <0.001 | 1.4 |
| **Aortic regurgitation, n (%)** | 14,413 (1.5%) | 1,871 (0.1%) | <0.001 | 15.6 | 1,511 (0.4%) | 1,312 (0.3%) | <0.001 | 0.9 |
| **Aortic stenosis, n (%)** | 17,171 (1.7%) | 1,872 (0.1%) | <0.001 | 17.3 | 1,897 (0.5%) | 1,307 (0.3%) | <0.001 | 2.4 |
| **Atrial fibrillation or flutter, n (%)** | 70,327 (7.2%) | 12,297 (0.7%) | <0.001 | 34 | 9,776 (2.6%) | 9,814 (2.6%) | 0.783 | 0.1 |
| **Sinus node disease, n (%)** | 6,031 (0.6%) | 638 (0%) | <0.001 | 10.2 | 626 (0.2%) | 419 (0.1%) | <0.001 | 1.5 |
| **Atrioventricular and/or LBBB, n (%)** | 26,492 (2.7%) | 3,765 (0.2%) | <0.001 | 21 | 2,847 (0.8%) | 2,868 (0.8%) | 0.78 | 0.1 |
| **Left BBB, n (%)** | 8,208 (0.8%) | 1,086 (0.1%) | <0.001 | 11.7 | 807 (0.2%) | 891 (0.2%) | 0.041 | 0.5 |
| **Right BBB, n (%)** | 14,132 (1.4%) | 2,643 (0.1%) | <0.001 | 14.7 | 1,786 (0.5%) | 1,802 (0.5%) | 0.789 | 0.1 |
| **Previous pacemaker, n (%)** | 10,674 (1.1%) | 1,213 (0.1%) | <0.001 | 13.5 | 1,196 (0.3%) | 885 (0.2%) | <0.001 | 1.6 |
| **Previous ICD, n (%)** | 9,305 (0.9%) | 724 (0%) | <0.001 | 13 | 844 (0.2%) | 547 (0.1%) | <0.001 | 1.8 |
| **Kidney disease, n (%)** | 136,316 (13.9%) | 11,969 (0.6%) | <0.001 | 52.8 | 14,255 (3.8%) | 11,710 (3.1%) | <0.001 | 3.7 |
| **Lung disease, n (%)** | 352,443 (35.9%) | 165,470 (8.9%) | <0.001 | 68.5 | 67,456 (17.8%) | 65,010 (17.2%) | <0.001 | 1.7 |
| **COPD, n (%)** | 58,197 (5.9%) | 7,011 (0.4%) | <0.001 | 32.2 | 6,656 (1.8%) | 6,080 (1.6%) | <0.001 | 1.2 |
| **Sleep apnoea syndrome, n (%)** | 125,767 (12.8%) | 17,351 (0.9%) | <0.001 | 48.3 | 14,499 (3.8%) | 13,657 (3.6%) | <0.001 | 1.2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Peripheral vascular disease, n (%)** | 31,285 (3.2%) | 2,327 (0.1%) | <0.001 | 24.2 | 2,772 (0.7%) | 2,250 (0.6%) | <0.001 | 1.7 |
| **Previous cancer, n (%)** | 194,455 (19.8%) | 61,032 (3.3%) | <0.001 | 53.6 | 30,679 (8.1%) | 26,503 (7%) | <0.001 | 4.2 |
| **Thyroid diseases, n (%)** | 141,622 (14.4%) | 47,816 (2.6%) | <0.001 | 43.5 | 29,258 (7.7%) | 31,371 (8.3%) | <0.001 | 2.1 |
| **Amyloidosis, n (%)** | 1,098 (0.1%) | 232 (0%) | <0.001 | 4 | 126 (0%) | 154 (0%) | 0.094 | 0.4 |
| **Malnutrition, n (%)** | 16,761 (1.7%) | 2,310 (0.1%) | <0.001 | 16.7 | 2,542 (0.7%) | 1,510 (0.4%) | <0.001 | 3.7 |
| **Cognitive impairment, n (%)** | 2,897 (0.3%) | 497 (0%) | <0.001 | 6.7 | 620 (0.2%) | 353 (0.1%) | <0.001 | 2 |
| **Total cholesterol (mg/dL), mean±SD** | 178.0 +/- 51.8 | 184.0 +/- 45.7 | <0.001 | 12.3 | 181.8 +/- 51.2 | 188.7 +/- 48.9 | <0.001 | 13.7 |
| **LDL cholesterol (mg/dL), mean±SD** | 100.4 +/- 40.7 | 109.3 +/- 36.8 | <0.001 | 23 | 103.3 +/- 40.3 | 113.3 +/- 39.5 | <0.001 | 25.1 |
| **HDL cholesterol (mg/dL), mean±SD** | 45.7 +/- 15.4 | 52.3 +/- 17.0 | <0.001 | 40.7 | 46.4 +/- 15.6 | 50.6 +/- 17.0 | <0.001 | 25.5 |
| **Triglyceride (mg/dL), mean±SD** | 174.1 +/- 198.3 | 122.0 +/- 98.6 | <0.001 | 33.3 | 177.3 +/- 229.0 | 134.0 +/- 114.0 | <0.001 | 24 |
| **Haemoglobin A1c (%), mean±SD** | 7.2 +/- 2.1 | 5.5 +/- 1.2 | <0.001 | 100.8 | 7.7 +/- 2.4 | 5.5 +/- 0.9 | <0.001 | 124.7 |
| **Body mass index (kg/m2), mean±SD** | 33.5 +/- 8.2 | 28.8 +/- 6.9 | <0.001 | 61.8 | 31.9 +/- 8.0 | 31.0 +/- 7.3 | <0.001 | 11.4 |
| **Systolic BP (mm Hg), mean±SD** | 130.4 +/- 20.7 | 125.2 +/- 18.2 | <0.001 | 26.7 | 129.7 +/- 19.7 | 130.7 +/- 20.5 | <0.001 | 5.1 |
| **Diastolic BP (mm Hg), mean±SD** | 75.8 +/- 13.0 | 76.4 +/- 11.7 | <0.001 | 4.9 | 76.5 +/- 12.2 | 78.9 +/- 13.0 | <0.001 | 18.5 |
| **Beta Blockers, n (%)** | 254,010 (25.9%) | 44,072 (2.4%) | <0.001 | 71.7 | 34,157 (9%) | 32,972 (8.7%) | <0.001 | 1.1 |
| **Calcium Channel Blockers, n (%)** | 170,827 (17.4%) | 28,811 (1.5%) | <0.001 | 56.2 | 23,085 (6.1%) | 22,551 (6%) | 0.01 | 0.6 |
| **ACE Inhibitors, n (%)** | 203,851 (20.8%) | 30,917 (1.7%) | <0.001 | 63.5 | 29,715 (7.9%) | 29,014 (7.7%) | 0.003 | 0.7 |
| **Angiotensin II Inhibitors, n (%)** | 116,305 (11.8%) | 17,038 (0.9%) | <0.001 | 45.9 | 15,595 (4.1%) | 15,072 (4%) | 0.002 | 0.7 |
| **Antiarrhythmic agents, n (%)** | 231,189 (23.5%) | 46,486 (2.5%) | <0.001 | 65.9 | 28,908 (7.6%) | 28,636 (7.6%) | 0.238 | 0.3 |
| **Digitalis glycosides, n (%)** | 10,046 (1%) | 667 (0%) | <0.001 | 13.6 | 1,003 (0.3%) | 521 (0.1%) | <0.001 | 2.8 |
| **Diuretics, n (%)** | 248,655 (25.3%) | 36,974 (2%) | <0.001 | 72.3 | 31,434 (8.3%) | 30,075 (8%) | <0.001 | 1.3 |
| **Lipid lowering drugs, n (%)** | 334,212 (34%) | 50,852 (2.7%) | <0.001 | 88.4 | 59,617 (15.8%) | 38,197 (10.1%) | <0.001 | 16.9 |
| **Glucose-lowering therapy, n (%)** | 400,832 (40.8%) | 0 (0%) | <0.001 | 117.5 | 123,395 (32.6%) | 0 (0%) | <0.001 | 98.4 |
| **Insulin, n (%)** | 187,291 (19.1%) | 0 (0%) | <0.001 | 68.7 | 54,702 (14.5%) | 0 (0%) | <0.001 | 58.2 |
| **Metformin, n (%)** | 233,147 (23.7%) | 0 (0%) | <0.001 | 78.9 | 73,918 (19.5%) | 0 (0%) | <0.001 | 69.7 |
| **Sulfonylureas, n (%)** | 61,455 (6.3%) | 0 (0%) | <0.001 | 36.5 | 20,771 (5.5%) | 0 (0%) | <0.001 | 34.1 |
| **Thiazolidinediones, n (%)** | 11,588 (1.2%) | 0 (0%) | <0.001 | 15.5 | 3,860 (1%) | 0 (0%) | <0.001 | 14.4 |
| **DPP4 inhibitors, n (%)** | 23,386 (2.4%) | 0 (0%) | <0.001 | 22.1 | 7,070 (1.9%) | 0 (0%) | <0.001 | 19.5 |
| **GLP-1 receptor agonists, n (%)** | 23,316 (2.4%) | 0 (0%) | <0.001 | 22.1 | 5,796 (1.5%) | 0 (0%) | <0.001 | 17.6 |
| **SGLT2 inhibitors, n (%)** | 16,915 (1.7%) | 0 (0%) | <0.001 | 18.7 | 4,304 (1.1%) | 0 (0%) | <0.001 | 15.2 |

Values are n (%) or mean ± SD. ACE = angiotensin converting enzyme; BBB = bundle branch block; BP = blood pressure; COPD = Chronic obstructive pulmonary disease; DPP4 = Dipeptidyl peptidase-4; GLP-1 = Glucagon-like peptide 1; ICD = implantable cardioverter defibrillator; SD = standard deviation; SGLT2i = Sodium-glucose cotransporter 2 inhibitors.

**Table 3.** Clinical outcomes during FU in the fully matched population with T2DM or no diabetes in PMSI database

| | Type 2 diabetes mellitus (n=408905) | | | No diabetes mellitus (n=408905) | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Person-time (patient.year)** | **Number of events** | **Incidence, %/year (95% CI)** | **Person-time (patient.year)** | **Number of events** | **Incidence, %/year (95% CI)** | **Hazard ratio (95% CI)** | **p value** |
| **Death during follow-up** | 1898838 | 157279 | 8.28 (8.24-8.32) | 1894441 | 153318 | 8.09 (8.05-8.13) | 1.024 (1.017-1.031) | <0.0001 |
| **Cardiovascular death** | 1898838 | 35851 | 1.89 (1.87-1.91) | 1894441 | 32138 | 1.70 (1.68-1.72) | 1.114 (1.097-1.130) | <0.0001 |
| **Incident MI** | 1864819 | 13033 | 0.70 (0.69-0.71) | 1867522 | 10110 | 0.54 (0.53-0.55) | 1.287 (1.254-1.321) | <0.0001 |
| **Heart failure** | 1757906 | 51237 | 2.92 (2.89-2.94) | 1778168 | 43417 | 2.44 (2.42-2.47) | 1.186 (1.171-1.202) | <0.0001 |
| **Incident Sinus node disease** | 1884494 | 4650 | 0.25 (0.24-0.25) | 1879901 | 4575 | 0.24 (0.24-0.25) | 1.012 (0.972-1.054) | 0.56 |
| **Incident AV block** | 1860147 | 13225 | 0.71 (0.70-0.72) | 1861848 | 10812 | 0.58 (0.57-0.59) | 1.220 (1.190-1.252) | <0.0001 |
| **Incident Left BBB** | 1883987 | 5352 | 0.28 (0.28-0.29) | 1881330 | 4749 | 0.25 (0.25-0.26) | 1.123 (1.080-1.168) | <0.0001 |
| **Incident Right BBB** | 1882365 | 5904 | 0.31 (0.31-0.32) | 1879961 | 5178 | 0.28 (0.27-0.28) | 1.136 (1.094-1.179) | <0.0001 |
| **Pacemaker or ICD during FU** | 1852894 | 14319 | 0.77 (0.76-0.79) | 1852747 | 12593 | 0.68 (0.67-0.69) | 1.134 (1.107-1.162) | <0.0001 |
| **ICD during FU** | 1890567 | 2393 | 0.13 (0.12-0.13) | 1886512 | 2324 | 0.12 (0.12-0.13) | 1.025 (0.969-1.086) | 0.39 |

BBB = bundle branch block; ICD = implantable cardioverter defibrillator; MI = myocardial infarction.

**Table 4.** Clinical outcomes during FU in the matched population of patients with T2DM in TriNetX network

| | Type 2 DM (n = 378132) | | No DM (n = 378132) | | | |
|---|---|---|---|---|---|---|
| | **Number of events** | **Yearly rate, %** | **Number of events** | **Yearly rate, %** | **Hazard ratio (95% CI)** | **p value** |
| **Death** | 16251 | 1.22 | 8904 | 0.65 | 1.831 (1.785-1.879) | <0.0001 |
| **Acute MI** | 18171 | 1.36 | 8644 | 0.63 | 2.138 (2.084-2.193) | <0.0001 |
| **Sinus node dysfunction** | 3318 | 0.25 | 2603 | 0.19 | 1.277 (1.213-1.344) | <0.0001 |
| **AV block** | 9119 | 0.68 | 6111 | 0.45 | 1.5 (1.452-1.549) | <0.0001 |
| **Left BBB** | 14249 | 1.06 | 9547 | 0.70 | 1.503 (1.465-1.543) | <0.0001 |
| **Right BBB** | 8028 | 0.59 | 5819 | 0.42 | 1.384 (1.338-1.432) | <0.0001 |
| **Pacemaker or ICD implantation** | 4238 | 0.31 | 2658 | 0.19 | 1.599 (1.524-1.679) | <0.0001 |
| **ICD implantation** | 3986 | 0.29 | 2259 | 0.16 | 1.768 (1.679-1.862) | <0.0001 |

BBB = bundle branch block; ICD = implantable cardioverter defibrillator; MI = myocardial infarction.

**Table 5.** Baseline characteristics of patients with T1DM before and after propensity score matching in TriNetX network

| | Before propensity-score matching | | | | After propensity-score matching | | | |
|---|---|---|---|---|---|---|---|---|
| | **Type 1 DM (n = 20,320)** | **No DM (n = 2,148,642)** | **P-Value** | **Std diff. (%)** | **Type 1 DM (n = 20,178)** | **No DM (n = 20,178)** | **P-Value** | **Std diff. (%)** |
| **Age at Index, n (%)** | 37.4 +/- 17.5 | 45.2 +/- 16.6 | <0.001 | 45.4 | 37.3 +/- 17.5 | 37.3 +/- 18.8 | 0.761 | 0.3 |
| **Men, n (%)** | 10,850 (53.4%) | 880,678 (41%) | <0.001 | 25 | 10,760 (53.3%) | 11,225 (55.6%) | <0.001 | 4.6 |
| **Hypertension, n (%)** | 4,835 (23.8%) | 167,389 (7.8%) | <0.001 | 45 | 4,711 (23.3%) | 4,933 (24.4%) | 0.01 | 2.6 |
| **Diabetes mellitus, n (%)** | 20,320 (100%) | 0 (0%) | <0.001 | - | 20,178 (100%) | 0 (0%) | <0.001 | - |
| **Smoker, n (%)** | 971 (4.8%) | 14,625 (0.7%) | <0.001 | 25.4 | 908 (4.5%) | 894 (4.4%) | 0.736 | 0.3 |
| **Overweight or obesity, n (%)** | 1,873 (9.2%) | 79,792 (3.7%) | <0.001 | 22.5 | 1,848 (9.2%) | 1,853 (9.2%) | 0.931 | 0.1 |
| **Dyslipidaemia, n (%)** | 5,554 (27.3%) | 130,008 (6.1%) | <0.001 | 59.5 | 5,432 (26.9%) | 5,511 (27.3%) | 0.376 | 0.9 |
| **Alcohol related diagnoses, n (%)** | 282 (1.4%) | 9,868 (0.5%) | <0.001 | 9.7 | 275 (1.4%) | 334 (1.7%) | 0.016 | 2.4 |
| **Heart failure, n (%)** | 887 (4.4%) | 9,631 (0.4%) | <0.001 | 25.8 | 829 (4.1%) | 787 (3.9%) | 0.286 | 1.1 |
| **Coronary artery disease, n (%)** | 1,639 (8.1%) | 25,080 (1.2%) | <0.001 | 33.3 | 1,547 (7.7%) | 1,436 (7.1%) | 0.035 | 2.1 |
| **Myocardial infarction, n (%)** | 554 (2.7%) | 10,575 (0.5%) | <0.001 | 17.8 | 526 (2.6%) | 555 (2.8%) | 0.371 | 0.9 |
| **Dilated cardiomyopathy, n (%)** | 40 (0.2%) | 588 (0%) | <0.001 | 5.1 | 38 (0.2%) | 39 (0.2%) | 0.909 | 0.1 |
| **Ischemic stroke, n (%)** | 419 (2.1%) | 15,385 (0.7%) | <0.001 | 11.5 | 400 (2%) | 546 (2.7%) | <0.001 | 4.8 |
| **Intracranial haemorrhage, n (%)** | 85 (0.4%) | 2,796 (0.1%) | <0.001 | 5.5 | 82 (0.4%) | 115 (0.6%) | 0.018 | 2.3 |
| **Valve disease, n (%)** | 307 (1.5%) | 5,141 (0.2%) | <0.001 | 13.7 | 280 (1.4%) | 247 (1.2%) | 0.148 | 1.4 |
| **Mitral regurgitation, n (%)** | 283 (1.4%) | 4,325 (0.2%) | <0.001 | 13.4 | 257 (1.3%) | 222 (1.1%) | 0.108 | 1.6 |
| **Mitral stenosis, n (%)** | 49 (0.2%) | 697 (0%) | <0.001 | 5.6 | 43 (0.2%) | 28 (0.1%) | 0.075 | 1.8 |
| **Aortic regurgitation, n (%)** | 165 (0.8%) | 2,425 (0.1%) | <0.001 | 10.3 | 155 (0.8%) | 124 (0.6%) | 0.063 | 1.9 |
| **Aortic stenosis, n (%)** | 185 (0.9%) | 2,478 (0.1%) | <0.001 | 11.1 | 174 (0.9%) | 115 (0.6%) | <0.001 | 3.5 |
| **Atrial fibrillation or flutter, n (%)** | 547 (2.7%) | 15,017 (0.7%) | <0.001 | 15.5 | 518 (2.6%) | 535 (2.7%) | 0.596 | 0.5 |
| **Sinus node disease, n (%)** | 67 (0.3%) | 865 (0%) | <0.001 | 6.7 | 61 (0.3%) | 29 (0.1%) | 0.001 | 3.4 |
| **Atrioventricular and/or LBBB, n (%)** | 278 (1.4%) | 4,453 (0.2%) | <0.001 | 13.2 | 261 (1.3%) | 216 (1.1%) | 0.038 | 2.1 |
| **Left BBB, n (%)** | 79 (0.4%) | 1,277 (0.1%) | <0.001 | 7 | 72 (0.4%) | 73 (0.4%) | 0.934 | 0.1 |
| **Right BBB, n (%)** | 163 (0.8%) | 3,098 (0.1%) | <0.001 | 9.6 | 152 (0.8%) | 113 (0.6%) | 0.016 | 2.4 |
| **Previous pacemaker, n (%)** | 120 (0.6%) | 1,554 (0.1%) | <0.001 | 9 | 112 (0.6%) | 72 (0.4%) | 0.003 | 2.9 |
| **Previous ICD, n (%)** | 92 (0.5%) | 928 (0%) | <0.001 | 8.2 | 84 (0.4%) | 79 (0.4%) | 0.695 | 0.4 |
| **Kidney disease, n (%)** | 2,504 (12.3%) | 14,448 (0.7%) | <0.001 | 48.6 | 2,371 (11.8%) | 2,247 (11.1%) | 0.052 | 1.9 |
| **Lung disease, n (%)** | 4,142 (20.4%) | 190,084 (8.8%) | <0.001 | 33.1 | 4,045 (20%) | 3,716 (18.4%) | <0.001 | 4.1 |

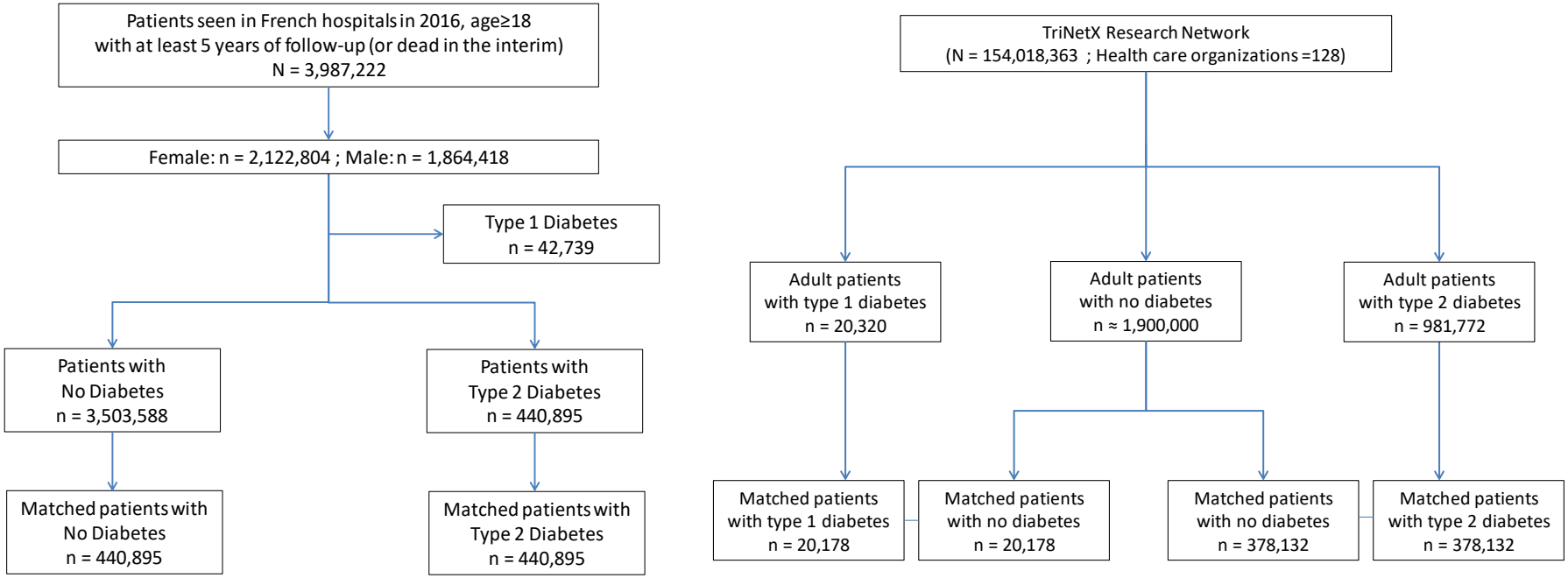
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **COPD, n (%)** | 352 (1.7%) | 9,008 (0.4%) | <0.001 | 12.8 | 327 (1.6%) | 281 (1.4%) | 0.06 | 1.9 |
| **Sleep apnoea syndrome, n (%)** | 654 (3.2%) | 20,051 (0.9%) | <0.001 | 16.1 | 635 (3.1%) | 580 (2.9%) | 0.109 | 1.6 |
| **Peripheral vascular disease, n (%)** | 353 (1.7%) | 3,027 (0.1%) | <0.001 | 16.6 | 325 (1.6%) | 278 (1.4%) | 0.054 | 1.9 |
| **Previous cancer, n (%)** | 1,580 (7.8%) | 68,456 (3.2%) | <0.001 | 20.3 | 1,526 (7.6%) | 1,346 (6.7%) | <0.001 | 3.5 |
| **Thyroid diseases, n (%)** | 3,695 (18.2%) | 55,651 (2.6%) | <0.001 | 52.9 | 3,616 (17.9%) | 3,630 (18%) | 0.856 | 0.2 |
| **Amyloidosis, n (%)** | 28 (0.1%) | 268 (0%) | <0.001 | 4.6 | 24 (0.1%) | 20 (0.1%) | 0.546 | 0.6 |
| **Malnutrition, n (%)** | 401 (2%) | 2,683 (0.1%) | <0.001 | 18.2 | 369 (1.8%) | 328 (1.6%) | 0.117 | 1.6 |
| **Cognitive impairment, n (%)** | 20 (0.1%) | 644 (0%) | <0.001 | 2.7 | 19 (0.1%) | 22 (0.1%) | 0.639 | 0.5 |
| **Total cholesterol (mg/dL), mean±SD** | 170.9 +/- 50.6 | 185.5 +/- 44.9 | <0.001 | 30.4 | 171.0 +/- 50.4 | 175.1 +/- 50.1 | <0.001 | 8.1 |
| **LDL cholesterol (mg/dL), mean±SD** | 95.4 +/- 35.3 | 110.7 +/- 36.6 | <0.001 | 42.7 | 95.5 +/- 35.2 | 103.1 +/- 39.9 | <0.001 | 20.2 |
| **HDL cholesterol (mg/dL), mean±SD** | 54.9 +/- 19.1 | 52.0 +/- 16.8 | <0.001 | 16.2 | 55.0 +/- 19.1 | 48.6 +/- 16.0 | <0.001 | 36 |
| **Triglyceride (mg/dL), mean±SD** | 118.4 +/- 146.6 | 122.0 +/- 95.6 | <0.001 | 2.9 | 118.1 +/- 146.8 | 126.2 +/- 110.8 | <0.001 | 6.2 |
| **Haemoglobin A1c (%), mean±SD** | 8.3 +/- 2.2 | 5.5 +/- 1.1 | <0.001 | 162.5 | 8.3 +/- 2.2 | 5.3 +/- 0.7 | <0.001 | 186.1 |
| **Body mass index (kg/m2), mean±SD** | 26.6 +/- 5.8 | 28.9 +/- 6.9 | <0.001 | 35.9 | 26.6 +/- 5.8 | 26.9 +/- 6.3 | <0.001 | 5.1 |
| **Systolic BP (mm Hg), mean±SD** | 123.3 +/- 17.3 | 125.8 +/- 18.5 | <0.001 | 13.6 | 123.3 +/- 17.2 | 122.9 +/- 18.7 | 0.08 | 1.9 |
| **Diastolic BP (mm Hg), mean±SD** | 73.4 +/- 11.3 | 76.6 +/- 11.8 | <0.001 | 27.2 | 73.4 +/- 11.2 | 74.3 +/- 12.8 | <0.001 | 6.9 |
| **Beta Blockers, n (%)** | 2,815 (13.9%) | 54,139 (2.5%) | <0.001 | 42.3 | 2,702 (13.4%) | 2,623 (13%) | 0.245 | 1.2 |
| **Calcium Channel Blockers, n (%)** | 1,840 (9.1%) | 38,782 (1.8%) | <0.001 | 32.4 | 1,764 (8.7%) | 1,735 (8.6%) | 0.608 | 0.5 |
| **ACE Inhibitors, n (%)** | 2,986 (14.7%) | 39,644 (1.8%) | <0.001 | 48 | 2,888 (14.3%) | 3,007 (14.9%) | 0.093 | 1.7 |
| **Angiotensin II Inhibitors, n (%)** | 1,260 (6.2%) | 23,107 (1.1%) | <0.001 | 27.6 | 1,218 (6%) | 1,255 (6.2%) | 0.443 | 0.8 |
| **Antiarrhythmic agents, n (%)** | 3,295 (16.2%) | 53,088 (2.5%) | <0.001 | 48.6 | 3,174 (15.7%) | 2,608 (12.9%) | <0.001 | 8 |
| **Digitalis glycosides, n (%)** | 102 (0.5%) | 810 (0%) | <0.001 | 9 | 93 (0.5%) | 68 (0.3%) | 0.048 | 2 |
| **Diuretics, n (%)** | 2,413 (11.9%) | 48,400 (2.3%) | <0.001 | 38.2 | 2,315 (11.5%) | 2,114 (10.5%) | 0.001 | 3.2 |
| **Lipid lowering drugs, n (%)** | 4,796 (23.6%) | 64,443 (3%) | <0.001 | 63.7 | 4,692 (23.3%) | 2,806 (13.9%) | <0.001 | 24.2 |

Values are n (%) or mean ± SD. ACE = angiotensin converting enzyme; BBB = bundle branch block; BP = blood pressure; COPD = Chronic obstructive pulmonary disease; ICD = implantable cardioverter defibrillator; SD = standard deviation.

**Table 6.** Clinical outcomes during FU in the matched population of patients with T1DM in TriNetX network

| | Type 1 DM (n = 20178) | | No DM (n = 20178) | | | |
|---|---|---|---|---|---|---|
| | **Number of events** | **Yearly rate, %** | **Number of events** | **Yearly rate, %** | **Hazard ratio (95% CI)** | **p value** |
| **Death** | 1133 | 2.97 | 473 | 0.99 | 3.034 (2.724-3.379) | <0.0001 |
| **Acute MI** | 273 | 0.74 | 303 | 0.63 | 1.11 (0.942-1.308) | 0.21 |
| **Sinus node dysfunction** | 44 | 0.12 | 110 | 0.22 | 0.482 (0.339-0.684) | <0.0001 |
| **AV block** | 148 | 0.39 | 230 | 0.47 | 0.788 (0.640-0.969) | 0.02 |
| **Left BBB** | 210 | 0.55 | 321 | 0.65 | 0.798 (0.670-0.951) | 0.01 |
| **Right BBB** | 117 | 0.31 | 212 | 0.45 | 0.689 (0.549-0.864) | 0.001 |
| **Pacemaker or ICD implantation** | 107 | 0.25 | 152 | 0.28 | 0.813 (0.634-1.042) | 0.1 |
| **ICD implantation** | 65 | 0.17 | 142 | 0.26 | 0.528 (0.394-0.709) | <0.0001 |

BBB = bundle branch block; ICD = implantable cardioverter defibrillator; MI = myocardial infarction.




**Flow chart of patients for the PMSI database**

**Flow chart of patients for the TriNetX network**

**Figure 1.** Flow chart of patients in the 2 analysis of the study

***PMSI database***

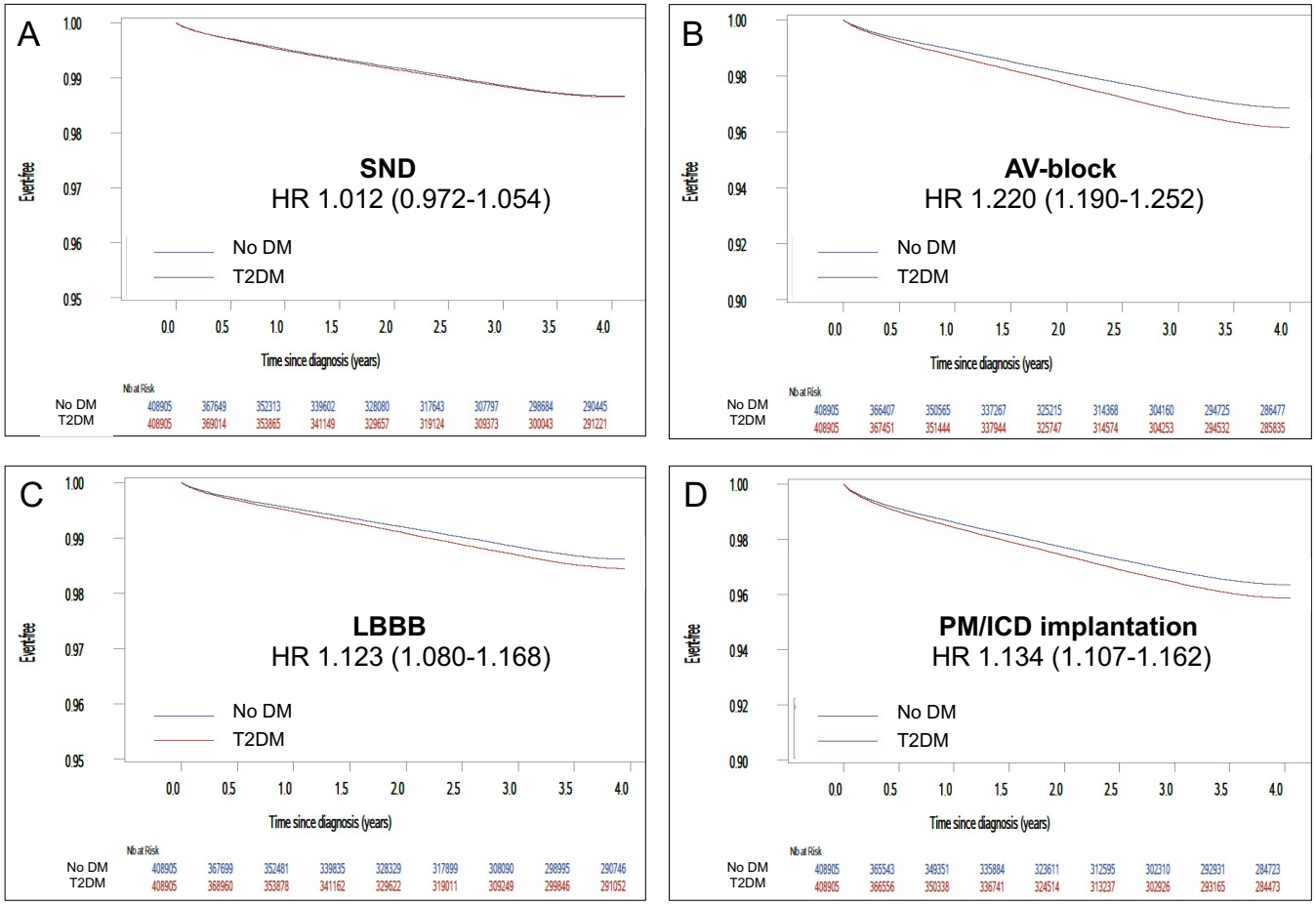



**Figure 2.** Kaplan–Meier analysis with event-free probabilities in patients from the PMSI database for A) sinus node disease, B) atrioventricular block, C) left bundle branch block and D) need for pacemaker or implantable cardioverter defibrillator implantation. Numbers below the figure represent individuals at risk.

***TrinetX network***

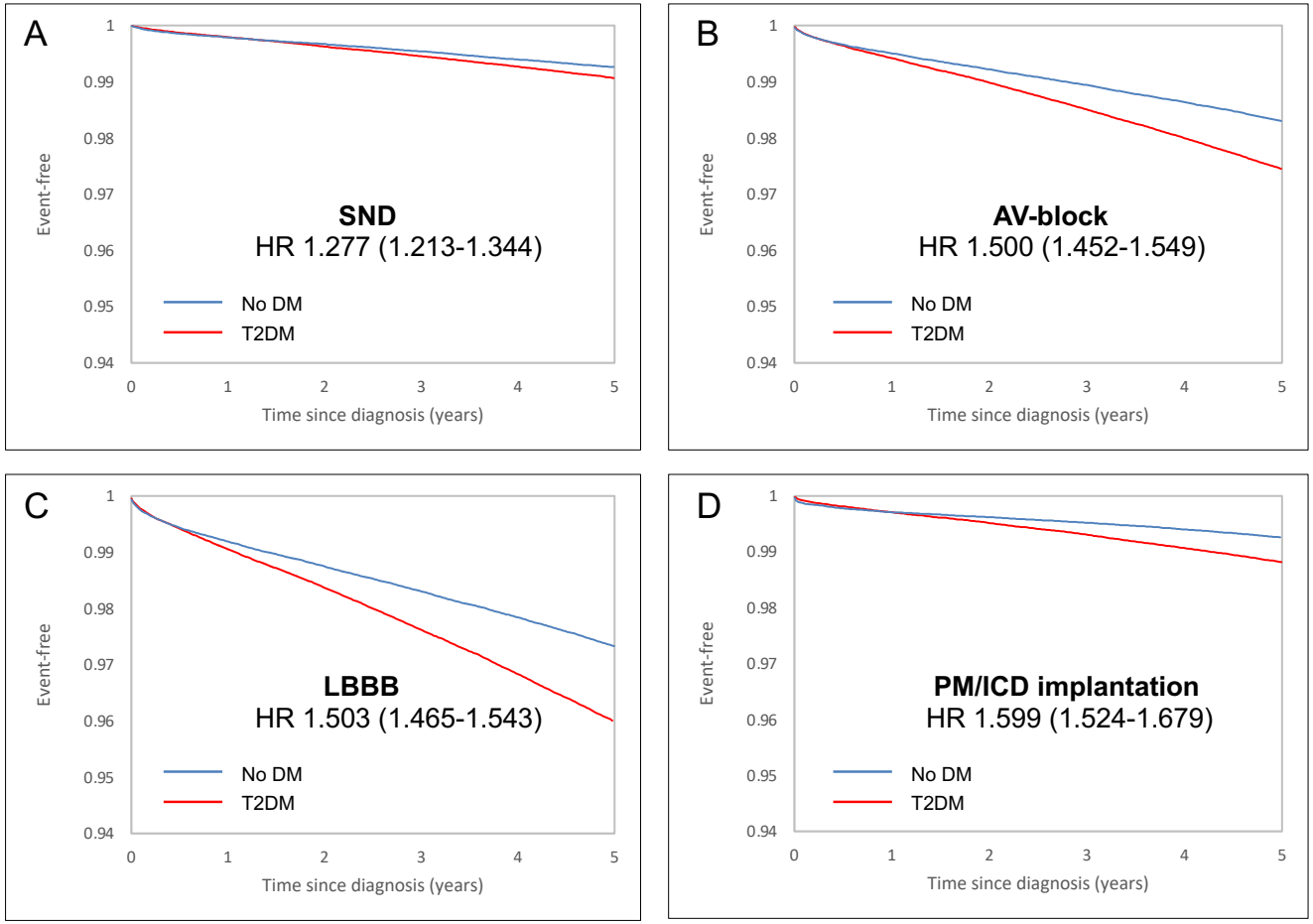



**Figure 3.** Kaplan–Meier analysis with event-free probabilities in patients from the TrinetX network for A) sinus node disease, B) atrioventricular block, C) left bundle branch block and D) need for pacemaker or implantable cardioverter defibrillator implantation.

# SUPPLEMENTAL FILE

**Table S1.** Codes in the 10th revision of the International Classification of Diseases (ICD-10) or in the classification commune des actes médicaux (CCAM, French classification for medical procedures) for diseases and comorbidities and in Anatomical Therapeutic Chemical (ATC) classification system for drugs.

| ***Diseases and comorbidities*** | ***Codes in the 10th revision of the International Classification of Diseases (ICD-10) or in the classification commune des actes médicaux (CCAM, French classification for medical procedures)*** |
|---|---|
| **Hypertension** | I10, I11, I12, I13, I14, I15 |
| **Diabetes mellitus** | E10, E11, E12, E13, E14 |
| **Heart failure** | I50, I11.0, I13.0, I13.2, J81, R570, I42, I43, I25.5 |
| **History of pulmonary oedema** | R570, J81 |
| **Aortic regurgitation** | I35.1 |
| **Mitral regurgitation** | I34.0 |
| **Previous endocarditis** | I330 |
| **Dilated cardiomyopathy** | I42, I43 |
| **Coronary artery disease** | I20, I21, I22, I23, I24, I25, Z955, DDAF006, DDAF001, DDAF003, DDAF004, DDAF007, DDAF008, DDAF009, DDAF010, Z951, DDMA003, DDMA004, DDMA005, DDMA006, DDMA007, DDMA008, DDMA009, DDMA011, DDMA012, DDMA013, DDMA015, DDMA016, DDMA017, DDMA018, DDMA019, DDMA020, DDMA021, DDMA022, DDMA023, DDMA024, DDMA025, DDMA026, DDMA027, DDMA028, DDMA029, DDMA030, DDMA031, DDMA032, DDMA033, DDMA034, DDMA035, DDMA036, DDMA037, DDMA038 |
| **Previous myocardial infarction** | I21, I22, I23 |
| **Previous PCI** | Z955, DDAF006, DDAF001, DDAF003, DDAF004, DDAF007, DDAF008, DDAF009, DDAF010 |
| **Previous CABG** | Z951, DDMA003, DDMA004, DDMA005, DDMA006, DDMA007, DDMA008, DDMA009, DDMA011, DDMA012, DDMA013, DDMA015, DDMA016, DDMA017, DDMA018, DDMA019, DDMA020, DDMA021, DDMA022, DDMA023, DDMA024, DDMA025, DDMA026, DDMA027, DDMA028, DDMA029, DDMA030, DDMA031, DDMA032, DDMA033, DDMA034, DDMA035, DDMA036, DDMA037, DDMA038 |
| **Atrial fibrillation** | I48 |
| **Sinus node disease** | I49.5 |
| **Left BBB** | I447 |
| **Right BBB** | I451 |
| **Ventricular tachycardia** | I47.2 |
| **Ventricular fibrillation** | I490 |

| | |
|---|---|
| **Cardiac arrest** | I46 |
| **Previous pacemaker or ICD** | Z95.0, Z45.0 |
| **Vascular disease** | I71, I790, I739, R02, Z958, Z959 |
| **Ischemic stroke** | I63 |
| **Intracranial bleeding** | I60, I61, I62, S06.4, S06.5, S06.6 |
| **Smoker** | I472 |
| **Dyslipidaemia** | E78 |
| **Obesity** | E65, E66 |
| **Alcohol related diagnoses** | E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, P04.3, Q86.0, T51, Y90, Y91, Z50.2, Z71.4, Z72.1 |
| **Poor nutrition** | E41, E43, E44, E46, F508, K912, R636 |
| **Abnormal renal function** | N18.3, N18.4, N18.5, T86.1, Z49, Z99.2 |
| **Lung disease** | J40-J70, J96.1 |
| **Sleep apnea syndrome** | G47.3 |
| **COPD** | J43, J44 |
| **Liver disease** | K70-K77 |
| **Gastroesophageal reflux** | K21 |
| **Thyroid diseases** | E0, E89.0 |
| **Inflammatory disease** | M05-M14, M45, M46, K50, K51, K52 |
| **Anaemia** | D50-D64 |
| **Previous cancer** | C00-C97 |
| **Previous cancer** | C00-C97 |
| **Cognitive impairment** | F00, F01, F02, F03, F106, F1073, F1173, F1273, F1373, F1473, F1573, F1673, F1773, F1873, F1973, G30, G310, G318, G938, I673 |
| **Gastro-intestinal bleeding** | I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K920, K921, K922 |
| **Urogenital bleeding** | N020, N021, N022, N023, N024, N025, N026, N027, N028, N029, N421, N920, N921, N923, N924, N930, N938, N939, N950, R31 |
| **Haemothorax** | J942 |
| **Haemorrhage and hematoma complicating a procedure** | T810 |
| **Other digestive bleeding and acute post-haemorrhagic anaemia** | I85.0, I98.3, K62.5, K92.2, D62 |
| **Any severe bleeding** | I850, I983, K625, K922 |
| **Other critical organ or site bleeding** | H313, H356, H431, H450, I230, I312, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I620, I621, M250, S064, S065, S066, S260 |
| **Other bleeding** | D62, D683, D698, D699, H113, H922, J942, K661, K762, R040, R041, R042, R048, R049, R58 , S271, T792 |

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention.

| *Drugs* | *Codes in Anatomical Therapeutic Chemical (ATC) Classification System* |
|---|---|
| **ACE inhibitor or ARB** | C09 |
| **Beta-blocker** | C07 |
| **Diuretic** | C03 |
| **K-sparing diuretics** | C03D |
| **Calcium channel blocker** | C08 |
| **Digoxin** | C01AA05 |
| **Antiarrhythmic agents** | C01B |
| **Amiodarone** | C01BD01 |
| **VKA** | B01AA |
| **Direct oral anticoagulant** | B01AE07, B01AF01, B01AF02, B01AF03 |
| **Dabigatran** | B01AE07 |
| **Rivaroxaban** | B01AF01 |
| **Apixaban** | B01AF02 |
| **Aspirin** | N02BA01 |
| **P2Y12 inhibitors** | B01AC04, B01AC22, B01AC24 |
| **Clopidogrel** | B01AC04 |
| **Prasugrel** | B01AC22 |
| **Ticagrelor** | B01AC24 |
| **Statin** | C10AA01 / 02 / 03 / 04 /05 / 07 / 08 |
| **Aspirin** | B01AC06 |
| **P2Y12 inhibitor** | B01AC04, B01AC22, B01AC24 |
| **Statin** | C10AA |
| **Antidiabetic** | A10 |
| **Metformin** | A10BA02 |
| **Insulin** | A10AB / C / D /E |
| **Sulfonylureas** | A10BB01 / 02 / 03 / 04 /05 / 06/09/12 |
| **GLP1-analogues** | A10BJ02 / 04 /05 / 06/07 |
| **DPP4-inhibitors** | A10BH01 / 02 / 03 /05 |
| **SGLT2-inhibitors** | A10BK01 / 02 / 03 /04 |

**Table S2.** Baseline characteristics of unmatched and age and sex- matched patients with T2DM or no diabetes in PMSI database

| | Before PS matching | | | | After PS matching | | | |
|---|---|---|---|---|---|---|---|---|
| | **No diabetes mellitus (n=3503588)** | **Type 2 diabetes mellitus (n=440895)** | **p** | **Standardized difference (%)** | **No diabetes mellitus (n=440895)** | **Type 2 diabetes mellitus (n=440895)** | **p** | **Standardized difference (%)** |
| **Age (years), mean±SD** | 59.9±18.9 | 68.2±14.9 | <0.0001 | 45.1 | 68.2±14.9 | 68.2±14.9 | 1.00 | 0.0 |
| **Sex (male), n (%)** | 1594833 (45.5) | 246989 (56.0) | <0.0001 | 21.1 | 246989 (56.0) | 246989 (56.0) | 1.00 | 0.0 |
| **Hypertension, n (%)** | 806876 (23.0) | 295091 (66.9) | <0.0001 | 102.8 | 134208 (30.4) | 295091 (66.9) | <0.0001 | 78.4 |
| **Diabetes mellitus, n (%)** | 6447 (0.2) | 415455 (94.2) | <0.0001 | 1071.1 | 988 (0.2) | 415455 (94.2) | <0.0001 | 558.9 |
| **Heart failure, n (%)** | 265572 (7.6) | 97129 (22.0) | <0.0001 | 50.6 | 45589 (10.3) | 97129 (22.0) | <0.0001 | 32.1 |
| **History of pulmonary oedema, n (%)** | 16852 (0.5) | 5247 (1.2) | <0.0001 | 9.5 | 2685 (0.6) | 5247 (1.2) | <0.0001 | 6.2 |
| **Valve disease, n (%)** | 101254 (2.9) | 28305 (6.4) | <0.0001 | 19.8 | 17504 (4.0) | 28305 (6.4) | <0.0001 | 11.1 |
| **Aortic stenosis, n (%)** | 42744 (1.2) | 14373 (3.3) | <0.0001 | 17.1 | 7848 (1.8) | 14373 (3.3) | <0.0001 | 9.5 |
| **Aortic regurgitation, n (%)** | 19655 (0.6) | 4409 (1.0) | <0.0001 | 5.6 | 3479 (0.8) | 4409 (1.0) | <0.0001 | 2.2 |
| **Mitral regurgitation, n (%)** | 42043 (1.2) | 11066 (2.5) | <0.0001 | 11.4 | 7187 (1.6) | 11066 (2.5) | <0.0001 | 6.2 |
| **Previous endocarditis, n (%)** | 4064 (0.1) | 1217 (0.3) | <0.0001 | 4.4 | 679 (0.2) | 1217 (0.3) | <0.0001 | 2.6 |
| **Dilated cardiomyopathy, n (%)** | 57809 (1.7) | 19532 (4.4) | <0.0001 | 20.1 | 9391 (2.1) | 19532 (4.4) | <0.0001 | 13.0 |
| **Coronary artery disease, n (%)** | 285542 (8.2) | 108240 (24.6) | <0.0001 | 55.5 | 50571 (11.5) | 108240 (24.6) | <0.0001 | 34.5 |
| **Previous MI, n (%)** | 52904 (1.5) | 16357 (3.7) | <0.0001 | 16.8 | 8553 (1.9) | 16357 (3.7) | <0.0001 | 10.7 |
| **Previous PCI, n (%)** | 79181 (2.3) | 29055 (6.6) | <0.0001 | 26.6 | 13844 (3.1) | 29055 (6.6) | <0.0001 | 16.1 |
| **Previous CABG, n (%)** | 8374 (0.2) | 4285 (1.0) | <0.0001 | 13.0 | 1627 (0.4) | 4285 (1.0) | <0.0001 | 7.4 |
| **Vascular disease, n (%)** | 219675 (6.3) | 81433 (18.5) | <0.0001 | 46.4 | 37961 (8.6) | 81433 (18.5) | <0.0001 | 29.1 |
| **Atrial fibrillation, n (%)** | 276783 (7.9) | 76672 (17.4) | <0.0001 | 33.4 | 49821 (11.3) | 76672 (17.4) | <0.0001 | 17.4 |
| **Sinus node disease, n (%)** | 21302 (0.6) | 5599 (1.3) | <0.0001 | 8.0 | 3805 (0.9) | 5599 (1.3) | <0.0001 | 4.0 |
| **AV block, n (%)** | 46948 (1.3) | 15960 (3.6) | <0.0001 | 18.2 | 8774 (2.0) | 15960 (3.6) | <0.0001 | 9.9 |
| **Right BBB, n (%)** | 22003 (0.6) | 7583 (1.7) | <0.0001 | 12.7 | 3756 (0.9) | 7583 (1.7) | <0.0001 | 7.7 |
| **Left BBB, n (%)** | 17238 (0.5) | 6084 (1.4) | <0.0001 | 11.6 | 3025 (0.7) | 6084 (1.4) | <0.0001 | 6.9 |
| **Previous pacemaker or ICD, n (%)** | 89692 (2.6) | 26718 (6.1) | <0.0001 | 20.7 | 16578 (3.8) | 26718 (6.1) | <0.0001 | 10.7 |
| **Previous pacemaker, n (%)** | 46948 (1.3) | 13535 (3.1) | <0.0001 | 14.1 | 9038 (2.1) | 13535 (3.1) | <0.0001 | 6.5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Previous ICD, n (%)** | 8584 (0.2) | 2954 (0.7) | <0.0001 | 7.9 | 1486 (0.3) | 2954 (0.7) | <0.0001 | 4.7 |
| **Ischemic stroke, n (%)** | 56057 (1.6) | 16093 (3.7) | <0.0001 | 15.3 | 9435 (2.1) | 16093 (3.7) | <0.0001 | 9.0 |
| **Intracranial bleeding, n (%)** | 33950 (1.0) | 6305 (1.4) | <0.0001 | 4.6 | 5158 (1.2) | 6305 (1.4) | <0.0001 | 2.3 |
| **Smoker, n (%)** | 223529 (6.4) | 42811 (9.7) | <0.0001 | 13.3 | 25351 (5.8) | 42811 (9.7) | <0.0001 | 14.9 |
| **Dyslipidaemia, n (%)** | 302710 (8.6) | 147788 (33.5) | <0.0001 | 80.7 | 50879 (11.5) | 147788 (33.5) | <0.0001 | 54.5 |
| **Obesity, n (%)** | 305863 (8.7) | 144525 (32.8) | <0.0001 | 77.9 | 38226 (8.7) | 144525 (32.8) | <0.0001 | 62.3 |
| **Alcohol related diagnoses, n (%)** | 166771 (4.8) | 30730 (7.0) | <0.0001 | 10.1 | 19355 (4.4) | 30730 (7.0) | <0.0001 | 11.2 |
| **Chronic kidney disease, n (%)** | 92845 (2.7) | 41620 (9.4) | <0.0001 | 37.7 | 14814 (3.4) | 41620 (9.4) | <0.0001 | 25.0 |
| **Lung disease, n (%)** | 279236 (8.0) | 67677 (15.4) | <0.0001 | 26.1 | 43031 (9.8) | 67677 (15.4) | <0.0001 | 16.9 |
| **Sleep apnoea syndrome, n (%)** | 127531 (3.6) | 53040 (12.0) | <0.0001 | 40.5 | 18694 (4.2) | 53040 (12.0) | <0.0001 | 28.8 |
| **COPD, n (%)** | 154508 (4.4) | 41488 (9.4) | <0.0001 | 23.1 | 25969 (5.9) | 41488 (9.4) | <0.0001 | 13.3 |
| **Liver disease, n (%)** | 88290 (2.5) | 34346 (7.8) | <0.0001 | 30.5 | 11331 (2.6) | 34346 (7.8) | <0.0001 | 23.7 |
| **Gastroesophageal reflux, n (%)** | 115268 (3.3) | 12433 (2.8) | <0.0001 | -2.7 | 14505 (3.3) | 12433 (2.8) | <0.0001 | -2.7 |
| **Thyroid diseases, n (%)** | 166771 (4.8) | 43957 (10.0) | <0.0001 | 23.2 | 22927 (5.2) | 43957 (10.0) | <0.0001 | 18.1 |
| **Inflammatory disease, n (%)** | 184289 (5.3) | 29628 (6.7) | <0.0001 | 6.4 | 22442 (5.1) | 29628 (6.7) | <0.0001 | 6.9 |
| **Anaemia, n (%)** | 257163 (7.3) | 66884 (15.2) | <0.0001 | 28.6 | 36727 (8.3) | 66884 (15.2) | <0.0001 | 21.4 |
| **Previous cancer, n (%)** | 495057 (14.1) | 71293 (16.2) | <0.0001 | 5.8 | 77333 (17.5) | 71293 (16.2) | <0.0001 | -3.7 |
| **Poor nutrition, n (%)** | 217222 (6.2) | 47661 (10.8) | <0.0001 | 18.5 | 33155 (7.5) | 47661 (10.8) | <0.0001 | 11.4 |
| **Cognitive impairment, n (%)** | 95298 (2.7) | 22750 (5.2) | <0.0001 | 14.3 | 16313 (3.7) | 22750 (5.2) | <0.0001 | 7.1 |
| **Frailty index, mean±SD** | 4.3±6.9 | 7.7±8.8 | <0.0001 | 47.5 | 5.3±7.6 | 7.7±8.8 | <0.0001 | 29.0 |

Values are n (%) or mean ± SD. BBB = bundle branch block; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter defibrillator; MI = myocardial infarction; PCI= percutaneous coronary intervention; SD = standard deviation.

**Table S3.** Baseline characteristics of patients with T2DM before and after propensity score (including age and sex) matching in TriNetX network

| | Before propensity-score matching | | | | After propensity-score matching | | | |
|---|---|---|---|---|---|---|---|---|
| | **Type 2 DM (n = 1181496)** | **No DM (n = 2485096)** | **P-Value** | **Std diff. (%)** | **Type 2 DM (n = 1099642)** | **No DM (n = 1099642)** | **P-Value** | **Std diff. (%)** |
| **Age at Index, n (%)** | 58.3 +/- 13.6 | 45.2 +/- 16.6 | <0.001 | 86.2 | 56.9 +/- 13.1 | 57.0 +/- 13.1 | 0.024 | 0.3 |
| **Men, n (%)** | 575103 (48.7%) | 1007401 (40.5%) | <0.001 | 16.4 | 521985 (47.5%) | 510894 (46.5%) | <0.001 | 2 |
| **Hypertension, n (%)** | 703504 (59.5%) | 174929 (7%) | <0.001 | 134.2 | 645296 (58.7%) | 118105 (10.7%) | <0.001 | 116.6 |
| **Diabetes mellitus, n (%)** | 1181496 (100%) | 0 (0%) | <0.001 | - | 1099642 (100%) | 0 (0%) | <0.001 | - |
| **Smoker, n (%)** | 101847 (8.6%) | 14991 (0.6%) | <0.001 | 38.9 | 91393 (8.3%) | 9961 (0.9%) | <0.001 | 35.9 |
| **Overweight or obesity, n (%)** | 307180 (26%) | 84170 (3.4%) | <0.001 | 67.4 | 293663 (26.7%) | 26518 (2.4%) | <0.001 | 73.4 |
| **Dyslipidaemia, n (%)** | 625118 (52.9%) | 139129 (5.6%) | <0.001 | 121.7 | 571441 (52%) | 96267 (8.8%) | <0.001 | 106.5 |
| **Alcohol related diagnoses, n (%)** | 25277 (2.1%) | 10162 (0.4%) | <0.001 | 15.5 | 24241 (2.2%) | 4734 (0.4%) | <0.001 | 15.6 |
| **Heart failure, n (%)** | 102004 (8.6%) | 10165 (0.4%) | <0.001 | 40.4 | 89078 (8.1%) | 7609 (0.7%) | <0.001 | 36.7 |
| **Coronary artery disease, n (%)** | 178070 (15.1%) | 25695 (1%) | <0.001 | 53.4 | 154461 (14%) | 21057 (1.9%) | <0.001 | 45.9 |
| **Myocardial infarction, n (%)** | 46347 (3.9%) | 10818 (0.4%) | <0.001 | 24.1 | 41281 (3.8%) | 7916 (0.7%) | <0.001 | 20.6 |
| **Dilated cardiomyopathy, n (%)** | 7314 (0.6%) | 607 (0%) | <0.001 | 10.5 | 6614 (0.6%) | 383 (0%) | <0.001 | 10.1 |
| **Ischemic stroke, n (%)** | 49533 (4.2%) | 16014 (0.6%) | <0.001 | 23.3 | 43342 (3.9%) | 11970 (1.1%) | <0.001 | 18.3 |
| **Intracranial haemorrhage, n (%)** | 7654 (0.6%) | 2860 (0.1%) | <0.001 | 8.7 | 6650 (0.6%) | 2023 (0.2%) | <0.001 | 6.7 |
| **Valve disease, n (%)** | 35068 (3%) | 5277 (0.2%) | <0.001 | 22.2 | 30335 (2.8%) | 3488 (0.3%) | <0.001 | 19.9 |
| **Mitral regurgitation, n (%)** | 32065 (2.7%) | 4447 (0.2%) | <0.001 | 21.4 | 27683 (2.5%) | 2996 (0.3%) | <0.001 | 19.2 |
| **Mitral stenosis, n (%)** | 4933 (0.4%) | 717 (0%) | <0.001 | 8.2 | 4332 (0.4%) | 461 (0%) | <0.001 | 7.6 |
| **Aortic regurgitation, n (%)** | 16079 (1.4%) | 2462 (0.1%) | <0.001 | 14.9 | 13354 (1.2%) | 1826 (0.2%) | <0.001 | 12.7 |
| **Aortic stenosis, n (%)** | 18956 (1.6%) | 2525 (0.1%) | <0.001 | 16.4 | 15185 (1.4%) | 2008 (0.2%) | <0.001 | 13.6 |
| **Atrial fibrillation or flutter, n (%)** | 82305 (7%) | 15820 (0.6%) | <0.001 | 33.6 | 67592 (6.1%) | 13515 (1.2%) | <0.001 | 26.3 |
| **Sinus node disease, n (%)** | 7209 (0.6%) | 880 (0%) | <0.001 | 10.1 | 5592 (0.5%) | 705 (0.1%) | <0.001 | 8.3 |
| **Atrioventricular and/or LBBB, n (%)** | 29936 (2.5%) | 4554 (0.2%) | <0.001 | 20.4 | 24727 (2.2%) | 3516 (0.3%) | <0.001 | 17.2 |
| **Left BBB, n (%)** | 8944 (0.8%) | 1302 (0.1%) | <0.001 | 11.1 | 7497 (0.7%) | 1058 (0.1%) | <0.001 | 9.4 |
| **Right BBB, n (%)** | 15892 (1.3%) | 3157 (0.1%) | <0.001 | 14.3 | 13462 (1.2%) | 2198 (0.2%) | <0.001 | 12.2 |
| **Previous pacemaker, n (%)** | 12855 (1.1%) | 1623 (0.1%) | <0.001 | 13.5 | 10154 (0.9%) | 1337 (0.1%) | <0.001 | 11.1 |
| **Previous ICD, n (%)** | 11413 (1%) | 956 (0%) | <0.001 | 13.1 | 10028 (0.9%) | 681 (0.1%) | <0.001 | 12.2 |
| **Kidney disease, n (%)** | 162065 (13.7%) | 15022 (0.6%) | <0.001 | 52.6 | 142170 (12.9%) | 10139 (0.9%) | <0.001 | 48.7 |
| **Lung disease, n (%)** | 405288 (34.3%) | 200038 (8%) | <0.001 | 67.9 | 376549 (34.2%) | 70067 (6.4%) | <0.001 | 73.9 |
| **COPD, n (%)** | 64509 (5.5%) | 9255 (0.4%) | <0.001 | 30.6 | 57210 (5.2%) | 7336 (0.7%) | <0.001 | 27.1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Sleep apnoea syndrome, n (%)** | 142875 (12.1%) | 20853 (0.8%) | <0.001 | 47 | 134017 (12.2%) | 10791 (1%) | <0.001 | 46.4 |
| **Peripheral vascular disease, n (%)** | 35623 (3%) | 3128 (0.1%) | <0.001 | 23.4 | 30295 (2.8%) | 2635 (0.2%) | <0.001 | 20.8 |
| **Previous cancer, n (%)** | 215383 (18.2%) | 70623 (2.8%) | <0.001 | 51.8 | 195174 (17.7%) | 39864 (3.6%) | <0.001 | 47 |
| **Thyroid diseases, n (%)** | 163470 (13.8%) | 57303 (2.3%) | <0.001 | 43.3 | 149934 (13.6%) | 30707 (2.8%) | <0.001 | 40.3 |
| **Amyloidosis, n (%)** | 1311 (0.1%) | 278 (0%) | <0.001 | 4 | 1053 (0.1%) | 214 (0%) | <0.001 | 3.2 |
| **Malnutrition, n (%)** | 19783 (1.7%) | 2778 (0.1%) | <0.001 | 16.7 | 17804 (1.6%) | 1493 (0.1%) | <0.001 | 16 |
| **Cognitive impairment, n (%)** | 3324 (0.3%) | 665 (0%) | <0.001 | 6.5 | 2298 (0.2%) | 645 (0.1%) | <0.001 | 4.1 |
| **Total cholesterol (mg/dL), mean±SD** | 176.3 +/- 51.5 | 186.0 +/- 44.5 | <0.001 | 20.1 | 177.7 +/- 51.7 | 191.8 +/- 44.8 | <0.001 | 29.1 |
| **LDL cholesterol (mg/dL), mean±SD** | 99.2 +/- 40.1 | 110.8 +/- 36.5 | <0.001 | 30.1 | 100.4 +/- 40.1 | 113.8 +/- 37.4 | <0.001 | 34.6 |
| **HDL cholesterol (mg/dL), mean±SD** | 41.2 +/- 19.3 | 50.5 +/- 18.9 | <0.001 | 48.5 | 41.3 +/- 19.1 | 51.4 +/- 19.9 | <0.001 | 51.4 |
| **Triglyceride (mg/dL), mean±SD** | 172.0 +/- 195.6 | 122.2 +/- 94.9 | <0.001 | 32.4 | 174.5 +/- 201.0 | 126.9 +/- 89.7 | <0.001 | 30.5 |
| **Haemoglobin A1c (%), mean±SD** | 7.3 +/- 2.1 | 5.5 +/- 1.1 | <0.001 | 108.3 | 7.3 +/- 2.1 | 5.6 +/- 1.1 | <0.001 | 101 |
| **Body mass index (kg/m2), mean±SD** | 33.5 +/- 8.2 | 29.0 +/- 6.9 | <0.001 | 59.7 | 33.8 +/- 8.3 | 29.0 +/- 6.3 | <0.001 | 65.6 |
| **Systolic BP (mm Hg), mean±SD** | 130.4 +/- 20.4 | 126.1 +/- 18.7 | <0.001 | 21.9 | 130.3 +/- 20.4 | 130.4 +/- 20.1 | 0.003 | 0.6 |
| **Diastolic BP (mm Hg), mean±SD** | 75.8 +/- 12.8 | 76.6 +/- 11.9 | <0.001 | 6.4 | 76.2 +/- 12.8 | 77.9 +/- 12.0 | <0.001 | 13.7 |
| **Beta Blockers, n (%)** | 320482 (27.1%) | 61953 (2.5%) | <0.001 | 73.9 | 288988 (26.3%) | 41344 (3.8%) | <0.001 | 66.4 |
| **Calcium Channel Blockers, n (%)** | 221730 (18.8%) | 42870 (1.7%) | <0.001 | 58.6 | 199677 (18.2%) | 29370 (2.7%) | <0.001 | 52.4 |
| **ACE Inhibitors, n (%)** | 261757 (22.2%) | 44243 (1.8%) | <0.001 | 66.1 | 242292 (22%) | 29470 (2.7%) | <0.001 | 61.5 |
| **Angiotensin II Inhibitors, n (%)** | 158796 (13.4%) | 25530 (1%) | <0.001 | 49.4 | 143369 (13%) | 18403 (1.7%) | <0.001 | 44.6 |
| **Antiarrhythmic agents, n (%)** | 287870 (24.4%) | 60804 (2.4%) | <0.001 | 67.9 | 263418 (24%) | 24263 (2.2%) | <0.001 | 68.1 |
| **Digitalis glycosides, n (%)** | 11897 (1%) | 917 (0%) | <0.001 | 13.5 | 10296 (0.9%) | 730 (0.1%) | <0.001 | 12.3 |
| **Diuretics, n (%)** | 322263 (27.3%) | 53973 (2.2%) | <0.001 | 75.8 | 294401 (26.8%) | 34721 (3.2%) | <0.001 | 70.2 |
| **Lipid lowering drugs, n (%)** | 434218 (36.8%) | 72274 (2.9%) | <0.001 | 93.7 | 394253 (35.9%) | 55015 (5%) | <0.001 | 82.8 |
| **Glucose-lowering therapy, n (%)** | 531029 (44.9%) | 0 (0%) | <0.001 | 127.8 | 496270 (45.1%) | 0 (0%) | <0.001 | 128.3 |
| **Insulin, n (%)** | 247271 (20.9%) | 0 (0%) | <0.001 | 72.8 | 227880 (20.7%) | 0 (0%) | <0.001 | 72.3 |
| **Metformin, n (%)** | 317585 (26.9%) | 0 (0%) | <0.001 | 85.7 | 300545 (27.3%) | 0 (0%) | <0.001 | 86.7 |
| **Sulfonylureas, n (%)** | 91598 (7.8%) | 0 (0%) | <0.001 | 41 | 84104 (7.6%) | 0 (0%) | <0.001 | 40.7 |
| **Thiazolidinediones, n (%)** | 20195 (1.7%) | 0 (0%) | <0.001 | 18.6 | 18622 (1.7%) | 0 (0%) | <0.001 | 18.6 |
| **DPP4 inhibitors, n (%)** | 43517 (3.7%) | 0 (0%) | <0.001 | 27.7 | 39643 (3.6%) | 0 (0%) | <0.001 | 27.3 |
| **GLP-1 receptor agonists, n (%)** | 37937 (3.2%) | 0 (0%) | <0.001 | 25.8 | 36501 (3.3%) | 0 (0%) | <0.001 | 26.2 |
| **SGLT2 inhibitors, n (%)** | 28442 (2.4%) | 0 (0%) | <0.001 | 22.2 | 26370 (2.4%) | 0 (0%) | <0.001 | 22.2 |

Values are n (%) or mean ± SD. ACE = angiotensin converting enzyme; BBB = bundle branch block; BP = blood pressure; COPD = Chronic obstructive pulmonary disease; DPP4 = Dipeptidyl peptidase-4 ; GLP-1 = Glucagon-like peptide 1; ICD = implantable cardioverter defibrillator; SD = standard deviation; SGLT2i = Sodium-glucose cotransporter 2 inhibitors.

**Table S4.** Clinical outcomes during FU in the age and sex matched population with T2DM or no diabetes in PMSI database

| | Type 2 diabetes mellitus (n=440895) | | | No diabetes (n=440895) | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Person-time (patient.year)** | **Number of events** | **Incidence, %/year (95% CI)** | **Person-time (patient.year)** | **Number of events** | **Incidence, %/year (95% CI)** | **Hazard ratio (95% CI)** | **p value** |
| **Death during follow-up** | 2061150 | 166702 | 8.09 (8.05-8.13) | 2169751 | 129990 | 5.99 (5.96-6.02) | 1.333 (1.323-1.343) | <0.0001 |
| **Cardiovascular death** | 2061150 | 38099 | 1.85 (1.83-1.87) | 2169751 | 24445 | 1.13 (1.11-1.14) | 1.618 (1.592-1.644) | <0.0001 |
| **Incident MI** | 2023516 | 14224 | 0.70 (0.69-0.72) | 2147153 | 8163 | 0.38 (0.37-0.39) | 1.822 (1.773-1.872) | <0.0001 |
| **Heart failure** | 1908832 | 54621 | 2.86 (2.84-2.89) | 2073337 | 37086 | 1.79 (1.77-1.81) | 1.562 (1.542-1.583) | <0.0001 |
| **Incident Sinus node disease** | 2045747 | 4983 | 0.24 (0.24-0.25) | 2158283 | 3493 | 0.16 (0.16-0.17) | 1.482 (1.419-1.548) | <0.0001 |
| **Incident AV block** | 2019252 | 14274 | 0.71 (0.70-0.72) | 2143647 | 8452 | 0.39 (0.39-0.40) | 1.765 (1.718-1.813) | <0.0001 |
| **Incident Left BBB** | 2044907 | 5840 | 0.29 (0.28-0.29) | 2160085 | 3456 | 0.16 (0.16-0.17) | 1.759 (1.687-1.835) | <0.0001 |
| **Incident Right BBB** | 2042970 | 6450 | 0.32 (0.31-0.32) | 2158641 | 3920 | 0.18 (0.18-0.19) | 1.713 (1.646-1.782) | <0.0001 |
| **Pacemaker or ICD during FU** | 2011626 | 15422 | 0.77 (0.76-0.78) | 2134080 | 10510 | 0.49 (0.48-0.50) | 1.529 (1.492-1.568) | <0.0001 |
| **ICD during FU** | 2051825 | 2718 | 0.13 (0.13-0.14) | 2165167 | 1382 | 0.06 (0.06-0.07) | 2.039 (1.911-2.175) | <0.0001 |

BBB = bundle branch block; ICD = implantable cardioverter defibrillator; MI = myocardial infarction.

**Table S5.** Clinical outcomes during FU in the age and sex-matched population of patients with T2DM in TriNetX network

| | Type 2 DM (n = 1099642) | | No DM (n = 1099642) | | | |
|---|---|---|---|---|---|---|
| | **Number of events** | **Yearly rate, %** | **Number of events** | **Yearly rate, %** | **Hazard ratio (95% CI)** | **p value** |
| **Death** | 66465 | 2.18 | 24607 | 0.67 | 3.409 (3.360-3.460) | <0.0001 |
| **Acute MI** | 51878 | 1.77 | 23582 | 0.64 | 2.847 (2.804-2.892) | <0.0001 |
| **Sinus node dysfunction** | 10709 | 0.36 | 8204 | 0.22 | 1.629 (1.583-1.677) | <0.0001 |
| **AV block** | 30640 | 1.03 | 16186 | 0.44 | 2.405 (2.359-2.451) | <0.0001 |
| **Left BBB** | 45396 | 1.54 | 25690 | 0.70 | 2.263 (2.229-2.298) | <0.0001 |
| **Right BBB** | 24658 | 0.83 | 15388 | 0.42 | 2.026 (1.985-2.067) | <0.0001 |
| **Pacemaker or ICD implantation** | 15902 | 0.51 | 6972 | 0.19 | 2.81 (2.732-2.891) | <0.0001 |
| **ICD implantation** | 14422 | 0.46 | 5580 | 0.15 | 3.148 (3.052-3.247) | <0.0001 |

BBB = bundle branch block; ICD = implantable cardioverter defibrillator; MI = myocardial infarction.

**Table S6.** Baseline characteristics of patients with T2DM according to HbA1c (< or ≥8%) before and after propensity score matching in TriNetX network

| | Before propensity-score matching | | | | After propensity-score matching | | | |
|---|---|---|---|---|---|---|---|---|
| | **DT2 HbA1sup8 (n = 218,097)** | **DT2 HbA1inf8 (n = 619,020)** | **P-Value** | **Std diff. (%)** | **DT2 HbA1sup8 (n = 216,622)** | **DT2 HbA1inf8 (n = 216,622)** | **P-Value** | **Std diff. (%)** |
| **Age at Index, n (%)** | 54.1 +/- 13.9 | 59.4 +/- 13.4 | <0.001 | 38.7 | 54.3 +/- 13.8 | 55.3 +/- 14.3 | <0.001 | 7.1 |
| **Men, n (%)** | 118,314 (54.2%) | 297,329 (48%) | <0.001 | 12.5 | 117,129 (54.1%) | 116,832 (53.9%) | 0.365 | 0.3 |
| **Hypertension, n (%)** | 113,277 (51.9%) | 392,113 (63.3%) | <0.001 | 23.2 | 113,103 (52.2%) | 114,858 (53%) | <0.001 | 1.6 |
| **Smoker, n (%)** | 13,552 (6.2%) | 71,985 (11.6%) | <0.001 | 19.1 | 13,549 (6.3%) | 13,003 (6%) | 0.001 | 1.1 |
| **Overweight or obesity, n (%)** | 47,570 (21.8%) | 186,654 (30.2%) | <0.001 | 19.1 | 47,513 (21.9%) | 47,230 (21.8%) | 0.298 | 0.3 |
| **Dyslipidaemia, n (%)** | 93,816 (43%) | 351,820 (56.8%) | <0.001 | 27.9 | 93,775 (43.3%) | 93,778 (43.3%) | 0.993 | 0 |
| **Alcohol related diagnoses, n (%)** | 4,063 (1.9%) | 16,972 (2.7%) | <0.001 | 5.9 | 4,056 (1.9%) | 3,775 (1.7%) | 0.001 | 1 |
| **Heart failure, n (%)** | 15,052 (6.9%) | 59,879 (9.7%) | <0.001 | 10.1 | 15,003 (6.9%) | 13,740 (6.3%) | <0.001 | 2.3 |
| **Coronary artery disease, n (%)** | 29,081 (13.3%) | 105,582 (17.1%) | <0.001 | 10.4 | 28,986 (13.4%) | 27,978 (12.9%) | <0.001 | 1.4 |
| **Myocardial infarction, n (%)** | 8,948 (4.1%) | 28,526 (4.6%) | <0.001 | 2.5 | 8,880 (4.1%) | 8,197 (3.8%) | <0.001 | 1.6 |
| **Dilated cardiomyopathy, n (%)** | 803 (0.4%) | 4,701 (0.8%) | <0.001 | 5.2 | 803 (0.4%) | 695 (0.3%) | 0.005 | 0.8 |
| **Ischemic stroke, n (%)** | 9,083 (4.2%) | 28,725 (4.6%) | <0.001 | 2.3 | 9,073 (4.2%) | 7,376 (3.4%) | <0.001 | 4.1 |
| **Intracranial haemorrhage, n (%)** | 1,238 (0.6%) | 4,535 (0.7%) | <0.001 | 2.1 | 1,236 (0.6%) | 1,011 (0.5%) | <0.001 | 1.4 |
| **Valve disease, n (%)** | 3,297 (1.5%) | 25,728 (4.2%) | <0.001 | 16 | 3,287 (1.5%) | 4,968 (2.3%) | <0.001 | 5.7 |
| **Mitral regurgitation, n (%)** | 3,025 (1.4%) | 23,481 (3.8%) | <0.001 | 15.2 | 3,015 (1.4%) | 4,589 (2.1%) | <0.001 | 5.5 |
| **Mitral stenosis, n (%)** | 542 (0.2%) | 3,630 (0.6%) | <0.001 | 5.2 | 541 (0.2%) | 701 (0.3%) | <0.001 | 1.4 |
| **Aortic regurgitation, n (%)** | 1,299 (0.6%) | 11,651 (1.9%) | <0.001 | 11.7 | 1,298 (0.6%) | 2,207 (1%) | <0.001 | 4.7 |
| **Aortic stenosis, n (%)** | 1,856 (0.9%) | 13,173 (2.1%) | <0.001 | 10.6 | 1,855 (0.9%) | 2,624 (1.2%) | <0.001 | 3.5 |
| **Atrial fibrillation or flutter, n (%)** | 10,052 (4.6%) | 52,003 (8.4%) | <0.001 | 15.4 | 10,052 (4.6%) | 9,371 (4.3%) | <0.001 | 1.5 |
| **Sinus node disease, n (%)** | 578 (0.3%) | 4,731 (0.8%) | <0.001 | 7 | 577 (0.3%) | 821 (0.4%) | <0.001 | 2 |
| **Atrioventricular and/or LBBB, n (%)** | 3,487 (1.6%) | 19,743 (3.2%) | <0.001 | 10.4 | 3,484 (1.6%) | 3,818 (1.8%) | <0.001 | 1.2 |
| **Left BBB, n (%)** | 1,078 (0.5%) | 5,998 (1%) | <0.001 | 5.6 | 1,078 (0.5%) | 1,164 (0.5%) | 0.069 | 0.6 |
| **Right BBB, n (%)** | 1,902 (0.9%) | 10,527 (1.7%) | <0.001 | 7.4 | 1,897 (0.9%) | 2,147 (1%) | <0.001 | 1.2 |
| **Previous pacemaker, n (%)** | 1,339 (0.6%) | 7,951 (1.3%) | <0.001 | 6.9 | 1,339 (0.6%) | 1,467 (0.7%) | 0.015 | 0.7 |
| **Previous ICD, n (%)** | 1,421 (0.7%) | 6,731 (1.1%) | <0.001 | 4.7 | 1,419 (0.7%) | 1,357 (0.6%) | 0.238 | 0.4 |
| **Kidney disease, n (%)** | 23,879 (10.9%) | 95,424 (15.4%) | <0.001 | 13.2 | 23,842 (11%) | 23,177 (10.7%) | 0.001 | 1 |
| **Lung disease, n (%)** | 59,764 (27.4%) | 252,633 (40.8%) | <0.001 | 28.6 | 59,739 (27.6%) | 59,013 (27.2%) | 0.013 | 0.8 |
| **COPD, n (%)** | 8,269 (3.8%) | 44,115 (7.1%) | <0.001 | 14.7 | 8,268 (3.8%) | 7,932 (3.7%) | 0.007 | 0.8 |
| **Sleep apnoea syndrome, n (%)** | 18,941 (8.7%) | 93,107 (15%) | <0.001 | 19.8 | 18,941 (8.7%) | 18,484 (8.5%) | 0.013 | 0.8 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Peripheral vascular disease, n (%)** | 4,570 (2.1%) | 21,603 (3.5%) | <0.001 | 8.5 | 4,569 (2.1%) | 4,370 (2%) | 0.033 | 0.6 |
| **Previous cancer, n (%)** | 24,563 (11.3%) | 144,880 (23.4%) | <0.001 | 32.5 | 24,563 (11.3%) | 24,774 (11.4%) | 0.313 | 0.3 |
| **Thyroid diseases, n (%)** | 21,110 (9.7%) | 104,224 (16.8%) | <0.001 | 21.2 | 21,107 (9.7%) | 20,819 (9.6%) | 0.139 | 0.4 |
| **Amyloidosis, n (%)** | 100 (0%) | 922 (0.1%) | <0.001 | 3.3 | 100 (0%) | 84 (0%) | 0.238 | 0.4 |
| **Malnutrition, n (%)** | 2,324 (1.1%) | 13,011 (2.1%) | <0.001 | 8.3 | 2,322 (1.1%) | 2,113 (1%) | 0.002 | 1 |
| **Cognitive impairment, n (%)** | 347 (0.2%) | 2,170 (0.4%) | <0.001 | 3.8 | 347 (0.2%) | 334 (0.2%) | 0.618 | 0.2 |
| **Total cholesterol (mg/dL), mean±SD** | 184.1 +/- 57.8 | 176.6 +/- 49.7 | <0.001 | 14 | 184.2 +/- 57.9 | 177.7 +/- 50.2 | <0.001 | 11.9 |
| **LDL cholesterol (mg/dL), mean±SD** | 103.5 +/- 43.4 | 99.7 +/- 39.7 | <0.001 | 9.3 | 103.5 +/- 43.4 | 100.9 +/- 39.7 | <0.001 | 6.3 |
| **HDL cholesterol (mg/dL), mean±SD** | 43.0 +/- 14.3 | 46.8 +/- 15.8 | <0.001 | 25.3 | 43.0 +/- 14.3 | 45.5 +/- 15.2 | <0.001 | 17 |
| **Triglyceride (mg/dL), mean±SD** | 212.4 +/- 304.0 | 161.6 +/- 157.2 | <0.001 | 21 | 212.4 +/- 303.9 | 169.8 +/- 185.8 | <0.001 | 16.9 |
| **Haemoglobin A1c (%), mean±SD** | 8.9 +/- 2.5 | 6.6 +/- 1.7 | <0.001 | 107.5 | 8.9 +/- 2.5 | 6.9 +/- 1.9 | <0.001 | 92 |
| **Body mass index (kg/m2), mean±SD** | 33.5 +/- 8.2 | 33.5 +/- 8.3 | 0.262 | 0.3 | 33.5 +/- 8.2 | 33.7 +/- 8.3 | <0.001 | 2 |
| **Systolic BP (mm Hg), mean±SD** | 131.5 +/- 21.3 | 129.8 +/- 20.4 | <0.001 | 8.5 | 131.6 +/- 21.4 | 130.4 +/- 20.2 | <0.001 | 5.7 |
| **Diastolic BP (mm Hg), mean±SD** | 76.8 +/- 13.4 | 75.4 +/- 12.9 | <0.001 | 10.5 | 76.8 +/- 13.4 | 76.7 +/- 12.8 | 0.001 | 1.1 |
| **Beta Blockers, n (%)** | 45,348 (20.8%) | 181,304 (29.3%) | <0.001 | 19.7 | 45,269 (20.9%) | 44,806 (20.7%) | 0.083 | 0.5 |
| **Calcium Channel Blockers, n (%)** | 28,861 (13.2%) | 128,477 (20.8%) | <0.001 | 20.1 | 28,847 (13.3%) | 28,750 (13.3%) | 0.664 | 0.1 |
| **ACE Inhibitors, n (%)** | 43,665 (20%) | 136,011 (22%) | <0.001 | 4.8 | 43,348 (20%) | 43,400 (20%) | 0.843 | 0.1 |
| **Angiotensin II Inhibitors, n (%)** | 19,857 (9.1%) | 86,826 (14%) | <0.001 | 15.4 | 19,844 (9.2%) | 19,965 (9.2%) | 0.525 | 0.2 |
| **Antiarrhythmic agents, n (%)** | 38,913 (17.8%) | 168,971 (27.3%) | <0.001 | 22.8 | 38,845 (17.9%) | 38,155 (17.6%) | 0.006 | 0.8 |
| **Digitalis glycosides, n (%)** | 1,489 (0.7%) | 7,265 (1.2%) | <0.001 | 5.1 | 1,488 (0.7%) | 1,251 (0.6%) | <0.001 | 1.4 |
| **Diuretics, n (%)** | 42,115 (19.3%) | 184,700 (29.8%) | <0.001 | 24.6 | 42,099 (19.4%) | 41,639 (19.2%) | 0.077 | 0.5 |
| **Lipid lowering drugs, n (%)** | 63,876 (29.3%) | 233,611 (37.7%) | <0.001 | 18 | 63,725 (29.4%) | 61,777 (28.5%) | <0.001 | 2 |
| **Glucose-lowering therapy, n (%)** | 109,969 (50.4%) | 239,462 (38.7%) | <0.001 | 23.8 | 109,234 (50.4%) | 80,424 (37.1%) | <0.001 | 27.1 |
| **Insulin, n (%)** | 62,811 (28.8%) | 95,807 (15.5%) | <0.001 | 32.5 | 62,302 (28.8%) | 30,970 (14.3%) | <0.001 | 35.7 |
| **Metformin, n (%)** | 58,975 (27%) | 146,251 (23.6%) | <0.001 | 7.9 | 58,651 (27.1%) | 50,751 (23.4%) | <0.001 | 8.4 |
| **Sulfonylureas, n (%)** | 22,384 (10.3%) | 29,749 (4.8%) | <0.001 | 20.8 | 22,302 (10.3%) | 11,290 (5.2%) | <0.001 | 19.1 |
| **Thiazolidinediones, n (%)** | 3,770 (1.7%) | 6,201 (1%) | <0.001 | 6.3 | 3,754 (1.7%) | 2,368 (1.1%) | <0.001 | 5.4 |
| **DPP4 inhibitors, n (%)** | 7,582 (3.5%) | 12,649 (2%) | <0.001 | 8.8 | 7,563 (3.5%) | 4,454 (2.1%) | <0.001 | 8.7 |
| **GLP-1 receptor agonists, n (%)** | 6,241 (2.9%) | 17,440 (2.8%) | 0.284 | 0.3 | 6,224 (2.9%) | 5,398 (2.5%) | <0.001 | 2.4 |
| **SGLT2 inhibitors, n (%)** | 5,581 (2.6%) | 10,657 (1.7%) | <0.001 | 5.8 | 5,568 (2.6%) | 3,230 (1.5%) | <0.001 | 7.7 |

Values are n (%) or mean ± SD. ACE = angiotensin converting enzyme; BBB = bundle branch block; BP = blood pressure; COPD = Chronic obstructive pulmonary disease; DPP4 = Dipeptidyl peptidase-4; GLP-1 = Glucagon-like peptide 1; ICD = implantable cardioverter defibrillator; SD = standard deviation; SGLT2i = Sodium-glucose cotransporter 2 inhibitors.

**Table S7.** Clinical outcomes during FU in the matched population of T2DM according to HbA1c (< or ≥8%) in TriNetX network

| | DT2 HbA1sup8 (n = 216622) | | DT2 HbA1inf8 (n = 216622) | | | |
|---|---|---|---|---|---|---|
| | **Number of events** | **Yearly rate, %** | **Number of events** | **Yearly rate, %** | **Hazard ratio (95% CI)** | **p value** |
| **Death** | 12861 | 1.85 | 10669 | 1.59 | 1.188 (1.158-1.219) | <0.0001 |
| **Acute MI** | 13178 | 1.96 | 10326 | 1.57 | 1.268 (1.236-1.302) | <0.0001 |
| **Sinus node dysfunction** | 1798 | 0.26 | 2101 | 0.31 | 0.843 (0.792-0.898) | <0.0001 |
| **AV block** | 5818 | 0.85 | 6248 | 0.94 | 0.916 (0.884-0.950) | <0.0001 |
| **Left BBB** | 9145 | 1.34 | 9121 | 1.37 | 0.987 (0.959-1.016) | 0.39 |
| **Right BBB** | 4932 | 0.72 | 4850 | 0.72 | 1.002 (0.963-1.043) | 0.91 |
| **Pacemaker or ICD implantation** | 3327 | 0.47 | 3066 | 0.45 | 1.074 (1.022-1.128) | 0.01 |
| **ICD implantation** | 3151 | 0.44 | 2641 | 0.37 | 1.184 (1.124-1.247) | <0.0001 |

BBB = bundle branch block; ICD = implantable cardioverter defibrillator; MI = myocardial infarction.

**Table S8.** Baseline characteristics of patients with T1DM before and after propensity score (including age and sex) matching in TriNetX network

| | Before propensity-score matching | | | | After propensity-score matching | | | |
|---|---|---|---|---|---|---|---|---|
| | **Type 1 DM (n = 19256)** | **No DM (n = 2485096)** | **P-Value** | **Std diff. (%)** | **Type 1 DM (n = 19256)** | **No DM (n = 19256)** | **P-Value** | **Std diff. (%)** |
| **Age at Index, n (%)** | 36.8 +/- 17.3 | 45.2 +/- 16.6 | <0.001 | 49.6 | 36.8 +/- 17.3 | 36.8 +/- 17.3 | 1 | 0 |
| **Men, n (%)** | 10037 (52.1%) | 1007401 (40.5%) | <0.001 | 23.4 | 10037 (52.1%) | 10037 (52.1%) | 1 | 0 |
| **Hypertension, n (%)** | 3842 (20%) | 174929 (7%) | <0.001 | 38.5 | 3842 (20%) | 1070 (5.6%) | <0.001 | 44.2 |
| **Diabetes mellitus, n (%)** | 19256 (100%) | 0 (0%) | <0.001 | - | 19256 (100%) | 0 (0%) | <0.001 | 0 |
| **Smoker, n (%)** | 531 (2.8%) | 14991 (0.6%) | <0.001 | 16.8 | 531 (2.8%) | 97 (0.5%) | <0.001 | 17.9 |
| **Overweight or obesity, n (%)** | 1349 (7%) | 84170 (3.4%) | <0.001 | 16.4 | 1349 (7%) | 924 (4.8%) | <0.001 | 9.4 |
| **Dyslipidaemia, n (%)** | 4920 (25.6%) | 139129 (5.6%) | <0.001 | 57.2 | 4920 (25.6%) | 862 (4.5%) | <0.001 | 61.7 |
| **Alcohol related diagnoses, n (%)** | 202 (1%) | 10162 (0.4%) | <0.001 | 7.5 | 202 (1%) | 84 (0.4%) | <0.001 | 7.1 |
| **Heart failure, n (%)** | 584 (3%) | 10165 (0.4%) | <0.001 | 20.3 | 584 (3%) | 78 (0.4%) | <0.001 | 20.3 |
| **Coronary artery disease, n (%)** | 1086 (5.6%) | 25695 (1%) | <0.001 | 25.9 | 1086 (5.6%) | 150 (0.8%) | <0.001 | 27.8 |
| **Myocardial infarction, n (%)** | 371 (1.9%) | 10818 (0.4%) | <0.001 | 13.8 | 371 (1.9%) | 64 (0.3%) | <0.001 | 15.1 |
| **Dilated cardiomyopathy, n (%)** | 29 (0.2%) | 607 (0%) | <0.001 | 4.3 | 29 (0.2%) | 10 (0.1%) | 0.002 | 3.1 |
| **Ischemic stroke, n (%)** | 283 (1.5%) | 16014 (0.6%) | <0.001 | 8.1 | 283 (1.5%) | 93 (0.5%) | <0.001 | 10 |
| **Intracranial haemorrhage, n (%)** | 49 (0.3%) | 2860 (0.1%) | <0.001 | 3.2 | 49 (0.3%) | 24 (0.1%) | 0.003 | 3 |
| **Valve disease, n (%)** | 192 (1%) | 5277 (0.2%) | <0.001 | 10.1 | 192 (1%) | 43 (0.2%) | <0.001 | 9.9 |
| **Mitral regurgitation, n (%)** | 172 (0.9%) | 4447 (0.2%) | <0.001 | 9.8 | 172 (0.9%) | 37 (0.2%) | <0.001 | 9.6 |
| **Mitral stenosis, n (%)** | 29 (0.2%) | 717 (0%) | <0.001 | 4.1 | 29 (0.2%) | 10 (0.1%) | 0.002 | 3.1 |
| **Aortic regurgitation, n (%)** | 83 (0.4%) | 2462 (0.1%) | <0.001 | 6.5 | 83 (0.4%) | 24 (0.1%) | <0.001 | 5.8 |
| **Aortic stenosis, n (%)** | 100 (0.5%) | 2525 (0.1%) | <0.001 | 7.5 | 100 (0.5%) | 14 (0.1%) | <0.001 | 8.2 |
| **Atrial fibrillation or flutter, n (%)** | 354 (1.8%) | 15820 (0.6%) | <0.001 | 10.9 | 354 (1.8%) | 98 (0.5%) | <0.001 | 12.4 |
| **Sinus node disease, n (%)** | 36 (0.2%) | 880 (0%) | <0.001 | 4.5 | 36 (0.2%) | 10 (0.1%) | <0.001 | 3.9 |
| **Atrioventricular and/or LBBB, n (%)** | 115 (0.6%) | 4554 (0.2%) | <0.001 | 6.6 | 115 (0.6%) | 38 (0.2%) | <0.001 | 6.4 |
| **Left BBB, n (%)** | 36 (0.2%) | 1302 (0.1%) | <0.001 | 3.9 | 36 (0.2%) | 13 (0.1%) | 0.001 | 3.4 |
| **Right BBB, n (%)** | 80 (0.4%) | 3157 (0.1%) | <0.001 | 5.5 | 80 (0.4%) | 22 (0.1%) | <0.001 | 5.9 |
| **Previous pacemaker, n (%)** | 58 (0.3%) | 1623 (0.1%) | <0.001 | 5.5 | 58 (0.3%) | 15 (0.1%) | <0.001 | 5.1 |
| **Previous ICD, n (%)** | 50 (0.3%) | 956 (0%) | <0.001 | 5.7 | 50 (0.3%) | 10 (0.1%) | <0.001 | 5.3 |
| **Kidney disease, n (%)** | 1845 (9.6%) | 15022 (0.6%) | <0.001 | 41.7 | 1845 (9.6%) | 116 (0.6%) | <0.001 | 41.7 |
| **Lung disease, n (%)** | 3208 (16.7%) | 200038 (8%) | <0.001 | 26.4 | 3208 (16.7%) | 2203 (11.4%) | <0.001 | 15.1 |
| **COPD, n (%)** | 222 (1.2%) | 9255 (0.4%) | <0.001 | 9 | 222 (1.2%) | 51 (0.3%) | <0.001 | 10.6 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Sleep apnoea syndrome, n (%)** | 357 (1.9%) | 20853 (0.8%) | <0.001 | 8.8 | 357 (1.9%) | 192 (1%) | <0.001 | 7.2 |
| **Peripheral vascular disease, n (%)** | 235 (1.2%) | 3128 (0.1%) | <0.001 | 13.4 | 235 (1.2%) | 19 (0.1%) | <0.001 | 13.9 |
| **Previous cancer, n (%)** | 1103 (5.7%) | 70623 (2.8%) | <0.001 | 14.3 | 1103 (5.7%) | 473 (2.5%) | <0.001 | 16.6 |
| **Thyroid diseases, n (%)** | 3324 (17.3%) | 57303 (2.3%) | <0.001 | 52 | 3324 (17.3%) | 384 (2%) | <0.001 | 53.6 |
| **Amyloidosis, n (%)** | 23 (0.1%) | 278 (0%) | <0.001 | 4.2 | 23 (0.1%) | 10 (0.1%) | 0.024 | 2.3 |
| **Malnutrition, n (%)** | 218 (1.1%) | 2778 (0.1%) | <0.001 | 13 | 218 (1.1%) | 36 (0.2%) | <0.001 | 11.7 |
| **Cognitive impairment, n (%)** | 20 (0.1%) | 665 (0%) | <0.001 | 3 | 20 (0.1%) | 10 (0.1%) | 0.068 | 1.9 |
| **Total cholesterol (mg/dL), mean±SD** | 171.6 +/- 49.0 | 186.0 +/- 44.5 | <0.001 | 30.7 | 171.6 +/- 49.0 | 176.0 +/- 44.3 | <0.001 | 9.5 |
| **LDL cholesterol (mg/dL), mean±SD** | 95.0 +/- 35.3 | 110.8 +/- 36.5 | <0.001 | 44 | 95.0 +/- 35.3 | 105.2 +/- 35.7 | <0.001 | 28.6 |
| **HDL cholesterol (mg/dL), mean±SD** | 51.4 +/- 23.9 | 50.5 +/- 18.9 | <0.001 | 4.5 | 51.4 +/- 23.9 | 47.9 +/- 17.6 | <0.001 | 17 |
| **Triglyceride (mg/dL), mean±SD** | 112.5 +/- 138.1 | 122.2 +/- 94.9 | <0.001 | 8.2 | 112.5 +/- 138.1 | 117.1 +/- 81.1 | 0.069 | 4.1 |
| **Haemoglobin A1c (%), mean±SD** | 8.3 +/- 2.2 | 5.5 +/- 1.1 | <0.001 | 165.1 | 8.3 +/- 2.2 | 5.4 +/- 1.0 | <0.001 | 175.1 |
| **Body mass index (kg/m2), mean±SD** | 26.5 +/- 5.6 | 29.0 +/- 6.9 | <0.001 | 39.7 | 26.5 +/- 5.6 | 28.6 +/- 7.1 | <0.001 | 32.8 |
| **Systolic BP (mm Hg), mean±SD** | 123.3 +/- 17.3 | 126.1 +/- 18.7 | <0.001 | 15.3 | 123.3 +/- 17.3 | 124.2 +/- 17.6 | <0.001 | 5.2 |
| **Diastolic BP (mm Hg), mean±SD** | 73.3 +/- 11.4 | 76.6 +/- 11.9 | <0.001 | 28.3 | 73.3 +/- 11.4 | 75.4 +/- 11.7 | <0.001 | 17.6 |
| **Beta Blockers, n (%)** | 2642 (13.7%) | 61953 (2.5%) | <0.001 | 42 | 2642 (13.7%) | 418 (2.2%) | <0.001 | 43.7 |
| **Calcium Channel Blockers, n (%)** | 1699 (8.8%) | 42870 (1.7%) | <0.001 | 32.2 | 1699 (8.8%) | 274 (1.4%) | <0.001 | 34 |
| **ACE Inhibitors, n (%)** | 2849 (14.8%) | 44243 (1.8%) | <0.001 | 48.6 | 2849 (14.8%) | 269 (1.4%) | <0.001 | 50.7 |
| **Angiotensin II Inhibitors, n (%)** | 1234 (6.4%) | 25530 (1%) | <0.001 | 28.7 | 1234 (6.4%) | 148 (0.8%) | <0.001 | 30.7 |
| **Antiarrhythmic agents, n (%)** | 2958 (15.4%) | 60804 (2.4%) | <0.001 | 46.6 | 2958 (15.4%) | 653 (3.4%) | <0.001 | 42 |
| **Digitalis glycosides, n (%)** | 80 (0.4%) | 917 (0%) | <0.001 | 8 | 80 (0.4%) | 10 (0.1%) | <0.001 | 7.5 |
| **Diuretics, n (%)** | 2042 (10.6%) | 53973 (2.2%) | <0.001 | 35 | 2042 (10.6%) | 320 (1.7%) | <0.001 | 37.9 |
| **Lipid lowering drugs, n (%)** | 4517 (23.5%) | 72274 (2.9%) | <0.001 | 63.8 | 4517 (23.5%) | 379 (2%) | <0.001 | 68.2 |

Values are n (%) or mean ± SD. ACE = angiotensin converting enzyme; BBB = bundle branch block; BP = blood pressure; COPD = Chronic obstructive pulmonary disease; ICD = implantable cardioverter defibrillator; SD = standard deviation.

**Table S9.** Clinical outcomes during FU in the age and sex- matched population of patients with T1DM in TriNetX network

| | Type 1 DM (n = 19256) | | No DM (n = 19256) | | | |
|---|---|---|---|---|---|---|
| | **Number of events** | **Yearly rate, %** | **Number of events** | **Yearly rate, %** | **Hazard ratio (95% CI)** | **p value** |
| **Death** | 648 | 1.79 | 223 | 0.47 | 4.303 (3.690-5.018) | <0.0001 |
| **Acute MI** | 146 | 0.44 | 179 | 0.37 | 1.237 (0.991-1.543) | 0.06 |
| **Sinus node dysfunction** | 26 | 0.09 | 63 | 0.13 | 0.629 (0.396-0.997) | 0.05 |
| **AV block** | 44 | 0.13 | 134 | 0.28 | 0.511 (0.362-0.720) | <0.0001 |
| **Left BBB** | 79 | 0.24 | 183 | 0.38 | 0.656 (0.503-0.857) | 0.002 |
| **Right BBB** | 45 | 0.13 | 155 | 0.32 | 0.448 (0.321-0.627) | <0.0001 |
| **Pacemaker or ICD implantation** | 47 | 0.14 | 59 | 0.12 | 1.214 (0.823-1.792) | 0.33 |
| **ICD implantation** | 42 | 0.13 | 38 | 0.08 | 1.607 (1.030-2.506) | 0.04 |

BBB = bundle branch block; ICD = implantable cardioverter defibrillator; MI = myocardial infarction.

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**68 pages – 16 tableaux – 2 figures**

**Background**. Type 1 diabetes (T1DM) and type 2 diabetes (T2DM) increase the risk of atheromatous cardiovascular events, heart failure and arrhythmias compared with non-diabetic populations. However, few studies have assessed the risk of conduction disorders in patients with diabetes.

**Methods**. We used two large databases: PMSI and TriNetX. All patients aged at least 18 years, seen in French hospitals in 2016, with a minimum subsequent follow-up of 5 years (unless they died in the meantime), were identified and categorized according to their diabetic status from the PMSI database. The international TriNetX network recruited patients who had been followed for 20 years until the 1st of August in 2024. A total of more than 20,000 patients with T1DM (TriNetX) and more than 900,000 patients with T2DM (TriNetX) and 440,895 patients with T2DM (PMSI) were identified. The event rates for all types of conduction disorders and the need to implant a definitive electrical cardiac stimulation or defibrillation device were compared between diabetic and non-diabetic populations, with matched analysis considering all the comorbidities which, on their own, may be factors favoring the onset of conduction disorders, or which may cause premature death before the onset of a conduction disorder. The incidence of ischemic heart disease during follow-up was also studied in the two databases, as was the influence of HbA1c levels.

**Results**. During follow-up, a higher risk of conductive disorders was found in patients with T2DM than in patients with no diabetes: AV block (HR 1.22 [1.19-1.25]) ; left BBB (HR 1.12 [1.08-1.17]) ; right BBB (HR 1.14 [1.09-1.18]) based on PMSI and sinus node dysfunction (HR 1.28 [1.21-1.34]) ; AV block (HR 1.50 [1.45-1.55]) ; left BBB (HR 1.50 [1.47-1.54]) ; right BBB (HR 1.38 [1.34-1.43]) according to TriNetX. A significant incidence of de novo or recurrent myocardial infarction during follow-up was also found for T2DM (HR 1.29 [1.25-1.32]) in PMSI and for TriNetX (HR 2.14 [2.08-2.19]) compared with T1DM (HR 1.11 [0.94-1.31]). However, HbA1c levels were not significantly associated with the occurrence of conductive disorders.

**Conclusion**. In this double study based on one independent national database and one international network, T2DM was associated with a higher rate of conduction disorders and cardiac device implantations compared with control patients after matched analysis considering associated comorbidities and was associated with a significant incidence of ischemic heart disease during follow-up. These observations were not found in T1DM populations. It is therefore possible that they concern macrovascular damage associated with the metabolic syndrome and the underlying course of ischemic heart disease in T2DM, which would not be the case in the more microvascular damage that is usually part of the course in patients with T1DM.

**Key words:** type 1 diabetes, type 2 diabetes, atrio-ventricular block, sinus dysfunction, bundle branch block, pacemaker, cardiomyopathy.

**Jury :**

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