SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3509.

KÉZDI ÁRPÁD

Anyagcsere betegségek
című program

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SHORT- AND LONG-TERM CARDIAC RESPONSES TO IATROGENIC EXPOSURES

PhD thesis

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Budapest
2026

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List of Abbreviations

AMI:	Acute myocardial infarction
BMI:	Body mass index
CGM:	Continuous subcutaneous glucose monitoring
CI:	Confidence interval
CVD:	Cardiovascular disease
DSPN:	Distal symmetric polyneuropathy
DT:	Deceleration time
E:	Early diastolic flow peak velocity of the mitral valve
e':	Early diastolic peak velocity of the mitral valve annulus
ECG:	Electrocardiogram
EF:	Left ventricle ejection fraction
EHRs:	Electronic health records
EMM:	Estimated marginal mean
ESC:	European Society of Cardiology
GLS:	Global longitudinal strain
HbA1c:	Glycated haemoglobin A1c
HDL:	High-density lipoprotein
HR:	Heart rate
IG:	Interstitial glucose
LCI:	Lower confidence interval
LDL:	Low-density lipoprotein
MACE:	Major adverse cardiovascular events
MD:	Mean difference
SD:	Standard deviations
TSH:	Thyroid stimulating hormone
TTE:	Transthoracic echocardiogram
UCI:	Upper confidence interval
VPB:	Ventricular premature beat

1. Introduction

1.1. General introduction

A wide range of physiological and pathological states modulate cardiac function dynamically with different time scales. Some of these states induce rapid, short-term changes in cardiac electrophysiology over minutes to hours, while others produce progressive, long-term alterations in myocardial structure and function over months to years. However, chronicity of these mechanisms could contribute to both arrhythmic risk and to the development of clinically relevant structural or cardiovascular disease (CVD). Furthermore, structural and vascular heart changes that occur in response to different pathological states could further increase the risk of arrhythmias per se (1).

Short-term exposures primarily impact cardiac electrophysiology. Acute metabolic changes, neurohumoral activation, autonomic dysfunction, and transient electrolyte shifts can rapidly modify heart rate (HR) and cardiac electrophysiology, particularly repolarization. These changes are best captured by electrocardiographic (ECG) measurements, including heart rate, QT interval, and parameters of electrophysiological variability, which serve as sensitive markers of dynamic electrical stress (2, 3).

In contrast, long-term exposures predominantly affect myocardial structure and mechanical function. Chronic exposure to persistent hemodynamic stress, metabolic dysregulation, inflammation, or cardiotoxic agents can lead to ventricular remodelling, impaired systolic and diastolic function, and progressive heart failure. These processes are routinely assessed by cardiac imaging, most commonly echocardiography, which allows non-invasive evaluation of myocardial mechanics and ventricular function (4, 5).

Within this framework, my PhD thesis focuses on two clinically relevant, but fundamentally distinct exposures. One is hypoglycaemia, a short-term, reversible metabolic disturbance that primarily affects cardiac electrophysiology, studied using ECG parameters. The other is chemotherapy that has long-term toxic effects on heart structure and function both of which are assessed by echocardiography. By separating these two aspects – acute electrical instability and chronic functional remodelling – my thesis aims to characterise how different, time-dependent effects impact the heart using modality-specific quantitative tools.

1.2. Changes of the cardiac electrical cycle in type 1 diabetes during hypoglycaemia

CVD is the leading cause of morbidity and mortality in patients with diabetes, with long-term glycaemic control being a most important determinant of vascular complications (6, 7). Given that in parallel with improving glycaemic control, the risk of hypoglycaemia is increasing in patients with type 1 diabetes, hypoglycaemia is the major limiting factor of glycaemic management (8). Starting with the publication of a case series of 22 young patients with type 1 diabetes who suffered an overnight death and in whom autopsy revealed no abnormalities, further reports described sudden cardiac death likely caused by hypoglycaemia ('dead-in-bed' syndrome) (9-12).

Although several theories exist, the exact pathomechanism of the 'dead-in-bed' phenomenon has not yet been elucidated. While night-time hypoglycaemia is an everyday problem in type 1 diabetes, 'dead-in-bed' syndrome is extremely rare, suggesting that an unfortunate combination of factors could trigger its development (13).

Hypoglycaemia can lead to a proarrhythmic state through several mechanisms including disturbances of intracellular and serum potassium and calcium metabolism, as well as increased beta-adrenergic sympathetic tone. Furthermore, micro-, and macrovascular diabetes complications are also associated with an increased risk of arrhythmias. All these mechanisms can lead to prolonged QT interval, increased HR, and more frequent occurrence of cardiac ectopias (14).

This is well supported by hypoglycaemic clamp studies that report substantial mean increases in the QTc interval (ranging from 30 to 230 ms) (15-19). In contrast, the increase of QTc interval is an order of magnitude smaller in free living patients (ranging from 3 to 30 ms, mostly 5-10 ms) (20-25) that is unlikely to trigger dangerous arrhythmias. However, these studies only describe mean changes of the QTc interval, and variability of the QTc intervals and the extremes of QTc values have not been investigated yet. Although even a single long QT beat may initiate life-threatening arrhythmia (26, 27).

1.3. Effects of taxane-anthracycline and taxane only treatment on cardiac function in breast cancer

Chemotherapy is widely used for the treatment of various malignancies. Breast cancer is one of the most frequently diagnosed malignancies and is the leading cause of cancer-related mortality among women with approximately 685 000 deaths worldwide in 2020

(28). With advanced, combined therapies the overall survival is improving and nearly 90% of women at any stage survive their diagnosis by at least 5 years and 75% by 10 years (29).

CVD associated death is the leading non-cancer related cause of mortality among women worldwide (30). As risk factors for CVD and breast cancer substantially overlap (31, 32); patients with breast cancer commonly present with multiple CV risk factors (33). However, given the bimodal age distribution of breast cancer, younger patients with fewer CV risk factors are also affected by breast cancer (34, 35). Furthermore, some of the conventional chemotherapies applied first line in patients with breast cancer are known to have cardiotoxic side effects (29). The combination of all these factors may explain why CVD (and not cancer itself) is the primary cause of death in patients aged ≥75 years with stage I or localized breast cancer (36, 37). The combination of the presence of cardiovascular risk factors, the cardiac toxicity of therapy, and the increasing survival of breast cancer patients highlights the need for cardiac monitoring during and after oncological treatment.

Identification of the stage and molecular subtype of breast cancer is crucial for the selection of proper treatment. In selected cases, no chemotherapy is required. However, if chemotherapy is recommended, anthracyclines (mainly doxorubicin or epirubicin) and taxanes (paclitaxel or docetaxel) are preferred options. Taxanes are usually considered to be safe from a cardiological standpoint, but anthracyclines have well-described and pronounced cardiac side effects. The risk of cardiac morbidity and mortality is increased by approximately fivefold after an anthracycline-based versus non-anthracycline regimens (38). Anthracycline-related cardiac events typically occur within the first year after treatment (39), although long-term cardiac damage and remodelling have also been described (40). Therefore, early detection of cardiac abnormalities during treatment is crucial.

In 2022, the European Society of Cardiology (ESC) published its first guideline on cardio-oncology with graded recommendations based on the totality of evidence (4). The ESC guideline covers the diagnosis, management and prevention of cardiovascular toxicity associated with cancer therapies including fifteen chemotherapeutic compounds. While the ESC guideline lists only anti-Her-2 and anthracycline-based treatments as harmful

from a cardiological standpoint, other authors advocate for monitoring of cardiac effects related to taxane-based regimens (29).

2. Objectives

2.1. Changes of the cardiac electrical cycle in type 1 diabetes during hypoglycaemia

To characterize the dynamic electrophysiological effects of hypoglycaemia in real-life conditions, we performed simultaneous continuous subcutaneous glucose (CGM) and long-term ECG monitoring in free living type 1 diabetes patients for approximately 7 days. This design allowed us to capture spontaneous hypoglycaemic and normoglycaemic episodes and to investigate their associated changes in cardiac electrical activity.

Using a case-control design, we compared the difference 1) in the means and 2) the standard deviations (SD) of each period of the cardiac cycle (i.e. PQ, QRS), as well as 3) HR and 4) frequency of ventricular ectopias between normoglycaemic and hypoglycaemic episodes.

By analysing both the average values and the beat-to-beat variability of ECG time periods, we aimed to determine whether hypoglycaemia is associated not only with small mean changes in ECG interval durations, but also with increased electrical instability and extreme values that could facilitate malignant arrhythmias and the ‘dead-in-bed’ syndrome.

2.2. Effects of taxane-anthracycline and taxane only treatment on cardiac function in breast cancer

To investigate the long-term cardiac effects of different chemotherapeutic regimens in breast cancer, we performed a retrospective echocardiographic analysis of patients treated at the Cardiology Outpatient Clinic of the Department of Internal Medicine and Oncology, Semmelweis University. During the study period, the most frequently used chemotherapeutic agents in breast cancer were anthracyclines and anti-HER-2 (drugs with pronounced cardiac side effects), as well as taxanes and aromatase inhibitors (drugs with less pronounced cardiac side effects) at the department. On this basis, the study focused on two clinically relevant exposure groups: patients receiving combined anthracycline–taxane therapy and those treated with taxane-only regimens. In designing the analysis, we followed the ESC recommendations in defining both predictors and outcomes (4).

By contrasting a well-known cardiotoxic regimen (anthracycline plus taxane) with a regimen considered to be less cardiotoxic (taxane only), our study aimed to clarify

whether taxane-based therapy is associated with myocardial dysfunction (4). In addition, we aimed to describe the type, the extent, and the temporality of cardiac changes associated with these chemotherapeutic regimens, with the goal of identifying early indicators of treatment-related cardiac stress and supporting strategies for monitoring and preventing long-term cardiovascular complications.

3. Methods

3.1. Setting

3.1.1. Changes of the cardiac electrical cycle in type 1 diabetes during hypoglycaemia

This study was conducted at the Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary between 19/JAN/2015 and 2/FEB/2016. Study protocol was approved by National Scientific and Ethics Committee of the Hungarian Medical Research Council (ETT TUKEB 507/2014).

Before inclusion in the study, we obtained oral and written informed consent from all participants. Thereafter, we checked the participants for eligibility. After baseline assessment, all included patients underwent a simultaneous 12-lead Holter ECG and single blinded CGM monitoring up to 168 hours while continuing their usual daily activities and diabetes management.

3.1.2. Effects of taxane-anthracycline and taxane only treatment on cardiac function in breast cancer

The oncology study was conducted also at the Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary between 1/APR/2018 and 1/APR/2023. For this retrospective analysis, ethical approval was obtained from the Regional Scientific and Research Ethics Committee of Semmelweis University (RKEB/34/2021) but no informed consent was required.

Patients with any stage of breast cancer requiring chemotherapy are regularly examined by a cardiologist according to local protocols. These examinations could be carried out either at the Cardiology Outpatient Clinic of the Department of Internal Medicine and Oncology or at an external hospital/outpatient clinic according to patient's choice. For the present analysis, patients were eligible, if they had their transthoracic echocardiogram (TTE) screening at our department. We screened the electronic health records (EHRs) of all patients examined at our cardiology clinic and selected patients with breast cancer that were treated with either a single taxane or an anthracycline plus taxane regimen. For all eligible patients, we extracted additional data from EHRs to a standardized questionnaire on medical history and medications, and anthropometrics. Furthermore, results of the TTE examination for the baseline and each follow-up visit were recorded.

3.2. Selection of participants

3.2.1. Changes of the cardiac electrical cycle in type 1 diabetes during hypoglycaemia

We selected a convenience sample of 31 individuals with insulin treated type 1 diabetes, aged 18-55 years, diabetes duration ≥5 years. Exclusion criteria were: treatment with antiarrhythmic drugs other than beta-blockers (e.g., amiodarone, sotalol); ECG abnormalities that could hinder differentiation of supraventricular and ventricular premature beats (e.g. complete bundle branch block, WPW syndrome), non-sinus rhythm (e.g., high degree atrioventricular block, atrial fibrillation); known macrovascular diabetes complications (acute myocardial infarction (AMI), stroke, transient ischemic attack, or peripheral arterial disease in the medical history); chronic kidney disease stages 3 and 4 (41); hypo- or hyperthyroidism unless thyroid stimulating hormone (TSH) was within the normal range.

Of the 31 included patients we excluded 6 patients (19%) due to lack of hypoglycaemic episodes during monitoring. Further 2 patients (6%) were excluded due to the lack of adequate control episodes. The final analytical sample represents data of 23 patients (74%).

The second level of exclusion is on the level of beats. Of the original 18,939,951 beats (31 patients), we excluded 3,177,501 beats (16.8%) that were collected in the 8 excluded patients. The remaining 23 patients had a total 15,762,450 beats. Given that the study utilized a 1:1 case-control analysis, we only included beats from hypoglycaemic and their respective control episodes (n=2,339,306 beats). Of these eligible beats we excluded those that were recorded during hypoglycaemic episodes shorter than 15 minutes or without an adequate control episode (altogether 569,516 beats, 24.4%). Finally, we excluded individual beats where the measured ECG parameters were clearly erroneous or improbable (clinically too low or high, 72,585 beats, 3.1%). Thus, the final analytical sample included 1,697,205 beats (72.6% of those eligible). (**Figure 1)**

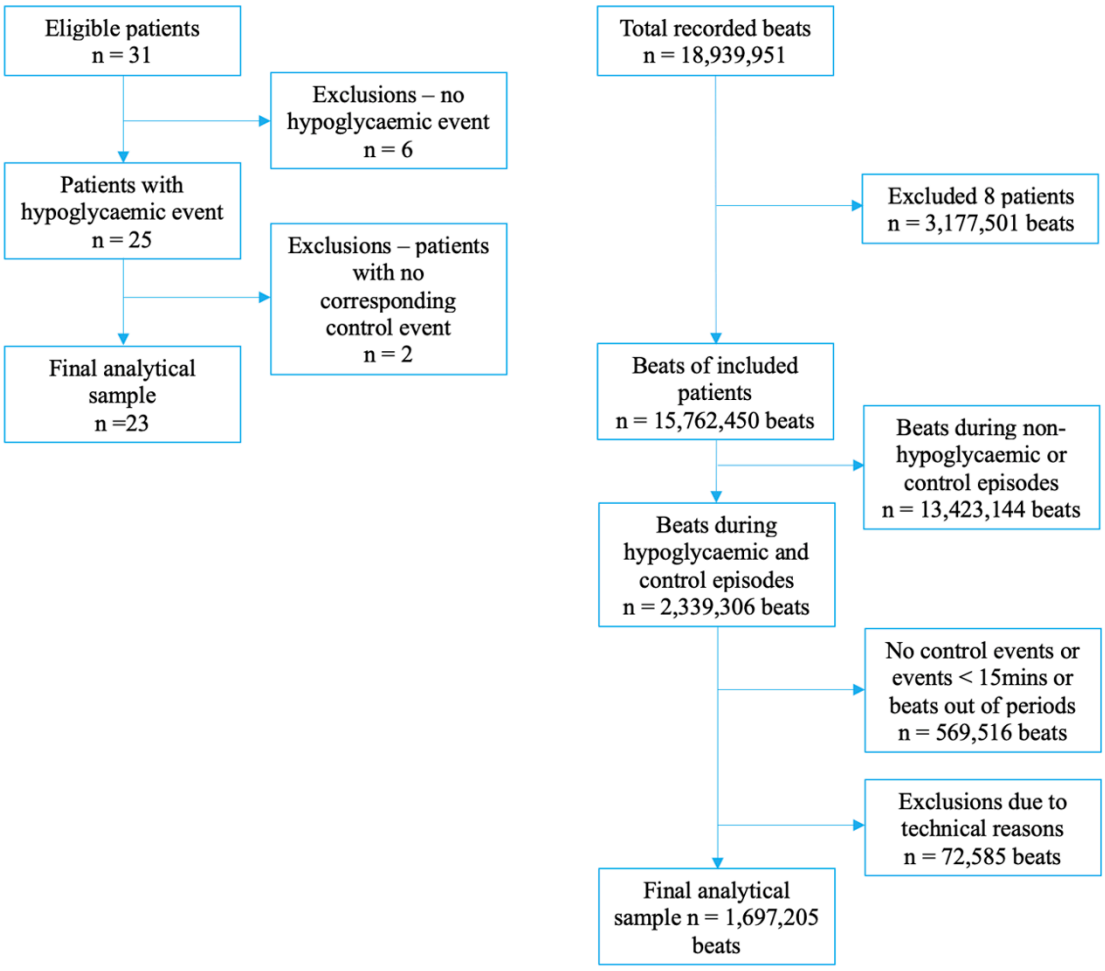

Figure 1 – Flow chart of participants' selection.

3.2.2. Effects of taxane-anthracycline and taxane only treatment on cardiac function in breast cancer

We checked eligibility based on data collected from the EHRs. *Inclusion criteria* were: female sex, age >18 years, diagnosis of a breast malignancy [diagnosis including stage and molecular status according to the current protocol of the Hungarian College of Radiotherapy and Oncology (42)], and receipt of treatment with a single taxane (group 1) or an anthracycline plus taxane (group 2) chemotherapy. Anthracycline dose was based on the treating oncologists' discretion in accordance with the most recent local guidelines and protocols (42). Most patients were treated with a 240 mg/m^2 cumulative dose of doxorubicin or a 300 mg/m^2 cumulative dose of epirubicin and an 80 mg/m^2 paclitaxel. We should note that according to national guidelines, anthracycline treatment is contraindicated for patients previously treated with cardiotoxic chemotherapies and thus

no patients in the anthracycline plus taxane group received prior chemotherapy, while approximately a quarter of those on single taxane therapy received prior chemotherapies. (**Table 1**)

Exclusion criteria were: lack of a baseline visit, lack of any follow-up visit after baseline, and prior chemotherapy within 365 days. We defined baseline as a visit that took place before or within 14 days of the start of the first chemotherapy treatment.

During the study period, a total of 1 113 oncology patients were examined at the Department of Internal Medicine and Oncology of Semmelweis University. Of these 1 113 patients, 368 patients (33.06%) were diagnosed with breast malignancy. Of these 368 patients we excluded 2 men (0.54% of patients with breast malignancy). We excluded further 152 patients (41.30%) due to missing baseline visit. Finally, we excluded 146 (39.67%) patients because they had no follow-up data. The final analytical sample represents data of 68 patients (18.5%) with 332 visits (28.1%). (**Figure 2)**

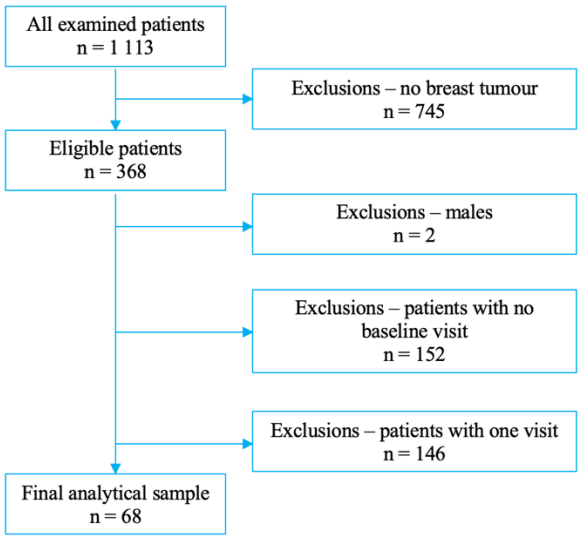

Figure 2 – Flow chart of participants' selection.

3.3. Baseline assessment and predictors

3.3.1. Changes of the cardiac electrical cycle in type 1 diabetes during hypoglycaemia

We collected data on age, medical history (type and duration of diabetes, macrovascular diabetes complications, etc.), and information on concomitant medications from EHRs and medical examination. We performed laboratory tests and a baseline 12-lead ECG (if not available in EHRs within 30 days) to check for exclusion criteria.

After testing for eligibility, we collected further data from EHRs and medical examinations including a questionnaire: details of insulin treatment (insulin doses and insulin delivery method), concurrent medications (beta-blockers, thyroid hormone replacement), smoking status, family history of AMI, anthropometric data (weight, height, BMI, waist and hip circumference), systolic and diastolic blood pressure, presence of sensory and autonomic neuropathy, and other laboratory data.

We coded smoking status as never, ex-, or current smoker (≥1 cigarettes/day). Positive family history of AMI included all relatives.

We measured body weight in light clothing without shoes on a calibrated digital scale (ADE M320000-01 electronic weight scale, ADE, Germany) and rounded to the nearest 0.1 kg. Height was measured without shoes rounded to the closest centimetre. We calculated BMI as weight (kg) / height^2 (m). We measured waist circumference in the midline between the iliac crest and the lowest point of the ribcage after a normal exhalation. Hip circumference was measured at the height of the greater trochanter. We rounded both to the nearest centimetre (43).

We measured resting sitting blood pressure thrice using a calibrated digital meter (OMRON M4-I, Omron Electronics Kft., Budapest, Hungary) after a 5-minute rest. We used the average of the three measurements.

We assessed cardiovascular autonomic neuropathy using the tests proposed by Ewing et al. apart from the handgrip test. We diagnosed cardiovascular autonomic neuropathy if at least 2 tests were abnormal (44, 45). For the diagnosis of distal symmetric polyneuropathy (DSPN), we used tuning fork and 10 g Semmes-Weinstein monofilament tests. If we found signs of polyneuropathy on both lower extremities (≤ 4 for or ≤ 6 for tuning fork), we diagnosed DSPN.

Serum creatinine, urinary albumin-to-creatinine ratio, TSH, HbA1c, serum lipids (total, HDL, LDL cholesterol), N-terminal prohormone of brain natriuretic peptide were measured, estimated glomerular filtration rate was calculated by the same central laboratory (Central Laboratory of the Semmelweis University) on automated systems, not earlier than 30 days before baseline examination. The laboratory is accredited by the Hungarian Association for Clinical Chemistry.

All patients underwent a maximum 168-hour long simultaneous 12-lead Holter ECG (Labtech EC-12H device, Labtech Ltd., Budapest, Hungary) (46) and CGM monitoring

(iPro2 CGM monitoring system with Enlite sensor, Medtronic Hungária KFT, Budapest, Hungary) (47), while continuing their usual daily activities and diabetes management. Calibrations with self-monitored blood glucose values were performed at least four times daily according to manufacturer's recommendation during the study period. The sensor reports interstitial glucose (IG) values between 2.2 and 22.2 mmol/l for every 5 minutes. These CGMs have been shown to be clinically accurate, with 97.3% of points within the A+B zones of the Clarke error grid against fingerprick blood glucose levels. The mean absolute difference between sensor and meter glucose values is ~14%, and hypoglycaemia detection rate is in the range of 80-90%. The lag time between meter glucose and sensor glucose was 8±13 min, suggesting that a lag time >34 min was rare (48, 49).

3.3.2. Effects of taxane-anthracycline and taxane only treatment on cardiac function in breast cancer

Participants completed a questionnaire that collected structured information on smoking history and cardiovascular medical history. We measured body weight, height, and blood pressure using the above-described methods and calibrated instruments.

In addition, we collected data on past and present cardiovascular comorbidities: hypertension, diabetes mellitus, hyperlipidaemia, and major adverse cardiovascular events [MACE - defined as prior acute myocardial infarction (ICD-10: I21x, I22x) or unstable angina (ICD-10: I200), ischaemic or haemorrhagic stroke (ICD-10: I60x-I64x); or peripheral arterial disease (ICD-10: I738, I739)]. We diagnosed hypertension, hyperlipidaemia, or diabetes mellitus if the proper ICD diagnostic code was present in the EHRs at least three times (hypertension: I10xx, hyperlipidaemia: E78xx; diabetes mellitus: E10xx, E11xx or E14xx). We also collected information on the date and type of chemotherapy treatments and concomitant medications, as well as the results of TTE examinations. We defined previous chemotherapy as anthracycline or anti-HER2 treatment beyond 365 days.

Patient questionnaires also contained information on cardiovascular comorbidities, details of chemotherapies, and concomitant medications. In the case of any discrepancies between EHR and questionnaire-based information, we rectified the data through discussion with the patient.

Finally, we stratified the patients into two treatment groups: *Group 1* – patients on single taxane chemotherapy without anthracycline. *Group 2* patients on anthracycline followed by taxane-based treatment.

3.4. Outcomes

3.4.1. Changes of the cardiac electrical cycle in type 1 diabetes during hypoglycaemia

3.4.1.1. CGM predictors

For the purposes of the current analysis, we defined non-hypoglycaemia as an IG value of >3.5 and hypoglycaemia as an IG ≤3.5 mmol/l. The latter value is between the generally accepted cut-offs for level 1 (3.9 mmol/l) and level 2 (3.0 mmol/l) hypoglycaemia (50, 51). We selected this cut-off because recent research suggests that the counter-regulatory mechanisms (thought to be partly responsible for the cardiovascular effects of hypoglycaemia) are triggered at glucose levels between level 1 and 2 hypoglycaemias (52).

We defined a valid hypoglycaemic episode as a continuous hypoglycaemic IG value for ≥15 minutes. The first reading of IG ≤3.5 mmol/l marked the start of hypoglycaemia, and the first reading of IG >3.5 mmol/l labelled the end of the episode. For each hypoglycaemic episode, we checked systematically for a control episode during the following or preceding days at the same time period. We used the first non-hypoglycaemic period as the control episode if no hypoglycaemia had been detected in the preceding 1 hour. Due to technical reasons, the length of the hypoglycaemic and control episodes could be somewhat different that was controlled for during statistical analysis.

For a sensitivity analysis, we defined a part of the hypoglycaemic episode that contained the lowest IG values as the nadir episode. We designated the lowest IG value within a given hypoglycaemic episode as the hypoglycaemic nadir. Starting with the nadir, the following 15-minute episode was designated the nadir episode. Given that none of the hypoglycaemic episodes ended within 15 minutes of the nadir, we made no exclusions. We selected the control episode for the nadir episode following the above-described procedure.

We conducted another sensitivity analysis using the definition for the main analysis except for the glucose cut-off value that was set at 3 mmol/l.

We categorised all hypoglycaemic and control episodes into daytime (6am to 10pm) and night-time (10pm to 6am) episodes.

3.4.1.2. ECG outcomes

For continuous 24-hour 12-lead ECG recordings we used a Labtech EC-12H digital Holter system with Cardiospy software (version 5.4) (53). We applied standard Mason–Likar electrode placement for 12-lead configuration. We recorded signals at a sampling frequency of 500 Hz with an analogue band-pass filter of 0.05–150 Hz and a 50 Hz notch filter. Recordings were automatically processed using CardioSpy that separates normal ECG traces from artifacts and detects arrhythmic events [such as ventricular premature beats (VPBs)] according to the manufacturer's default event definitions. An experienced investigator reviewed the automatic evaluation manually. The investigator inspected artefacts, noise, and ectopic beats visually and corrected or excluded them according to the standards of heart rate variability analysis (54, 55).

3.4.1.3. Arrhythmia analysis

The definition of VPBs included both simple and complex VPBs (such as couplets and runs). The number of verified VPBs for each episode was the unit of analysis.

3.4.1.4. Analysis of normal beats

For the analysis of normal beats, we selected only beats detected as normal by Cardiospy and not excluded by the expert investigator. We considered the following intervals in the analysis: RR interval, P-wave length, PQ, QRS, QT, and QTc intervals. We also expressed RR values as HR [HR=1000*60/RR (ms)].

As most previous reports on the effect of hypoglycaemia on QTc lengths were based on Bazett's formula, we selected this method for the main analysis. For sensitivity analyses, we also calculated QTc using the Friderica, Framingham, and Hodges corrections (20-22, 24, 25, 56, 57). Furthermore, we determined the frequency of normal beats with QTc>500 ms (Bazett's correction) for each episode for a sensitivity analysis, as this is generally accepted to be associated with an increased risk of malignant arrhythmia (58).

For each episode, we used the simple arithmetic mean and the SD (as a measure of variability) of each interval (e.g., mean of P-wave lengths; SD of P-wave lengths) as outcomes in further analysis. We selected the SD based on the generally accepted

hypothesis that arrhythmias are induced by beats with extreme characteristics that would be better reflected by a combination of dispersity and the mean (26, 27).

3.4.2. Effects of taxane-anthracycline and taxane only treatment on cardiac function in breast cancer

An expert echocardiographer performed a TTE during each visit using the same Siemens Acuson X300 machine and P5-1 transducer (Siemens Hungary KFT, Budapest) (59, 60). Echocardiographic measurements were taken according to the current ESC recommendations (61). Echocardiographers were unaware of the chemotherapy regimen used and thus could be considered blinded. We discussed results with other specialists only in cases of inconsistencies (e.g., discrepancies between markers characterizing systolic or diastolic function). We measured the following parameters in triplicates, and their average was used as a unit for analysis: left ventricle ejection fraction with Simpson's method (biplane method of disks by using the apical four-chamber and two-chamber views; EF; %), deceleration time (from apical four chamber view, calculated as the time between the peak of E wave and the upper deceleration slope extrapolated to zero line; DT; msec), early diastolic flow peak velocity of the mitral valve (apical four chamber view; E; cm/sec) and early diastolic peak velocity of the mitral valve annulus (apical four chamber view; average of medial and lateral velocities; e'; cm/sec). To estimate diastolic performance of the heart, we used DT and the ratio of E and e' (E/e').
We divided follow-up into 5 discrete periods based on the timing of clinical visits. The time-periods were the following:
- *Period 0*: data measured within 14 days (baseline visit),
- *Period 1*: data measured between 15 and 180 days,
- *Period 2*: data measured between 181 and 365 days,
- *Period 3*: data measured between 366 and 545 days,
- *Period 4*: data measured beyond 546 days.

3.5. Statistical analysis

3.5.1. Changes of the cardiac electrical cycle in type 1 diabetes during hypoglycaemia

We performed no formal power calculations before the study. We expected sufficient power since former studies with similar or smaller sample sizes detected significant increases in QTc interval (20, 23-25).

We provided descriptive statistics for all baseline characteristics as mean ± SD for normally distributed and median (interquartile range [IQR]) for skewed continuous variables, percent (%) for categorical variables. We investigated differences between included and excluded participants using Mann-Whitney U tests and independent samples t-tests for skewed and normally distributed continuous variables, or chi-square tests for categorical variables.

Next, we provided descriptive statistics for hypoglycaemic and control episodes. Given that each participant could have provided more than one hypoglycaemic episode for analysis, we analysed differences between hypoglycaemic and control episodes as well as daytime and night-time episodes using linear mixed models with a random effect for each participant and each event within participants with an unstructured covariance matrix, with duration of episodes and lowest IG within each episode as outcomes and hypoglycaemia status and time of day (daytime/night-time) as fixed effects. We took the square root of episode durations for analysis due to the skewed distribution of the data. We presented data separately for daytime and night-time episodes.

For continuous outcomes, we constructed similar models (normal beats analysis) with mean and SD of RR interval, P-wave length, PQ, QRS, QT, and QTc intervals as outcomes.

Finally, we report our results on categorical outcomes. Given that each participant could have provided more than one hypoglycaemic episodes for analysis, we compared the frequency of VPBs and of beats with prolonged QTc (>500 ms) between hypoglycaemic and control episodes during daytime and night-time using a generalized linear mixed model (negative binomial distribution with log link to control for overdispersion) with the time of day (day or night) and episode type (hypoglycaemic or control episode) as fixed factors, the natural log transformed values of episode duration as offset.

Given that the main analysis included altogether 26 comparisons (13 outcomes, 2 analyses per outcome), we applied a combined approach to control for multiple testing. First, we selected 2 co-primary outcomes (QTc and its SD during the night) where we applied Bonferroni correction and set a statistically significant p-value at <0.025. If these tests were significant, we proceeded with the analyses of the rest of the outcomes (secondary outcomes, n=24 tests). Here (given the hypothesis generating nature of our

study), we controlled for false discovery rate (15%) with the Benjamini-Hochberg procedure. We used SPSS (version 28.0.1.0; IBM, Chicago, IL) for all statistical analyses.

3.5.2. Effects of taxane-anthracycline and taxane only treatment on cardiac function in breast cancer

For descriptive statistics, we used similar methods described for the hypoglycaemia analysis. Because DT and E/e' values had a skewed distribution, we included their natural logarithms in analysis.

Given that each patient provided at least two measurement points for outcome trajectories (changes in TTE parameters during follow-up periods) linear mixed models were applied. We run three hierarchical models for each TTE outcome. *Model 1* included the type of chemotherapy, the follow-up periods, and their interaction as fixed effects. *Model 2* additionally included cardiometabolic risk factors as fixed effects (age, BMI, hypertension, diabetes mellitus, hyperlipidaemia, current smoking, MACE, previous chemotherapy). Finally, for the third model we excluded in a stepwise manner risk factors that were statistically non-significant in the second model to reach the most parsimonious model (*Model 3*).

As most patients were on concurrent anti-HER2 treatment (40/45 patients in the single taxane and 18/23 patients in the anthracycline plus taxane group) we run a sensitivity analysis limited to participants that received anti-HER2 therapy in addition to their chemotherapy (single taxane or anthracycline plus taxane). Given the limited number of participants in this analysis, we only run *Model 1*.

We used SPSS (version 28.0.1.0; IBM, Chicago, IL) for all statistical analyses.

4. Results

4.1. Changes of the cardiac electrical cycle in type 1 diabetes during hypoglycaemia

4.1.1. Baseline characteristics and general description of episodes

Baseline characteristics of included and excluded participants showed no significant difference. (**Table 1)**

Table 1 – Baseline characteristics of participant by exclusion status. Data are mean ± SD, median [IQR], or n (%). p values were calculated by independent samples t-test, Mann-Whitney U test, or chi-square test as appropriate.

Variable	**Included**	**Excluded**	**p**
n	23	8	
Male, n (%)	8 (34.8%)	3 (37.5%)	1.000
Age, years	36.9±13.7	37.1±8.3	0.968
Diabetes duration, years	20.7±13	15.5±7.5	0.295
Bolus insulin dose, IU	26±9	21±8	0.205
Basal insulin dose, IU	22±10	25±9	0.390
Waist, cm	86±11	85±8	0.901
Hip, cm	101±9	102±7	0.888
Weight, kg	70.4±14.7	69.1±10.3	0.818
Height, m	170±9	166±7	0.228
BMI, kg/m^2	24.2±3.4	25.1±3.2	0.547
Systolic blood pressure, mmHg	124±16	123±7	0.783
Diastolic blood pressure, mmHg	73±9	77±6	0.312
HbA1c, %	8.1 [7.7, 8.6]	8.3 [7.8, 9.1]	0.642
HbA1c, mmol/mol	65 [61, 70]	67 [62, 76]	0.642
Total cholesterol, mmol/l	4.6 [4.3, 5.5]	5.4 [4.7, 5.8]	0.132
LDL cholesterol, mmol/l	2.7 [2.2, 3.4]	3.4 [3.2, 3.6]	0.074
HDL cholesterol, mmol/	1.5 [1.4, 1.8]	1.5 [1.4, 1.7]	0.520
Brain natriuretic peptide, pg/ml	14 [5, 18]	22 [5, 36]	0.249
Urinary albumin concentration, mg/l	4.6 [3.1, 7.3]	3.5 [0.5, 7.3]	0.321
TSH, mIU/l	1.1 [0.9, 1.5]	1.6 [1.1, 4.1]	0.132
Insulin pump treatment, n (%)	4 (17.4%)	2 (25.0%)	0.634
Family history of myocardial infarction, n (%)	8 (34.8%)	4 (50.0%)	0.418
Current smoking, n (%)	5 (21.7%)	3 (37.5%)	0.393

Use of beta-blocker, n (%)	4 (17.4%)	1 (12.5%)	1.000
Sensory neuropathy, n (%)	6 (26.1%)	2 (25.0%)	1.000
Autonomic neuropathy, n (%)	9 (39.1%)	3 (37.5%)	1.000
Thyroxin replacement, n (%)	1 (4.3%)	1 (12.5%)	0.389

The 23 included patients had a total of 113 hypoglycaemic and 113 control episodes. Of these episodes, 84 occurred at night and 29 during the day.

Altogether the 226 episodes lasted for 378 hours and represent 1,697,205 beats. Daytime recording lasted 227 hours (hypoglycaemic episodes: 115 hours, 550,940 beats; control episodes: 112 hours, 519,561 beats), while the night-time recordings lasted 151 hours (hypoglycaemic episodes: 78 hours, 315,915 beats, control episodes: 73 hours, 310,789 beats). Night-time episodes were longer compared to daytime episodes both for hypoglycaemic and control episodes ($p<0.01$ for both). Mean IG levels were lower during night-time than daytime hypoglycaemic episodes. In contrast, mean IG levels were similar during night-time and daytime control episodes. (**Table 2**)

Table 2 – Characteristics of hypoglycaemic and control episodes. * shows statistically significant differences. EMMs (95% CIs) and p-values are based on linear mixed models.

	Hypoglycaemic episodes			**Control episodes**		
	daytime	**night-time**	**p**	**daytime**	**night-time**	**p**
Number of episodes	84	29	-	84	29	-
Duration of episodes, min	66 (57-75)	159 (128-192)	<0.001*	63 (55-71)	150 (124-178)	<0.001*
Nadir glucose, mmol/l	2.6 (2.6-2.7)	2.5 (2.3-2.6)	0.030*	6.3 (5.8;6.8)	6.7 (5.8-7.7)	0.455

4.1.2. Arrhythmia analysis

We detected altogether 1,121 VPBs during hypoglycaemic episodes, most during daytime (daytime: n=949, night-time: n=172). We detected a similar number of VPBs during the control episodes (daytime: n=943, night-time: n=217). The rate of VPBs was numerically lower at night compared to the day but we found no difference between hypoglycaemic and control episodes (daytime: 8.3, 95%CI: 3.7-18.7 vs 8.4. 95%CI: 2.4-30.1 VPB/hour,

p=0.96; night-time: 2.2, 95%CI: 0.6-8.9 vs 3.0, 95%CI: 0.9-9.4 VPB/hour, p=0.47, respectively). (**Figure 3**)

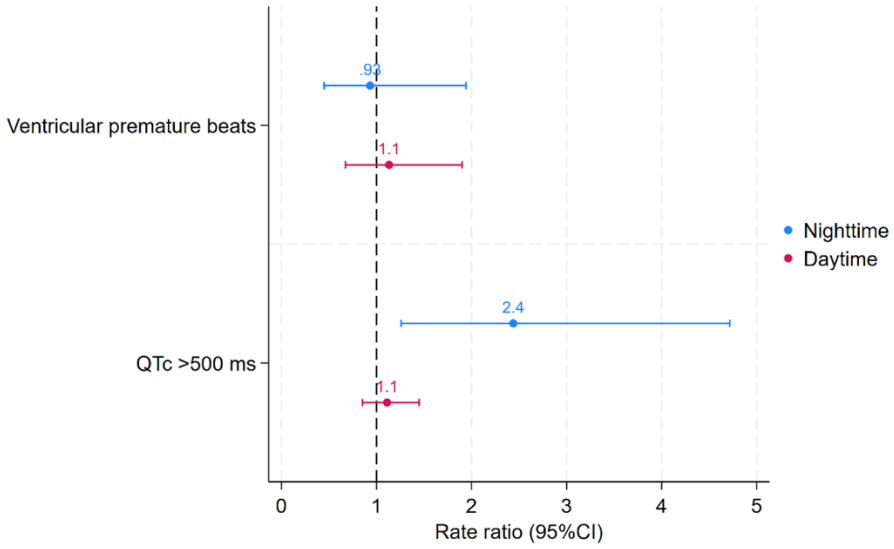

Figure 3 –Rate ratios of ventricular premature beats and beats with prolonged QTc (>500 ms) during hypoglycaemic vs control episodes stratified by time of day. Rate ratios are based on generalized linear models. Error bars represent 95% CIs.

4.1.3. Analysis of normal beats

HR (calculated from the RR intervals) was lower at night compared to the day. However, we found no significant difference between hypoglycaemic and control episodes in HR (night-time: 72.7, 95%CI: 68.7-76.6 vs 71.9, 95%CI: 67.9-75.8 bpm; daytime: 87.1, 95%CI: 84.8-89.5 vs 86.2, 95%CI: 83.9-88.5 bpm). (**Table 3**)

Table 3 – Frequency of VPBs and lengths of ECG intervals during hypoglycaemic and control periods stratified by time of day. P values are given for the difference between hypoglycaemic and control episodes based on linear mixed models and generalized linear models. * shows statistically significant differences. QTc intervals were calculated using Bazett's formula.

Night-time (n = 58 episodes)							
	Hypoglycaemic episodes	**Control episodes**	**p**		**Hypoglycaemic episodes**	**Control episodes**	**p**
	EMM (95%CI)	**EMM (95%CI)**			**EMM (95%CI)**	**EMM (95%CI)**	
VPBs, n/hour	2.4 (0.8-7.6)	2.6 (0.9-7.6)	0.853				
RR, ms	856 (818-895)	863 (825-902)	0.727	SD of RR, ms	102 (89-114)	84 (72-97)	0.010*
P, ms	112 (108-116)	113 (110-117)	0.296	SD of P, ms	8 (6-10)	6 (4-8)	0.018*
PQ, ms	163 (157-170)	162 (155-168)	0.384	SD of PQ, ms	11 (9-14)	8 (5-11)	0.014*
QRS, ms	97 (94-100)	96 (93-99)	0.123	SD of QRS, ms	7 (5-9)	6 (4-8)	0.065
QT, ms	404 (394-414)	402 (392-412)	0.611	SD of QT, ms	17 (15-19)	13 (11-15)	0.002*
QTc, ms	440 (432-448)	435 (427-443)	0.003*	SD of QTc, ms	21 (18-23)	16 (14-18)	<0.001*
Daytime (n = 168 episodes)							
	Hypoglycaemic episodes	**Control episodes**	**p**		**Hypoglycaemic episodes**	**Control episodes**	**p**
	EMM (95%CI)	**EMM (95%CI)**			**EMM (95%CI)**	**EMM (95%CI)**	
VPBs, n/hour	7.6 (3.5-16.3)	6.7 (2.5-17.8)	0.616				
RR, ms	710 (688-733)	715 (692-737)	0.722	SD of RR, ms	74 (66-81)	70 (63-77)	0.335
P, ms	109 (107-111)	110 (107-112)	0.343	SD of P, ms	9 (8-10)	9 (8-10)	0.714
PQ, ms	149 (146-153)	150 (146-153)	0.625	SD of PQ, ms	14 (13-16)	15 (13-16)	0.656
QRS, ms	98 (97-100)	98 (97-100)	0.986	SD of QRS, ms	11 (10-12)	11 (10-12)	0.855
QT, ms	369 (364-375)	371 (366-377)	0.455	SD of QT, ms	15 (13-16)	14 (12-15)	0.248
QTc, ms	441 (437-446)	442 (437-446)	0.684	SD of QTc, ms	20 (19-21)	19 (18-20)	0.112

Next, we compared mean length of the P-wave, as well as PQ, QRS, QT, and QTc intervals during hypoglycaemic and control episodes stratified by the time of day. Except for a longer night-time QTc interval during hypoglycaemic episodes (mean difference

[MD]: 5, 95%CI: 2-8 ms), we found no difference in the above parameters between hypoglycaemic and control episodes. (**Table 3**, **Figure 4, Figure 5**)

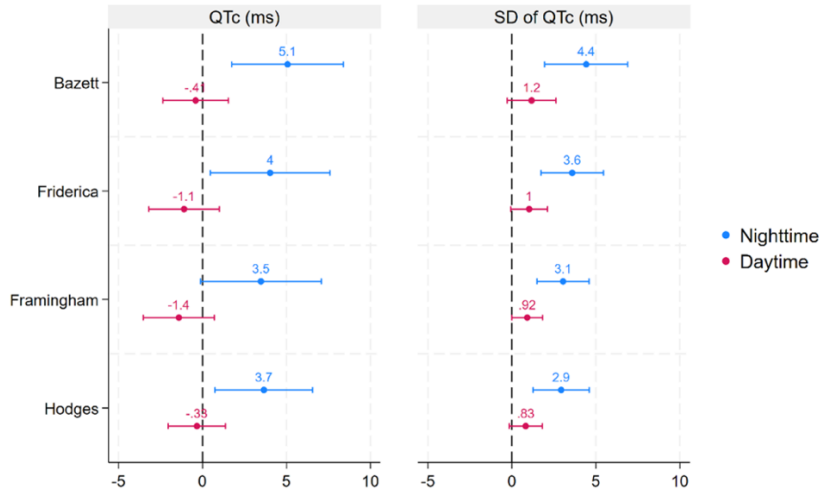

Figure 4 – Estimated difference in the co-primary outcomes (QTc and its SD based on Bazett's correction) as well as QTc and its SD using different methods for QT correction between hypoglycaemic and control episodes stratified by time of day. Estimated differences are based on linear mixed models. Error bars represent 95% CIs.

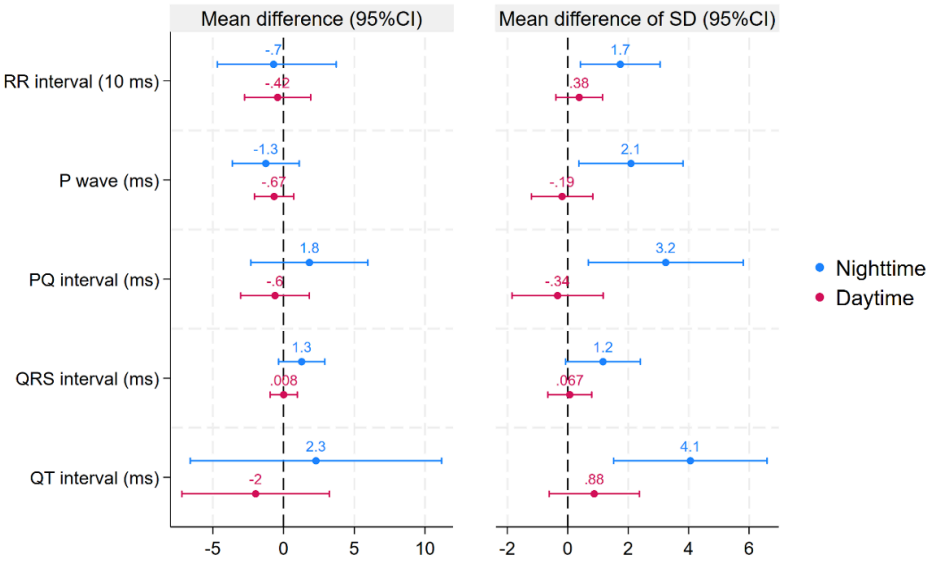

Figure 5 – Estimated differences in the secondary outcomes between hypoglycaemic and control episodes stratified by time of day. Estimated differences are based on linear mixed models. Error bars represent 95% CIs.

The last analysis concerns the SD of the ECG parameters. At night, the SD of all parameters (except for the QRS interval) increased (RR interval MD: 17, 95%CI: 4-31;

P-wave MD: 2, 95%CI: 0-4; PQ interval MD: 3, 95%CI: 1-6; QT interval MD: 4, 95%CI: 2-7; QTc interval MD: 4, 95%CI: 2-7). In contrast, we found no significant difference between hypoglycaemic and control episodes in any of these variables during the day. (**Table 3**, **Figure 4, Figure 5**)

4.1.4. Sensitivity analyses

The first set of sensitivity analyses investigated the robustness of our findings on the increase of QTc interval and its SD using different methods for QT correction. These analyses confirmed both findings with point estimates similar to those of the main analysis. Furthermore, the rate of normal beats with a prolonged QTc was more than doubled (rate ratio [RR]: 2.43, 95% CI: 1.26-4.72) during night-time hypoglycaemic compared to control episodes further supporting our findings on the co-primary outcomes. (**Figure 4**, **Figure 5**)

The other 2 sensitivity analyses used different definitions for hypoglycaemic episodes. These analyses largely confirmed our main findings in terms of a significantly larger dispersity (SD) of QTc intervals during hypoglycaemia compared to control episodes at night. Furthermore, the difference in point estimates between hypoglycaemic and control episodes were similar but the CIs included 0 for mean of QT and QTc, as well as SD of QT intervals at night. Similarly to our main analysis, we found no difference in hypoglycaemic and control episodes in any of the investigated parameters during the day. (**Figure 6**, **Figure 7**)

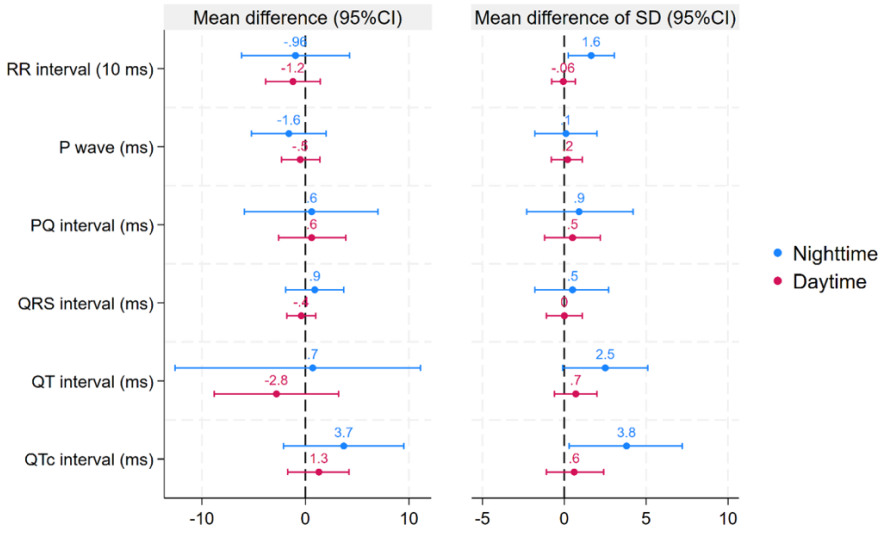

Figure 6 – Differences in primary and secondary outcomes between nadir hypoglycaemic and control episodes stratified by time of day (sensitivity analysis). Estimated differences are based on linear mixed models. Error bars represent 95% CIs.

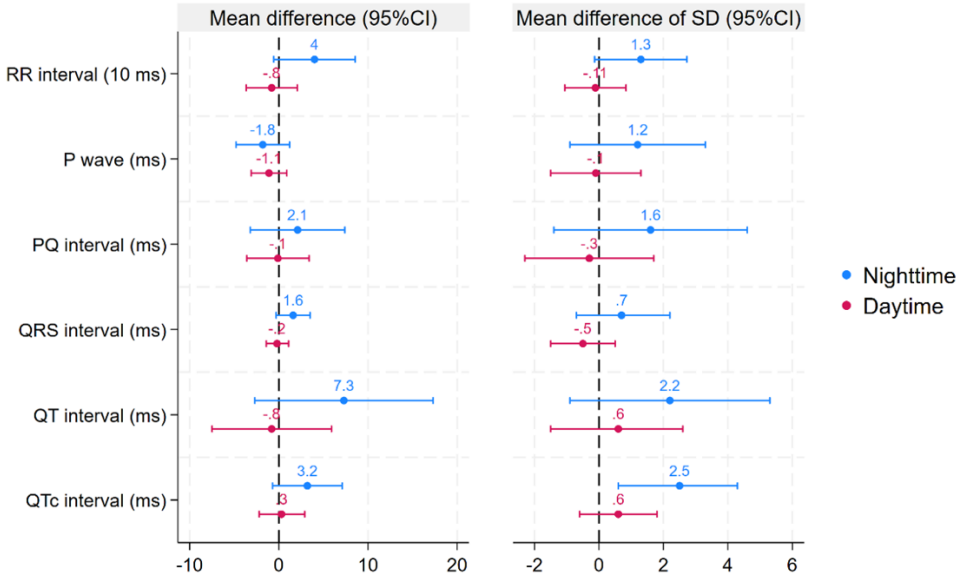

Figure 7 – Differences in primary and secondary outcomes between hypoglycaemic and control episodes using 3 mmol/l as the cut-off for events stratified by time of day (sensitivity analysis). Estimated differences are based on linear mixed models. Error bars represent 95% CIs.

4.2. Effects of taxane-anthracycline and taxane only treatment on cardiac function in breast cancer

4.2.1. Baseline characteristics

Included and excluded patients had similar baseline characteristics (age, BMI, presence of hypertension, diabetes mellitus, and hyperlipidaemia, current smoking, previous MACE; all p>0.05), suggesting no major selection bias in these parameters. (**Table 4)**

Table 4. Baseline participant characteristics by exclusion and type of treatment. Data are mean ± SD or n/total (%). p value was calculated by independent samples t-test or chi-square test. $p < 0.05$ was considered as statistically significant. * shows statistically significant differences.

Variable	**By exclusion**			**By type of treatment**		
	Excluded	**Included**	**p**	**Group 1**	**Group 2**	**p**
n	300	68	-	45	23	-

Age (years)	57.1±13.3	54.3±13.4	0.116	55.2±13.1	52.7±14.1	0.475
BMI (kg/m2)	27±5.6	25.7±4.8	0.069	25.7±4.8	25.7±5	0.983
Hypertension	118/300 (39.3%)	24/68 (35.3%)	0.583	17/45 (37.8%)	7/23 (30.4%)	0.602
Diabetes mellitus	41/300 (13.7%)	6/68 (8.8%)	0.322	3/45 (6.7%)	3/23 (13%)	0.399
Hyperlipidaemia	36/300 (12%)	8/68 (11.8%)	1	3/45 (6.7%)	5/23 (21.7%)	0.109
Current smoking	44/300 (14.7%)	13/68 (19.1%)	0.357	8/45 (17.8%)	5/23 (21.7%)	0.750
MACE	14/300 (4.7%)	2/68 (2.9%)	0.746	0/45 (0%)	2/23 (4.3%)	0.111
Previous chemotherapy	-	-	-	12/45 (26.7%)	0/23 (0%)	0.006*
EF (%)	-	-	-	64.3±4.2	65±4.7	0.527
DT (msec)	-	-	-	212.5±1.3	229.1±1.2	0.225
E/e'	-	-	-	6.5±1.3	6.4±1.3	0.834

Baseline characteristics (including TTE parameters) of the treatment groups were also similar except for more prevalent history of a previous chemotherapy in the single taxane group (group 1 – 26.7% vs group 2 – 0%, p=0.006). (**Table 4**)

Among the 12 patients on single taxane therapy that received a previous chemotherapy, 10 received anthracycline and 6 anti-HER2 therapies. Previous chemotherapy was given a median 2,791 days before baseline (range: 707 – 5,107 days).

In the single taxane group, 45 patients had a total of 228 visits, in the anthracycline plus taxane group, 23 patients had 104 visits. All patients had at least two visits, with the highest number of visits being 23 for the single taxane and 17 for the anthracycline plus taxane group. The number of visits stratified by the follow-up periods was as follows: all patients (group1/group2: 45/23) had a single baseline visit (period 0), 40/24 visits happened in period 1, 55/21 visits in period 2, 37/14 visits in period 3, and 51/22 visits in period 4.

4.2.2. Transthoracic echocardiography

In the single taxane group we found no significant change compared to baseline in any of the TTE parameters in either of the three models, although one patient's EF dropped from a baseline of 63% to 49% in period 4. On further follow-up the EF of this participant returned to normal. Exclusion of this patient did not alter the main results (**Table 5**).

Table 5. Estimated marginal means (EMMS) of EF, DT, E/e' by type of treatment and by follow-up period. Estimates are based on linear mixed models. $p < 0.05$ was considered as statistically significant. * shows statistically significant differences vs baseline (0-14 days). First column shows the time since first chemotherapy (days). Column Diff shows the difference in EMMs compared to baseline (0-14 days). *Model 1* included the type of chemotherapy and follow-up periods as fixed effects. *Model 2* additionally included age, body mass index, hypertension, diabetes mellitus, hyperlipidaemia, current smoking, major adverse cardiac events, and previous chemotherapy as fixed effects. Model 3 included only those variables as fixed effects that remained statistically significant using a stepwise elimination procedure of Model 2 covariates.

Days	Model 1			Model 2			Model 3		
	EMM (LCI;UCI)	Diff	p	EMM (LCI;UCI)	Diff	p	EMM (LCI;UCI)	Diff	p
Group 1 – EF (%)									
0-14	64.3 (63;65.7)	0.0	-	65.6 (62.6;68.7)	0.0	-	64.8 (63.4;66.1)	0.0	-
15-180	63.4 (61.9;64.8)	-0.9	0.495	64.8 (61.7;67.9)	-0.8	0.431	64 (62.5;65.4)	-0.8	0.421
181-365	63 (61.8;64.3)	-1.3	0.149	64.4 (61.4;67.4)	-1.2	0.146	63.6 (62.3;64.9)	-1.2	0.131
366-545	65.1 (63.6;66.6)	0.8	0.152	66.7 (63.5;69.8)	1.0	0.193	65.9 (64.3;67.4)	1.1	0.183
>545	64.7 (63.1;66.2)	0.3	0.577	66.5 (63.4;69.7)	0.9	0.282	65.7 (64.1;67.3)	1.0	0.198
Group 1 – DT (msec)									
0-14	212.5 (198.3;227.7)	0.0	-	215.9 (183.6;253.9)	0.0	-	-	-	-
15-180	208.9 (193.6;225.4)	-3.6	0.104	212.1 (179.8;250.1)	-3.9	0.123	-	-	-
181-365	207.7 (194.6;221.6)	-4.8	0.293	210.8 (179.6;247.4)	-5.1	0.361	-	-	-
366-545	201.7 (186.6;217.9)	-10.8	0.739	203.6 (172.6;240.3)	-12.4	0.768	-	-	-
>545	204.6 (189.6;221)	-7.9	0.329	206.4 (174.9;244)	-9.5	0.675	-	-	-
Group 1 - E/e'									
0-14	6.5 (1.8;2)	0.0	-	6.6 (5.6;7.7)	0.0	-	6.8 (6.3;7.4)	0.0	-
15-180	6.4 (1.8;2)	0.0	0.279	6.5 (5.6;7.6)	-0.1	0.329	6.8 (6.2;7.4)	-0.1	0.316
181-365	6.7 (1.8;2)	0.2	0.947	6.8 (5.8;7.9)	0.2	0.838	7 (6.5;7.7)	0.2	0.904
366-545	6.9 (1.8;2)	0.4	0.488	7 (6;8.2)	0.4	0.402	7.2 (6.6;7.9)	0.4	0.357

>545	6.8 (1.8;2)	0.4	0.907	6.8 (5.8;8)	0.2	0.869	7 (6.4;7.7)	0.2	0.853
Group 2 – EF (%)									
0-14	65 (63.2;66.9)	0.0	-	65.5 (62.5;68.6)	0.0	-	65.4 (63.5;67.2)	0.0	-
15-180	63.1 (61.2;65)	-2.0	0.101	63.5 (60.5;66.6)	-2.0	0.093	63.3 (61.5;65.2)	-2.0	0.091
181-365	61.6 (59.6;63.6)	-3.5	0.006*	62.1 (59;65.3)	-3.4	0.007*	61.9 (59.9;63.9)	-3.5	0.006*
366-545	63.4 (61;65.8)	-1.7	0.242	64.4 (60.9;67.9)	-1.2	0.415	64.2 (61.8;66.6)	-1.2	0.412
>545	64.4 (62.2;66.7)	-0.6	0.661	64.6 (61.2;68.1)	-0.9	0.510	64.2 (62;66.4)	-1.2	0.382
Group 2 – DT (msec)									
0-14	229.1 (207.7;252.9)	0.0	-	227.9 (194;267.5)	0.0	-	-	-	-
15-180	197.2 (178.8;217.7)	-31.9	0.022*	197.4 (168;231.8)	-30.6	0.028*	-	-	-
181-365	205.2 (183.6;229.3)	-23.9	0.118	206.2 (174.2;244.2)	-21.7	0.159	-	-	-
366-545	210.6 (183.5;242)	-18.5	0.306	208.9 (171.9;253.9)	-19.0	0.294	-	-	-
>545	202.4 (179.3;228.4)	-26.7	0.095	209.6 (173.6;253.2)	-18.4	0.285	-	-	-
Group 2 - E/e'									
0-14	6.4 (5.5;7.3)	0.0	-	6.7 (5.8;7.8)	0.0	-	6.9 (6.2;7.6)	0.0	-
15-180	6.8 (5.9;7.8)	0.4	0.225	7.1 (6.1;8.3)	0.4	0.298	7.3 (6.6;8.1)	0.4	0.284
181-365	6.6 (5.7;7.6)	0.2	0.594	7 (6;8.3)	0.3	0.454	7.1 (6.4;8)	0.3	0.518
366-545	7.2 (6.1;8.4)	0.8	0.080	7.6 (6.4;9.1)	0.9	0.063	7.9 (6.9;9)	1.0	0.051
>545	6.8 (5.7;8.1)	0.4	0.411	7 (5.8;8.5)	0.3	0.560	7.2 (6.2;8.4)	0.3	0.548

In the anthracycline plus taxane group, the baseline EMM of EF of 65.0% (95% CI: 63.2-66.9%) decreased significantly to 61.6% (95% CI: 59.6-63.6%, p=0.006) in period 2, followed by an improvement in later periods reaching 64.4% (95% CI: 62.2-66.7%, p=0.661) in period 4. Further adjustment for cardiovascular risk factors had no major effect on the observed U-shaped trajectories. (**Table 5, Figure 8**)

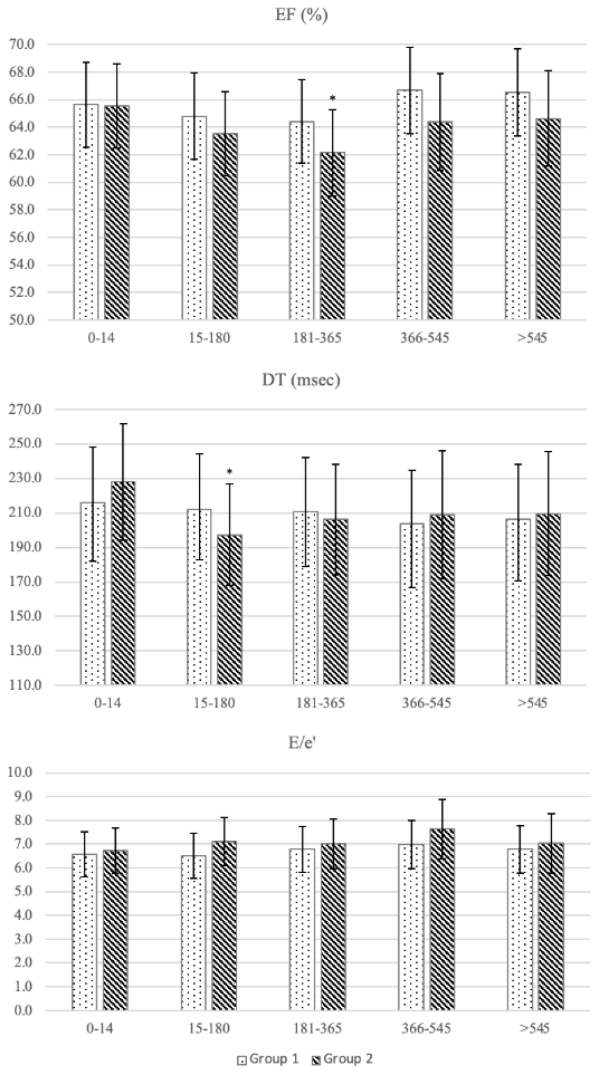

Figure 8. Estimated marginal means (EMMs and 95% Cis) of EF, DT, E/e' by type of treatment over the follow-up periods based on *Model 2*. Estimates are based on linear mixed model. Bars show EMMs, error bars show 95% CIs. Follow-up periods are given in days. * mark EMMs that are significantly different compared to baseline (0-14 days). Group 1 received taxane-based chemotherapy treatment without anthracycline. Group 2 received anthracycline followed by taxane-based treatment.

Model 3 included age and the presence of hypertension as independent determinants of EF. According to this final model, older age (EMMs: -0.1, 95% CI: -0.2;0.0 /year, p=0.006) and the presence of hypertension (EMMs: -2.8, 95% CI: -4.8;-0.8, p=0.006) were associated with lower EF. (**Table 6**) The trajectories based on *Model 3* were like those of *Model 1* and *2*. Baseline EF was 65.4% (95% CI: 63.5-67.2%) in the anthracycline plus taxane group that decreased to 61.9% (95% CI: 59.9-63.9%, p=0.006) in period 2, finally reaching 64.2% (95% CI: 62.0-66.4%, p=0.382) in period 4. (**Table**

5) In *Model 3* of anthracycline plus taxane group, data showed association with hypertension (EMMs: -3.1, 95% CI: -4.8;-1.3, p<0.001) and age (EMMs: -0.1, 95% CI: -0.2;0.0, p=0.006). (**Table 6**)

Table 6. Independent determinants of EF, DT, E/e' in the anthracycline-taxane group (*Group 2*) based on *Model 2* and *3*. Estimates based on linear mixed models. *Model 2* included age, body mass index, hypertension, diabetes mellitus, hyperlipidaemia, current smoking, major adverse cardiac events, previous chemotherapy as fixed effects. *Model 3* included only those variables as fixed effects that remained statistically significant using a stepwise elimination procedure of Model 2 covariates.

Variables	Model 2		Model 3	
	Beta (95%CI)	p	Beta (95%CI)	p
EF (%)				
Age	-0.1 (-0.2;0)	0.006	-0.1 (-0.2;0)	0.006
Hypertension	-2.8 (-4.8;-0.8)	0.006	-3.1 (-4.8;-1.3)	<0.001
DT (msec)				
-	-	-	-	-
E/e'				
Age	1 (1;1)	<0.001	1 (1;1)	<0.001
BMI	1 (1;1)	0.044	1 (1;1)	0.01
Hypertension	0.8 (0.7;0.9)	0.002	0.9 (0.8;0.9)	0.004
Diabetes	0.8 (0.7;1)	0.021	0.9 (0.8;1)	0.095

DT in anthracycline plus taxane group (similarly to EF) also showed a U-shaped trajectory over time. However, it reached its lowest point in period 1 (vs. period 2 for EF). The EMM of DT decreased from 229.1 (95% CI: 207.7-252.9) at baseline to 197.2 (95% CI: 178.8-217.7) msec in period 1 (p=0.022) according to *Model 1*. The DT values in none of the other periods were significantly different from DT at baseline. Further adjustment in *Model 2* had no major effect on the estimates. As none of the cardiovascular risk factors added in *Model 2* were significantly associated with DT, *Model 3* is not presented. (**Table 5, Figure 8**)

Although E/e' did not change significantly over follow-up, (**Table 5, Figure 8**) we found that older age (Beta: 1.0, 95% CI: 1.0;1.0, p<0.001), higher BMI (Beta: 1.0, 95% CI: 1.0;1.0, p=0.044), presence of hypertension (Beta: 0.8, 95% CI: 0.7;0.9, p=0.002) and

diabetes mellitus (Beta: 0.8, 95% CI: 0.7;1.0, p=0.021) were associated with higher E/e' values (*Model 2* and *Model 3)*. (**Table 6**)

Our sensitivity analysis (after the exclusion of patients not receiving concurrent anti-HER2 therapy) showed similar findings to our main analysis. In the single taxane group, we found no difference compared to baseline in any of the TTE parameters over follow-up. In the anthracycline plus taxane group, EF decreased from 65.7% (95% CI: 63.7-67.8%) to 62.6% (95% CI: 60.6-64.4%, p=0.020) in period 1 and decreased further to 61.9% (95% CI: 59.9-63.9%, p=0.004) in period 2. DT decreased from 233.0 (95% CI: 209.35-259.0) at baseline to 194.0 (95% CI: 174.5-215.7, p=0.012) in period 1. E/e' values showed no changes over time. (**Table 7**)

Table 7. Estimated marginal means (EMMS) of EF, DT, E/e' by type of treatment and by follow-up period in a sensitivity analysis restricted to patients on Anti-HER2 therapy. Estimates are based on linear mixed models. $p < 0.05$ was considered as statistically significant. * shows statistically significant differences vs baseline (0-14 days). Group 1 patients received taxane-based and Anti-HER2 chemotherapy treatment without anthracycline. Group 2 patients received anthracycline and Anti-HER2 chemotherapy followed by taxane-based treatment. First column shows the time since first chemotherapy (days). Column Diff shows the difference in EMMs compared to baseline (0-14 days).

Days	EMM (LCI;UCI)	Diff	p
Group 1 - EF (%)			
0-14	64.9 (63.5;66.3)	0.0	-
15-180	63.8 (62.3;65.2)	-1.1	0.220
181-365	63.4 (62.1;64.6)	-1.5	0.139
366-545	65.3 (63.8;66.8)	0.4	0.136
>545	64.8 (63.4;66.3)	-0.1	0.470
Group 1 - DT (msec)			
0-14	218.1 (203.0;234.2)	0.0	-
15-180	209.3 (193.6;226.1)	-8.8	0.108
181-365	212.3 (198,9;226.6)	-5.8	0.231
366-545	205.2 (190.0;221.8)	-12.9	0.693
>545	205.6 (190.9;221.6)	-12.5	0.368
Group 1 - E/e'			
0-14	6.4 (5.8;7.0)	0.0	-
15-180	6.4 (5.8;7.2)	0.0	0.455

181-365	6.6 (6.0;7.3)	0.2	0.941
366-545	6.8 (6.1;7.5)	0.2	0.766
>545	6.8 (6.1;7.5)	0.0	0.936
Group 2 - EF (%)			
0-14	65.7 (63.7;67.8)	0.0	-
15-180	62.6 (60.6;64.6)	-3.1	0.020*
181-365	61.9 (59.9;63.9)	-3.8	0.004*
366-545	63.5 (61.1;66.0)	-2.2	0.143
>545	64.5 (62.3;66.7)	-1.2	0.364
Group 2 - DT (msec)			
0-14	233.0 (209.3;259.0)	0.0	-
15-180	194.0 (174.5;215.7)	-39.0	0.012*
181-365	204.4 (183.5;227.9)	-28.6	0.075
366-545	210.8 (182.7;243.2)	-22.2	0.251
>545	202.6 (180.4;227.7)	-30.4	0.066
Group 2 - E/e'			
0-14	6.1 (5.2;7.2)	0.0	-
15-180	6.5 (5.6;7.7)	0.4	0.263
181-365	6.3 (5.4;7.4)	0.2	0.593
366-545	6.7 (5.6;8.0)	0.6	0.227
>545	6.6 (5.4;7.9)	0.5	0.394

5. Discussion

5.1. Changes of the cardiac electrical cycle in type 1 diabetes during hypoglycaemia

In this observational study of 23 type 1 diabetes patients free from known CVD and severe diabetes complications (1,697,205 heartbeats), we assessed ECG changes associated with hypoglycaemic episodes. The night-time episodes were longer than daytime episodes. Mean IG levels were lower in night-time compared to daytime hypoglycaemic episodes, while they were similar during night-time and daytime control episodes. We found no difference in the number of VPBs and in HR between hypoglycaemic and control episodes (neither at night-time, nor at daytime). In the normal beats analysis, we found a longer QTc interval together with an increased SD of QTc during night-time hypoglycaemic episodes. Furthermore, we found increases in the SD of the P-wave, PQ, QRS, and QT intervals during night-time hypoglycaemic episodes, although the means of these parameters were similar during hypoglycaemic and control episodes. We found no difference in any of the investigated parameters between hypoglycaemic and control episodes during the day.

Although the 'dead-in-bed' syndrome has been described for decades, its underlying causes remain uncertain (13, 14). Most reports hypothesize the role of hypoglycaemia induced QTc prolongation as a direct cause of malignant arrhythmia. Experimental studies using hypoglycaemic clamps reporting significant QTc elongations seem to support this hypothesis (15-19). However, studies in free-living diabetes patients found only moderate QTc increases that are unlikely to cause severe arrhythmias (20-25, 62, 63).

Most studies (similarly to our findings) reported no difference, or clinically non-significant increases in HR during hypoglycaemic vs control episodes in type 1 (21, 62, 63) or type 2 diabetes (56, 64-66). Based on these findings, changes in HR are unlikely triggers of sudden cardiac death.

Previous studies using Holter ECG for <5 days (22, 25, 63) or a loop recorder for 21 days (67) similarly to our findings, showed no difference in the number of VPBs between hypoglycaemic and control episodes in type 1 diabetes. In contrast, type 2 diabetes patients with high cardiovascular risk had a higher rate of VPBs during daytime (56) or both daytime and night-time hypoglycaemia (68).

Given the plausibility of QTc elongation being a potential cause of malignant arrhythmias, previous studies frequently investigated QTc length. Most of these reported a mean 5-10 ms prolongation in type 1 diabetes, mostly during night-time hypoglycaemia (20, 23, 24). One study reported QTc increase during the day (25), and one reported a non-significant increase (3 ms) (21). Our findings parallel those reporting a modest increase during night-time hypoglycaemia. In contrast, studies in type 2 diabetes showed no changes in QTc (56, 64, 65), although one study reported increased QTc during the day (68). Overall, the observed slight QTc elongation is an unlikely cause of malignant arrhythmias.

It is well accepted that a single beat with an extreme QTc duration may initiate malignant arrhythmia (26, 27). Thus, the higher end of the QTc time distribution of individual beats reflected by changes in the dispersity of the QTc length, could be a better reflection of arrhythmia risk than changes in the mean QTc length. To the best of our knowledge, no previous studies compared the distribution of QTc lengths during normoglycaemia and hypoglycaemia. We found that in addition to a slight increase in QTc, the SD of QTc is also increased during night-time hypoglycaemic vs control episodes. In line with this observation, we also found that the proportion of beats with QTc>500 ms is more than doubled during night-time hypoglycaemic compared to control events. Altogether these statistics are compatible with an increased but still very low risk of malignant arrhythmia during night-time hypoglycaemia. Furthermore, additional congenital factors (e.g. channelopathies), or acquired conditions (e.g. diarrhoeal infection) can increase baseline QTc, further exacerbating arrhythmia risk.

While we found no changes in mean P-wave, PQ and QRS interval lengths, the SDs of P-wave length and the PQ interval increased significantly during night-time hypoglycaemias. Although the importance of these changes is not known, they point to a systemic change in the whole cardiac electric cycle.

Our study has strengths that must be acknowledged. First, our study benefits from a long observation period (~7 days) of each individual participant. Our data provides ample statistical power with the use of gold standard statistical methods (mixed models) that takes into account the similarity of within person hypoglycaemia episodes. Second, our study using strict inclusion and exclusion criteria has excellent internal validity. Third, during data collection and clearing, investigators were blinded to IG values. Furthermore,

automatic arrhythmia analysis was supervised by the same specialist. Fourth, to control for diurnal changes of physiology, we used a case-control design where hypoglycaemic and control episodes were matched for the time of day as well as patient. Fifth, based on previous study results and theoretical assumptions, we selected 2 co-primary outcomes (QTc and a novel outcome: SD of normal beat times) where we corrected p values for multiple testing and run a set of sensitivity analyses utilizing different methods of QT correction. Furthermore, we investigated the frequency of beats with prolonged QTc intervals. All these sensitivity analyses confirmed our main finding. Finally, for the secondary outcomes, we corrected for multiple comparisons controlling for false discovery rate and run sensitivity analyses using different methods to define hypoglycaemic events. These sensitivity analyses further confirmed our main findings.
Our study has considerable limitations that must be addressed. The sensor used (Enlite) is an outdated device with a lower precision compared to more recent devices. Altogether the good detection rate of hypoglycaemic events reported in the literature, the fact that the hypoglycaemic events were much longer than the reported lag time between sensor and meter glucose values argues against any serious bias related to the limited precision of the Enlite sensor. This device also requires fingerprick calibration and the quality of the glucose measurement could bias our findings. However, all participants had long-standing diabetes and substantial experience in performing self-monitoring. Given, the strict inclusion criteria and the monoethnic patient population, external validity is limited. Furthermore, our study was not powered to investigate the cut-off glucose value where changes in cardiac cycle begin, and the setting did not allow us to investigate the association between sensor glucose values as a continuous value and cardiac cycle parameters.

5.2. Effects of taxane-anthracycline and taxane only treatment on cardiac function in breast cancer

In this retrospective study, we analysed changes of TTE parameters during and after chemotherapy of women with breast cancer treated with single taxane or anthracycline plus taxane-based regimens. We used EF defined by TTE as a marker of systolic function, while DT and the ratio of E and e' (E/e') were used to estimate diastolic function of the heart. Given the retrospective nature of our analysis, we didn’t analyse changes in ECG data As the ESC guideline recommends ECG testing only before treatment

(recommendation level I), but not afterwards (4), we didn't have repeated ECG recordings and couldn't analyse ECG data.

Our analysis controlled for major cardiovascular risk factors based on the ESC guideline (4). The ESC guideline specifically addresses risk factors that should be considered before starting anthracycline-based treatment, but the same recommendations are frequently applied to patients starting taxane-based treatment. These risk factors include previous MACE and previous chemotherapy with potential cardiovascular adverse effects (high risk), older age (high or medium risk depending on its value), as well as higher BMI, presence of hypertension, diabetes mellitus, hypercholesterolemia, and smoking (low risk). The guideline considers three additional factors to be very high risk: presence of heart failure, cardiomyopathy, and cardiac dysfunction caused by previous chemotherapy. However, none of these very high-risk states were present in our participants, as they would preclude receipt of the studied chemotherapy regimens.

By using linear mixed models, we found a temporary decrease of EF in patients on anthracycline plus taxane chemotherapy during 181-365 days after baseline. Thereafter, EF improved and became similar to the baseline value. Important cross-sectional determinants of EF were older age and the presence of hypertension among the known cardiovascular risk factors according to *Model 3, but* previous MACE, previous chemotherapy, BMI, diabetes mellitus, hypercholesterolemia, and smoking had no independent association with EF.

Among the markers representing diastolic function, DT showed a significant decrease in period 1 (15-180 days after treatment) compared to baseline. Thereafter, DT values improved and became similar to baseline. None of the investigated cardiovascular risk factors were independently related to DT. For E/e', we found no significant alterations over time. According to *Model 3*, independent determinants of E/e' were older age, higher BMI, presence of hypertension, and diabetes.

No statistically or clinically significant changes were detected in the measured cardiac functions in patients treated with single taxane chemotherapy. The single taxane group included 12 patients with previous (beyond 365 days) cardiotoxic chemotherapy, which is considered as a high-risk risk factor for the development of cardiovascular events according to the ESC guideline (4). Of these 12 patients, 10 received anthracycline and 6

anti-HER2 therapy. As taxane chemotherapy was not associated with any changes in any of the TTE parameters tested, no further models were run in this subgroup.

As most patients were on concurrent anti-HER2 treatment (40/45 patients in the single taxane group and 18/23 patients in the anthracycline plus taxane group) we run a sensitivity analysis after the exclusion those 5 patients not on anti-HER2 therapy. The results reinforce our findings in the main analysis showing 1) no changes in any TTE parameters in the single taxane group over time, and 2) statistically significant temporary decreases in ejection fraction with nadirs in period 2 and in deceleration time in period 1 in the anthracycline plus taxane group compared to baseline.

As the incidence, prevalence and survival rate of breast cancer improves (29), it becomes more important to follow-up patients for potential side effects of anti-cancer agents. Among them anthracyclines and taxanes have special interest, as they are frequently used. With single taxane chemotherapy, no severe cardiac side effects are expected (69) and taxane may be safer in patients with pre-existing left ventricular dysfunction in whom anthracyclines should be avoided (70). During single taxane therapy, regular monitoring of cardiac function is not recommended by the ESC Guidelines (4). However, combinations of taxane and anthracyclines requires special attention as taxanes reduce the elimination of doxorubicin, leading to higher plasma levels (71). In this setting, paclitaxel seems to be more cardiotoxic than docetaxel (72). Furthermore, docetaxel in combination with or even after anthracyclines may also increase the incidence of heart failure (73). Our findings that taxanes are not associated with clinically significant alterations of TTE parameters of systolic and diastolic function are in line with the above literature and extend these to even those patients that have a history of cardiotoxic chemotherapy.

On the contrary, anthracyclines have long been recognized as cardiotoxic agents (74), with approximately 1% of unexplained cardiomyopathy cases related to anthracyclines (75). Acute anthracycline toxicity is uncommon, often asymptomatic, and manifests as arrhythmias, pericarditis, or myocarditis (76). In line with this, our study sample did not show evidence of acute toxicity. However, subacute or chronic forms of anthracycline-related cardiotoxicity are more frequent and needs attention. In one study, early-onset chronic progressive anthracycline toxicity appeared in 20–30% of patients with new left ventricular dysfunction on imaging and 1.6–2.1% with symptomatic heart failure during

treatment. It has to be noted that anthracycline-induced cardiotoxicity associated mortality did not differ in this study from that of a matched idiopathic dilatative cardiomyopathy group (77). Also, it has been shown that delayed onset (e.g. years after treatment) cardiac dysfunction may be relatively refractory to heart failure treatment and is associated with a poor prognosis (78).

A systematic review and meta-analysis of randomized controlled trials showed a pronounced effect of anthracycline-based therapies not only on cardiac function but also on cardiac death (38). Another study found that the overall incidence of anthracycline cardiotoxicity was 9% and the median time between end of chemotherapy and cardiotoxicity development was 3.5 months. In line with our observations this study also suggested that anthracyclines related cardiac side effects develop within the first year of treatment (39). In contrast to our findings that the temporary EF decrease was present only in the first year after chemotherapy, a randomized study found that subclinical impairment of cardiac function persisted over 2 years after the end of anthracycline-based treatment protocols (40). In untreated cases, progressive decline of left ventricular function and a subsequent heart failure was observed (39). Multiple studies have shown that the risk of heart failure rises with increasing cumulative doses (79, 80).

Age is an important risk factor of heart failure in general and in breast cancer patients. Various studies found that patients over 65 years or 76 years of age have an increased incidence of congestive heart failure compared to younger ones following anthracycline containing chemotherapies (80, 81). In contrast, in our study, EF and DT recovered in patients on anthracycline-based regimen after a temporary drop, which could be related to differences in included populations and treatment regimens. First and foremost, the patients were younger than those in the aforementioned studies. Age is a remarkably strong risk factor for cardiovascular diseases; and the severity of cardiotoxicity was mainly dependent on the age of the patients (80, 81). As the repair and regeneration capacity of the heart is limited, older individuals have a greater tendency to develop cardiac disorders (82).

It has also been pointed out that for patients with pre-existing cardiovascular comorbidities undergoing different chemotherapy regimens (83) and specifically anthracycline based treatments (84-86), optimal cardiovascular treatment and care is of utmost importance to prevent early myocardial chemotherapy-induced dysfunction. Our

patients had a relatively low CV risk factor burden, and none of them had congestive heart failure at or before baseline. It should also be noted that chemotherapy protocols could differ across different studies. For example, trastuzumab augments the cardiotoxic effects of anthracyclines (87). Therefore, direct comparison of studies investigating the consequences of anthracycline therapy in breast cancer (including our results) is limited. However, our data is reassuring as it suggests that in younger patients with low CV risk burden breast cancer treatment even with an anthracycline is relatively safe and severe and irreversible cardiotoxic side effects are rare.

On the other hand, there are emerging methods that may be more sensitive to cardiac damage or may help detect changes of cardiac function earlier in patients receiving cardiotoxic chemotherapies. For example, measuring global longitudinal strain (GLS) with speckle tracking echocardiography could provide a valuable tool for the early detection of cardiac dysfunction even among patients with normal left ventricular EF. Despite its known limitations, completion of a GLS measurement is recommended for patients with moderate or high cardiovascular risk preceding potentially cardiotoxic chemotherapy. However, if serial GLS measurements are planned, it should be performed using the same machine/software by the same investigator (4). For the time being, GLS measurement is not yet available in routine practice in our department, but it may be a valuable tool for the adjustment of cardiovascular therapy in the future. Elevation of cardiac biomarkers (e.g. troponin T, natriuretic peptides) is useful to identify both clinical and subclinical forms of anthracycline-induced cardiotoxicity. These biomarkers have a reasonably high negative predictive value, but their use in clinical practice without typical symptoms (mainly chest pain, dyspnoea, or syncope) is not recommended presently in our clinic. Furthermore, cardiac MRI is also a valuable tool for detecting subclinical changes after anthracycline based therapy (61), but its routine clinical usage is limited by its high cost and time-consuming nature, as well as sparse availability.

The mechanisms of anthracycline associated cardiotoxicity are complex and a matter of debate. There are various signalling mechanisms involved in doxorubicin cardiotoxicity, including oxidative stress and cardiac mitochondrial damage, which may present within a few hours after the administration of doxorubicin (88). It is also well known that oxidative stress plays a critical role in the aging process (89). Anthracycline induces ultrastructural damage to cardiomyocytes, which eventually becomes clinically detected

due to cumulative damage. Vacuolization of the cytoplasm and loss of myofibrils are characteristic features of the myocardium undergoing fibrosis and inflammation (89). However, it has to be noted that the aging myocardium also acquires deleterious structural changes, including progressive cardiomyocyte hypertrophy, interstitial fibrosis, and inflammation, ultimately contributing to diastolic and systolic dysfunction (90). A study directly comparing the alterations found in cardiomyocytes due to aging and anthracycline-based chemotherapy has yet to be completed.

Our study has strengths that must be acknowledged. Our study has excellent internal validity, given that only a limited number of expert echocardiographers performed all investigations using standard protocols. Furthermore, the collected measures are widely used in clinical practice and supporting the practicality of our findings. Given that the ECS guideline considers taxane treatment generally safe, its effect on TTS parameters is rarely investigated in the literature. In contrast, our institutional protocol requires similar follow-up for single taxane and anthracycline containing therapies, that provides data for a negative control group. Also, the use of the gold standard method for handling time-series data provides excellent power to detect mild alterations in the outcomes despite a relatively small sample.

Our study has considerable weaknesses that must be addressed. We excluded a large proportion of potential participants because their baseline cardiological evaluations were performed in other clinics. While this resulted in the exclusion of 152 patients, we think that this exclusion is mostly related to the distance between the patient home and our hospital and thus it is unlikely to bias our findings. Another large proportion of exclusions is related to missing follow-up visits (n=146) that could indeed cause selection bias although these patients had similar baseline characteristics to included patients. Although included and excluded patients were similar in terms of the investigated characteristics, the high exclusion rate raises the possibility of selection bias and unmeasured confounders.

The timing of the follow-up visits also showed a great degree of variability. Some patients opted for regular follow-up at their local clinics but came to our clinic for baseline and some follow-up visits (is. end or change of treatment) leading to more spaced visit intervals, while other had all their follow-up visits at our institution. Given that individual visits could follow each other from every few weeks to several years, we created wide

windows of follow-up periods in our modelling. Given that most patients received anti-HER2 therapy on top of their chemotherapy regimen, we were unable to control for its effect in our analysis. However, the observation that anti-HER2 therapy had no effect on the trajectories of the investigated echocardiographic parameters in the taxane group, strongly suggests that our findings in the anthracycline group are reflecting anthracycline related changes.

6. Conclusions

6.1. Changes of the cardiac electrical cycle in type 1 diabetes during hypoglycaemia

We found no difference in hypoglycaemic and control episodes in any of the investigated parameters during the day, suggesting that daytime hypoglycaemia has no major effect on cardiac electrophysiology and is an unlikely cause of malignant arrhythmias in otherwise healthy type 1 diabetes patients. In contrast, we found slightly increased QTc duration during night-time hypoglycaemias. Although this change (which well corresponds to the literature) is mostly incompatible with a clinically increased risk of malignant arrhythmias, the fact that the SD of QTc also significantly increased, means that rarely beats may have long enough duration for triggering malignant arrhythmias, although our study sample did not include any such events. Our findings are compatible with the extremely rare observation of the 'dead-in-bed' syndrome. Overall, our results suggest that fear (and the very low theoretical risk) of malignant arrhythmias should not be a major concern when deciding on the individual glycaemic target of type 1 diabetes patients without macrovascular complications.

6.2. Effects of taxane-anthracycline and taxane only treatment on cardiac function in breast cancer

We found that anthracyclines caused temporary deteriorations in ejection fraction and deceleration time in a relatively healthy young patient population treated for breast cancer, while E/e' did not change significantly. In line with recent guidelines, we found taxane treatment to be safe from a cardiological standpoint even in patients that received a previous cardiotoxic chemotherapy or concurrent anti-HER2 therapy. The pattern of changes suggests a temporary deterioration first in diastolic function, followed by a temporary decrease in EF. This observation highlights the weakness of follow up based on EF alone, as changes in diastolic function may precede changes is systolic function. Some low-risk risk factors according to the ESC guideline (such as diabetes mellitus, hypercholesterolemia, smoking) were not independent determinants of diastolic or systolic function, while older age (high- or medium-risk risk factors according to the ESC guideline) and hypertension (low-risk risk factor according to the ESC guideline) were independent determinants of both EF and E/e'. Further studies are required to better

describe those patients most prone to clinically significant cardiac dysfunction related to anthracycline therapies.

7. Summary

Cardiac function is influenced by a variety of physiological and pathological factors acting over different time scales. Short-term exposures primarily affect cardiac electrophysiology, whereas long-term exposures can induce structural and functional alterations of the myocardium. Both mechanisms affect the risk of arrhythmias and overall cardiovascular health, but the type and extent of their effects differ.

In this thesis, we investigated two clinically relevant exposures: acute hypoglycaemia in type 1 diabetes and different chemotherapeutic regimens give for breast cancer. In type 1 diabetes, we performed continuous ECG and glucose monitoring in free-living patients. Our findings showed no significant changes during daytime hypoglycaemic episodes. Night-time hypoglycaemias were associated with a slight prolongation of QTc and increased variability of several ECG intervals, although mean heart rate and the frequency of ventricular ectopias remained unchanged. These results suggest that while the theoretical risk of malignant arrhythmias exists, it is extremely low in otherwise healthy patients and unlikely to represent a major concern for individual glycaemic targets.

For breast cancer patients, we investigated trajectories of echocardiographic measures in a retrospective cohort of women treated with either anthracycline–taxane combination therapy or taxane-only regimens. EF was used to evaluate systolic function, while DT and E/e' ratio for diastolic function. Anthracycline plus taxane treatment led to temporary reductions in EF and DT, which recovered over time. Single taxane therapy was not associated with clinically relevant alterations in any measured parameters. These observations indicate that taxane-based regimens are generally safe from a cardiological perspective, while anthracycline-containing treatments require careful monitoring.

In summary, these two studies illustrate the differences in the effect of short- and long-term cardiovascular exposures on the heart. Acute hypoglycaemia induces subtle electrophysiological alterations with a very low risk of serious arrhythmias, while anthracycline-based chemotherapy can temporarily impair myocardial function, particularly in diastolic performance. Our findings underscore the value of modality-specific monitoring – ECG for acute electrical instability and echocardiography for long-term functional changes – and provide evidence to inform clinical management strategies aimed at minimizing cardiovascular risk in both patient populations.

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9. Bibliography of the candidate's publications

Publications related to the thesis

1. Kézdi, Árpád; Horváth, Viktor J.; Vass, Viktor; Svébis, Márk M.; Kocsis, Győző; Ferencz, Viktória; Jávorfi, Tamás; Domján, Beatrix A.; Tabák, Ádám G.
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1. Kiss, ÁT - Kézdi, Á; Békeffy, M; Koós, CsG; Körei, A; Menyhart, A; Balogh, D; Kempler, P; Tabák, Á; Horváth, VJ
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10. Acknowledgements

I would like to express my sincere gratitude to Prof. Dr. Ádám Gy. Tabák for his invaluable support and guidance throughout my research. I am also deeply thankful to my advisor, Dr. Viktor J. Horváth, for his continuous mentorship, insightful feedback, and encouragement during the course of my PhD studies.