Universitätsspital Zürich
Klinik für Kardiologie
Direktor: Prof. Dr. med. Dr. h.c. Frank Ruschitzka

Betreuung der Masterarbeit: PD Dr. med. Jelena-Rima Templin-Ghadri
Leitung der Masterarbeit: Prof. Dr. med. Dr. rer. nat. Christian Templin

Diabetes Mellitus In Takotsubo Syndrome

MASTERARBEIT

zur Erlangung des akademischen Grades
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vorgelegt von
Anna Flurina Famos (13-779-012)

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Inhaltsverzeichnis

1. Zusammenfassung

Einleitung: Die Rolle von Diabetes mellitus (DM) bei Takotsubo Syndrom (TTS) ist unklar. Es wird vermutet, dass DM möglicherweise ein protektiver Faktor für die Entstehung von TTS sei und dass DM den Verlauf von TTS günstig beeinflussen könne. In dieser Studie wurde der Einfluss von DM auf TTS mittels einer grossen Patientenkohorte untersucht.

Methoden: Die Prävalenz von DM bei Patienten mit TTS wurde untersucht. Bei TTS Patienten mit und ohne DM wurde der klinische Verlauf, sowie die Mortalität und die Rate schwerer kardialer und zerebrovaskulärer Komplikationen (MACCE) im Kurz- und Langzeitverlauf verglichen. In einer Subgruppenanalyse von TTS Patienten mit DM wurde der Einfluss einer Insulintherapie auf den klinischen Verlauf, sowie die Mortalitäts- und MACCE-Rate nach jeweils 30 Tagen untersucht.

Resultate: Von 2061 Patienten mit TTS hatten 316 (15.3%) einen DM. TTS Patienten mit DM hatten einen ungünstigeren klinischen Verlauf. Die Mortalitäts- und MACCE-Rate nach jeweils 30 Tagen waren nicht signifikant unterschiedlich in beiden Gruppen. Die 5-Jahres-Mortalitätsrate war signifikant höher bei TTS Patienten mit DM als bei TTS Patienten ohne DM. In einer Subgruppenanalyse der TTS Patienten mit DM hatten TTS Patienten mit Insulintherapie einen komplikationsärmeren Verlauf als TTS Patienten ohne Insulintherapie. Die Mortalitäts- und MACCE-Rate nach jeweils 30 Tagen waren nicht signifikant unterschiedlich zwischen TTS Patienten mit und ohne Insulintherapie.

Konklusion: Die ermittelte Prävalenz von DM bei Patienten mit TTS liegt bei 15.3%. TTS Patienten mit und ohne DM haben eine ähnliche Kurzzeitprognose, obwohl der klinische Verlauf von TTS Patienten mit DM komplikationsreicher ist. Die Langzeitprognose ist für TTS Patienten mit DM schlechter als für TTS Patienten ohne DM. Die Subgruppenanalyse weist auf einen potentiell milderen Verlauf von TTS bei Patienten mit Insulintherapie hin.

2. Begleittext

2.1. Einleitung

Beim Takotsubo Syndrom (TTS) handelt es sich um ein akutes, reversibles Herzinsuffizienzsyndrom (1,2). Das TTS ist gekennzeichnet durch eine akute Wandbewegungsstörung mit oftmals reduzierter Ejektionsfraktion (1–3). Typischerweise sind Frauen postmenopausalen Alters betroffen und dem TTS kann ein physischer oder emotionaler Trigger vorangehen (1). Der ursächliche Mechanismus des TTS ist immer noch ungeklärt, es wird allerdings vermutet, dass dem TTS eine Überaktivität des sympathischen Nervensystems zugrunde liegt (4,5).

Aufgrund einer niedrigeren Prävalenz von Diabetes mellitus (DM) bei Patienten mit TTS im Vergleich zur Normalpopulation wird postuliert, dass das Vorliegen eines DM protektiv auf die Entstehung eines TTS wirke (6,7). Eine mögliche pathophysiologische Erklärung wäre die sympathische kardiale Denervierung in Folge einer fortgeschrittenen diabetischen autonomen Neuropathie, welche eine sympathische Überaktivität am Herzen verhindern könnte (8,9). Einige kleinere Studien weisen darauf hin, dass TTS Patienten mit DM eine bessere Prognose haben als TTS Patienten ohne DM (10–12). Aufgrund dieser Resultate wird vermutet, dass DM den Verlauf eines TTS begünstigen könnte. Möglicherweise gibt es auch einen Zusammenhang zwischen dem Schweregrad eines DM und dem Verlauf eines TTS (11,12). Limitationen dieser oben genannten Studien beinhalten jedoch die relativ kleinen untersuchten Patientenzahlen. Auch untersuchte das jeweilige Studiendesign nicht direkt die Rolle von DM bei TTS. Eine neuere Studie mit einem grösseren Patientenkollektiv ergab keine Hinweise auf einen positiven Effekt von DM auf den Verlauf eines TTS (13).

Angesichts der obig präsentierten widersprüchlichen Datenlage bezüglich eines potentiell protektiven Effekts von DM auf TTS versucht die vorliegende Studie diesen Effekt mit Hilfe einer grossen, internationalen Patientenkohorte zu evaluieren.

2.2. Material und Methoden

Patienten und Studiendesign: Die Daten für die vorliegende Studie wurden retrospektiv aus den Patientenakten des Internationalen Takotsubo Register

(InterTAK Register) erhoben (1,14). Dieses erfasste zum Zeitpunkt der Studie 2098 Patienten aus 35 Zentren in 11 Ländern. Als Einschlusskriterium für das Vorliegen eines TTS galten die InterTAK Kriterien (1,15). Für diese Studie diente zusätzlich ein vorliegender DM Status bei den Patienten des InterTAK Registers als Einschlusskriterium.

Ethik: Das Studienprotokoll wurde von der lokalen Ethikkommission begutachtet und bewilligt (Ethiknummer: ID PB_2017-00279).

Ziel der Studie: Um einen möglicherweise protektiven Einfluss von DM auf die Entstehung eines TTS zu finden, wurde zunächst die Prävalenz von DM bei den Patienten des InterTAK Registers erhoben. In einem nächsten Schritt wurden die Patienten des InterTAK Registers mit und ohne DM bezüglich des klinischen Verlaufs und der Prognose verglichen, um einen möglichen protektiven Faktor von DM auf den Verlauf eines TTS zu untersuchen. Hinsichtlich des klinischen Verlaufs wurde das Auftreten eines kardiogenen Schocks, die Notwendigkeit zur invasiven und nicht-invasiven Beatmung oder zur Katecholamingabe sowie die Mortalität während des Spitalaufenthaltes berücksichtigt. Für die Abschätzung der Prognose wurde die Mortalitätsrate und Rate der «Major adverse cardiac and cerebrovascular events» (MACCE) nach jeweils 30 Tagen und 5 Jahren ermittelt. Hierbei wurde MACCE als ein kombinierter Endpunkt aus Myokardinfarkt, transitorisch ischämische Attacke, zerebrovaskulärer Insult, TTS Rezidiv oder Exitus letalis definiert.

In einer Subgruppenanalyse wurden TTS Patienten mit DM mit und ohne Insulintherapie verglichen, um einen Zusammenhang des Schweregrads des DM mit dem Verlauf eines TTS zu untersuchen. Der klinische Verlauf und die Kurzzeitprognose (Mortalitäts- und MACCE-Rate nach jeweils 30 Tagen) wurden untersucht.

Statistik: Kontinuierliche Variablen wurden als Mittelwerte und Standardabweichungen oder als Mediane und Interquartilabstände, kategorische Variablen als Zahlen mit Prozentwerten dargestellt. Der Mann-Whitney-U-Test wurde verwendet, um kontinuierliche Variablen zu vergleichen, der Pearson Chi-Square Test oder Fisher's Exact Test für kategorische Variablen. Die Überlebensanalysen wurden anhand der Kaplan-Meier Methode ermittelt und die Unterschiede wurden mittels dem log-rank Test untersucht. Ein $P<0.05$ wurde als statistisch signifikant

definiert. Die statistischen Analysen wurden mit SPSS Version 23.0 durchgeführt (IBM Corp, Armonk, NY, USA). Alle Abbildungen wurden mit der Prism 7 Software (GraphPad, La Jolla, CA, USA) erstellt.

2.3. Resultate

Prävalenz von DM: 2061 Patienten aus dem InterTAKRegister mit bekanntem Diabetes-Status wurden in die Studie eingeschlossen. Davon hatten 316 Patienten einen DM (15.3% insgesamt, 14.5% der Frauen und 23.1% der Männer).

Klinischer Verlauf: TTS Patienten mit DM entwickelten häufiger einen kardiogenen Schock und mussten häufiger invasiv und nicht-invasiv beatmet werden als TTS Patienten ohne DM. Die intrahospitale Mortalität und die Notwendigkeit zur Katecholamingabe unterschieden sich nicht signifikant zwischen den beiden Gruppen (intrahospitale Mortalität: 4.7% vs. 4.2%, P=.65, Katecholamingabe: 14.9% vs. 11.6%, P=.10).

Prognose: Es gab keinen signifikanten Unterschied in der Mortalitäts- und MACCE-Rate nach 30 Tagen zwischen den TTS Patienten mit und ohne DM. Beim Follow-up nach 5 Jahren war die Mortalitäts- und MACCE-Rate bei TTS Patienten mit DM signifikant höher als bei TTS Patienten ohne DM.

Subgruppenanalyse: Von 198 TTS Patienten mit DM waren Daten zur Therapie vorhanden. 63 TTS Patienten hatten eine Insulintherapie, 135 TTS Patienten waren unter oralen Antidiabetika oder diätetischer Kontrolle. Die TTS Patienten unter Insulintherapie waren häufiger männlich, hatten häufiger physische Trigger und eine höhere Herzfrequenz bei Spitaleintritt. Zusätzlich benötigten sie weniger häufig eine Katecholamingabe während der Hospitalisation und erlitten weniger häufig einen kardiogenen Schock. In den 30 Tagen nach dem TTS Ereignis verstarben 10 Patienten (7%) ohne Insulintherapie und 2 Patienten (3%) mit Insulintherapie. Ausser diesen 10 Todesfällen trat in der Gruppe ohne Insulintherapie kein weiteres MACCE-Event auf. In der Gruppe mit Insulintherapie trat noch 1 zusätzlicher MACCE innerhalb der ersten 30 Tage auf.

2.4. Konklusion

Die präsentierte Studie ermittelte eine Prävalenz von DM von 15.3% bei Patienten mit vorliegendem TTS, wobei Geschlechterunterschiede festgestellt wurden. Für die weiblichen Patienten (n=1862, 90.3%) mit TTS lag die Prävalenz von

DM bei 14.5% und war somit niedriger als die Prävalenz von DM in den Normalpopulationen aller Regionen, aus welchen die Patientendaten des InterTAK Registers stammen (16). Diese Daten legen die Schlussfolgerung nahe, dass weibliche Patienten mit DM im Vergleich zur Normalpopulation durchaus ein niedrigeres Risiko für das Entwickeln eines TTS haben könnten. Die Prävalenz von DM bei männlichen Patienten mit TTS liess sich aufgrund der geringen Anzahl der in diese Studie eingeschlossenen männlichen Patienten (n=199, 9.7%) nicht reliabel interpretieren.

Der klinische Verlauf von TTS war bei Patienten mit DM kritischer (häufigere Notwendigkeit der invasiven und nicht-invasiven Beatmung, häufigeres Auftreten eines kardiogenen Schocks). Dennoch waren die Mortalitäts- und MACCE-Rate nach 30 Tagen bei beiden untersuchten Patientengruppen nicht signifikant unterschiedlich. Dies könnte auf einen potentiell protektiven Effekt von DM auf den Kurzzeitverlauf eines TTS hinweisen. Beim Follow-Up nach 5 Jahren war die Prognose für TTS Patienten mit DM allerdings signifikant schlechter als für TTS Patienten ohne DM. Ein langfristiger protektiver Effekt von DM scheint demzufolge eher unwahrscheinlich.

Die Subgruppenanalyse der TTS Patienten mit DM zeigte für TTS Patienten mit Insulintherapie einen milderen klinischen Verlauf (weniger häufiges Auftreten eines kardiogenen Schocks, weniger häufige Notwendigkeit der Katecholamingabe), aber eine ähnliche Kurzzeitprognose wie für TTS Patienten ohne Insulintherapie. Obwohl die Patientenzahl der Subgruppenanalyse klein ist, könnten diese Resultate auf einen milderen Verlauf eines TTS bei DM im fortgeschrittenen Stadium hindeuten.

2.5. Eigenleistung

Meine Eigenleistung bestand in der Datenerhebung für die präsentierte Studie. Aus den Patientenakten des InterTAK Registers erhob ich eine Vielzahl der für diese Studie relevanten Parameter: Diabetestyp (DM Typ 1, DM Typ 2, DM Typ 3), diabetesassoziierte Komorbiditäten (z.B. diabetische Neuropathie, diabetischer Fuss, diabetische Nephropathie), Hba1c-Wert, Glukosewerte bei Eintritt, maximale und minimale Glukosewerte während der Hospitalisation, Diabetestherapie (Insulintherapie, Orale Antidiabetika (Biguanid-Derivate, Glitazone, Sulfonylharnstoffe, Glinide, Inkretine, DPP-4-Inhibitoren, Alpha-Glucosidasehemmer, SGLT-2-Inhibitoren), diätetische Therapie).

Nachdem ich die Daten aller Patienten zusammengetragen und bereinigt hatte, erwarb ich Grundkenntnisse in der Anwendung der Statistikprogramme SPSS und Prism. Mit der Unterstützung des InterTAK Teams konnte ich die kategorischen und kontinuierlichen Daten der Subgruppenanalyse mittels Pearson Chi-Square Test und Mann-Whitney-U-Test auswerten.

In einem nächsten Schritt besuchte ich den Kurs «Erfolgreiches Recherchieren für die Masterarbeit», um mich optimal auf das wissenschaftliche Arbeiten vorzubereiten. Durch die im Kurs erworbenen Fähigkeiten und mit Hilfe des InterTAK Teams konnte ich eine erste Version der Kapitel «Introduction» und «Study Population» des Manuskripts formulieren. Diese wurden danach vom InterTAK Team überarbeitet.

Das Manuskript wird aktuell durch die Koautoren begutachtet. Das Paper wird anschliessend beim European Journal of Heart Failure mit folgender Autorenliste eingereicht werden:

Sebastiano Gili, MD; Davide Di Vece, MD; Ken Kato, MD, PhD; Stjepan Jurisic; Victoria L. Cammann; Jozef Micek; **Flurina Famos**; Alessandro Candreva, MD; Beatrice Bacchi; Konrad A. Szawan; MD; Aurelio Rossi, Eduardo Bossone, MD; Rodolfo Citro, MD, PhD; Jennifer Franke, MD; L. Christian Napp, MD; Milosz Jaguszewski, MD; Michel Noutsias, MD; Thomas Münzel, MD; Maike Knorr, MD; Susanne Heiner, MD; Hugo A. Katus, MD, PhD; Christof Burgdorf, MD; Heribert Schunkert., MD; Holger Thiele, MD; Johann Bauersachs, MD; Carsten Tschöpe, MD; Burkert. Pieske, MD; Lawrence Rajan, MD; Guido Michels, MD; Roman Pfister, MD; Alessandro Cuneo, MD; Claudius Jacobshagen, MD; Gerd Hasenfuß, MD; Mahir Karakas., MD; Wolfgang Koenig, MD; Wolfgang Rottbauer, MD; Samir M. Said, MD; Ruediger C. Braun-Dullaeus, MD; Adrian Banning, MD; Florim Cuculi, MD; Richard Kobza, MD; Thomas A. Fischer, MD; Tuija Vasankari MD; K.E. Juhani Airaksinen, MD; Grzegorz Opolski, MD; Rafal Dworakowski, MD; Philip MacCarthy, MD; PhD; Christoph Kaiser, MD; Stefan Osswald, MD; Leonarda Galiuto, MD; Filippo Crea, MD; Wolfgang Dichtl, MD, PhD; Klaus Empen, MD; Stephan B. Felix., MD; Clément Delmas, MD; Olivier Lairez, MD, PhD; Ibrahim El-Battrawy, MD; Ibrahim Akin, MD; Martin Borggrefe, MD; Ekaterina Gilyarova, MD; Alexandra Shilova, MD, PhD; Mikhail Gilyarov, MD, PhD; John D. Horowitz, MBBS, PhD; Martin Kozel, MD; Petr Tousek, MD; Petr Widimský, MD, PhD; David E. Winchester, MD; Christian Ukena,

MD; Carlo Di Mario, MD, PhD; Jeroen J. Bax, MD, PhD; Abhiram Prasad, MD; Michael Böhm, MD, Thomas F. Lüscher, MD; Fabrizio D'Ascenzo, MD, PhD; Jelena R. Ghadri, MD; Christian Templin, MD, PhD

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3. Paper

DIABETES MELLITUS IN TAKOTSUBO SYNDROME

Sebastiano Gili[1,2], MD; Davide Di Vece[1], MD; Ken Kato[1], MD, PhD; Stjepan Jurisic[1]; Victoria L. Cammann[1]; Jozef Micek[1]; Flurina Famos[1]; Alessandro Candreva[1], MD; Beatrice Bacchi[1]; Konrad A. Szawan[1]; MD; Aurelio Rossi[1], Eduardo Bossone[3], MD; Rodolfo Citro[3], MD, PhD; Jennifer Franke[4], MD; L. Christian Napp[5], MD; Milosz Jaguszewski[6], MD; Michel Noutsias[7], MD; Thomas Münzel[8], MD; Maike Knorr[8], MD; Susanne Heiner[8], MD; Hugo A. Katus[4], MD, PhD; Christof Burgdorf[9], MD; Heribert Schunkert[10,11], MD; Holger Thiele[12], MD; Johann Bauersachs[5], MD; Carsten Tschöpe[13], MD; Burkert. Pieske[13], MD; Lawrence Rajan[14], MD; Guido Michels[15], MD; Roman Pfister[15], MD; Alessandro Cuneo[16], MD; Claudius Jacobshagen[17], MD; Gerd Hasenfuß[17], MD; Mahir Karakas[18,19], MD; Wolfgang Koenig[10,11], MD; Wolfgang Rottbauer[20], MD; Samir M. Said[21], MD; Ruediger C. Braun-Dullaeus[21], MD; Adrian Banning[22], MD; Florim Cuculi[23], MD; Richard Kobza[23], MD; Thomas A. Fischer[24], MD; Tuija Vasankari[25] MD; K.E. Juhani Airaksinen[25], MD; Grzegorz Opolski[26], MD; Rafal Dworakowski[27], MD; Philip MacCarthy[27], MD; PhD; Christoph Kaiser[28], MD; Stefan Osswald[28], MD; Leonarda Galiuto[29], MD; Filippo Crea[29], MD; Wolfgang Dichtl[30], MD, PhD; Klaus Empen[31,32], MD; Stephan B. Felix[31,32], MD; Clément Delmas[33], MD; Olivier Lairez[33], MD, PhD; Ibrahim El-Battrawy[34,35], MD; Ibrahim Akin[34,35], MD; Martin Borggrefe[34,35], MD; Ekaterina Gilyarova[36], MD; Alexandra Shilova[36], MD, PhD; Mikhail Gilyarov[36], MD, PhD; John D. Horowitz[37], MBBS, PhD; Martin Kozel[38], MD; Petr Tousek[38], MD; Petr Widimský[38], MD, PhD; David E. Winchester[39], MD; Christian Ukena[40], MD; Carlo Di Mario[41], MD, PhD; Jeroen J. Bax[42], MD, PhD; Abhiram Prasad[43], MD; Michael Böhm[40], MD, Thomas F. Lüscher[44,45], MD; Fabrizio D'Ascenzo[46], MD, PhD; Jelena R. Ghadri[1], MD; Christian Templin[1,#], MD, PhD

[1] University Heart Center, Department of Cardiology, University Hospital Zurich, Zurich, Switzerland

[2] Centro Cardiologico Monzino, IRCCS, Milan, Italy

[3] Heart Department, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy

[4] Department of Cardiology, Heidelberg University Hospital, Heidelberg, Germany

[5] Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany

[6] First Department of Cardiology, Medical University of Gdansk, Gdansk, Poland

[7] Department of Internal Medicine III, Division of Cardiology, Angiology and Intensive Medical Care, University Hospital Halle, Martin-Luther-University Halle, Halle (Saale), Germany

[8] Center for Cardiology, Cardiology 1, University Medical Center Mainz, Mainz, Germany

[9] Heart and Vascular Centre Bad Bevensen, Bad Bevensen, Germany

[10] Deutsches Herzzentrum München, Technische Universität München, Munich, Germany

[11] DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany

[12] Heart Center Leipzig, University Hospital, Department of Internal Medicine/Cardiology, Leipzig, Germany

[13] Department of Cardiology, Charité, Campus Rudolf Virchow, Berlin, Germany

[14] TJ Health Partners Heart and Vascular, Glasgow KY, USA

[15] Department of Internal Medicine III, Heart Center University of Cologne, Cologne, Germany

[16] Krankenhaus „Maria Hilf" Medizinische Klinik, Stadtlohn, Germany

[17] Clinic for Cardiology and Pneumology, Georg August University Goettingen, Goettingen, Germany

[18] Department of General and Interventional Cardiology, University Heart Center Hamburg, Hamburg, Germany

[19] DZHK (German Centre for Cardiovascular Research), partner site Hamburg/Kiel/Luebeck, Hamburg, Germany

[20] Department of Internal Medicine II – Cardiology, University of Ulm, Medical Center, Ulm, Germany

[21] Internal Medicine/Cardiology, Angiology, and Pneumology, Magdeburg University, Magdeburg, Germany

[22] Department of Cardiology, John Radcliffe Hospital, Oxford University Hospitals, Oxford, United Kingdom

[23] Department of Cardiology, Kantonsspital Lucerne, Lucerne, Switzerland

[24] Department of Cardiology, Kantonsspital Winterthur, Winterthur, Switzerland

[25] Heart Center, Turku University Hospital and University of Turku, Turku, Finland

[26] Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

[27] Department of Cardiology, Kings College Hospital, Kings Health Partners, London, United Kingdom

[28] Department of Cardiology, University Hospital Basel, Basel, Switzerland

[29] Department of Cardiovascular Sciences, Catholic University of the Sacred Heart Rome, Rome, Italy

[30] University Hospital for Internal Medicine III (Cardiology and Angiology), Medical University Innsbruck, Innsbruck, Austria

[31] University Medicine Greifswald, Department of Internal Medicine B, Greifswald, Germany

[32] DZHK (German Centre for Cardiovascular Research), partner site Greifswald, Greifswald, Germany

[33] Department of Cardiology and Cardiac Imaging Center, University Hospital of Rangueil, Toulouse, France

[34] First Department of Medicine, Faculty of Medicine, University Medical Centre Mannheim (UMM) University of Heidelberg, Mannheim, Germany

[35] DZHK (German Center for Cardiovascular Research), Partner Site, Heidelberg-Mannheim, Mannheim, Germany

[36] Intensive coronary care Unit, Moscow City Hospital # 1 named after N. Pirogov, Moscow, Russia

[37] Discipline of Medicine, Basil Hetzel Institute, Queen Elizabeth Hospital, University of Adelaide, Australia

[38] Third Medical Faculty, Charles University in Prague and University Hospital Kralovske Vinohrady, Prague, Czech Republic

[39] Department of Medicine, College of Medicine, University of Florida, Gainesville FL, USA

[40] Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany

[41] Structural Interventional Cardiology, University Hospital Careggi, Florence, Italy

[42] Department of Cardiology, Leiden University Medical Centre, Leiden, The Netherlands

[43] Department of Cardiovascular Diseases Mayo Clinic, Rochester MN, USA
[44] Center for Molecular Cardiology, Schlieren Campus, University of Zurich, Switzerland
[45] Royal Brompton and Harefield Hospitals Trust and Imperial College, London, UK

[46] Division of Cardiology, Department of Medical Sciences, AOU Citta della Salute e della Scienza, University of Turin, Turin, Italy

Address of correspondence:
Christian Templin, MD, PhD, FESC
Professor of Cardiology, Director Acute Cardiac Care
Andreas Grüntzig Heart Catheterization Laboratories
University Hospital Zurich
University Heart Center - Department of Cardiology
Raemistrasse 100
8091 Zurich, Switzerland
Phone: +41 (0)44 255 9585
E-mail: Christian.Templin@usz.ch

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ABSTRACT

Aims. Diabetes mellitus (DM) is believed to have a protective role in takotsubo syndrome (TTS), although no data are available to confirm this hypothesis. In the present study, we aimed to investigate the prognostic impact of DM in TTS patients.

Methods and Results. The prevalence, clinical characteristics, and outcome of TTS patients were assessed using data from the International Takotsubo Registry. Furthermore, the type of DM and anti-diabetic therapy administered were evaluated. Of 2061 patients (90.3% females; mean age, 66.9±12.8 years), 316 (15.3%) had DM. DM type 2 was more prevalent, and 5 patients had DM type 1. Patients with DM were older, more frequently male, and presented with physical triggers more often. They had more comorbidities including hypertension, hypercholesterolemia, chronic kidney disease, and coronary artery disease, but fewer acute neurologic disorders. On admission, they showed lower left ventricular ejection fraction and a higher prevalence of atrial fibrillation. Laboratory values, including creatine kinase, C-reactive protein, white blood cells, and creatinine, were higher in patients with DM. Patients with DM also developed cardiogenic shock more frequently and required assisted ventilation more often. In-hospital and 30-day mortality rates did not differ between patients with and without DM, although DM was associated with a higher 5-year mortality rate.

Conclusions. DM has a low prevalence in TTS patients. Despite having a higher burden of comorbidities and a more severe acute clinical course, patients with DM did not show higher in-hospital or 30-day mortality rates. The long-term mortality rates were greater in patients with DM.

Key words: Takotsubo syndrome, broken heart syndrome, diabetes mellitus, outcome.

INTRODUCTION

Diabetes mellitus (DM) has been recently hypothesized to exert a protective role in takotsubo syndrome (TTS). Based on the results of a systematic literature review and of a metanalysis, which reported a lower prevalence of DM in TTS patients than in the general population, it was postulated that patients with DM may have a lower risk of developing TTS.[1,2] Further studies indicated that DM might not only prevent TTS, but may also lead to more favorable outcomes in patients developing TTS. A small study reported that patients with DM and TTS experienced a lower incidence of a composite end-point at 1 year compared to patients without DM.[3] Another single-center report not only found that patients with DM and TTS had lower rates of in-hospital complications, but also noted that patients with DM and diabetic neuropathy had fewer in-hospital complications, as compared to patients with DM and without neuropathy.[4,5] However, a recent study challenged this theory, and showed that DM does not influence the short-term outcome of TTS patients, and that DM is associated with a higher mortality at long-term follow-up.[6]

The proposed pathophysiological explanation for the potential role of DM in TTS focuses on the effects of DM on the sympathetic nervous system. Diabetic autonomic neuropathy has been shown to affect the heart from the apex towards the base, thus replicating the pattern of typical TTS forms[7]. Moreover, DM is associated with an increased catecholaminergic tone, which may lead to the downregulation of heart beta-receptors, thus explaining a potentially diminished sensitivity of myocytes to adrenergic stimulation. [8,9]

However, definite conclusions on the role of DM in TTS cannot be drawn based on current knowledge. In fact, studies supporting the protective role of DM are limited by a small sample size and the lack of a study design that directly assesses the role of DM in TTS. Therefore, in the present study, we aimed to assess whether DM affects the outcomes of patients with TTS in a large cohort of patients with TTS.

METHODS

Study population

The present analysis is based on the International Takotsubo (InterTAK) registry, which is an international multicenter registry [10,11] involving 35 centers from 11 countries in Europe, America, and Australia. Data were collected according to the guidelines of the institutional review boards and in accordance with the principles of the declaration of Helsinki.

A core team of investigators from the University Hospital of Zurich centrally reviewed all medical records of patients included in the registry, and determined the diagnosis of TTS based on an amended version [10] of the 2008 Mayo Clinic diagnostic criteria.[12] Further details on the inclusion criteria and procedures have been extensively reported.[10]

For the present analysis, all medical records were reviewed to assess the presence of DM, as well as the glycemic values on admission and during hospitalization. The DM type (type 1 and type 2) and administration of anti-diabetic therapy (insulin therapy vs. oral therapy or dietetic control) were recorded for the patients with DM. [13,14]

Study outcomes

The different in-hospital complications (death, cardiogenic shock) and acute-care treatments (invasive or non-invasive ventilation, catecholamine administration) were assessed.

The main outcome measure of the study was 30-day mortality. Mortality at 5 years was also analyzed, along with the rate of major adverse cardiovascular and cerebrovascular events (MACCE: a composite of death, myocardial infarction, stroke/transient ischemic attack [TIA], and TTS recurrence) at 30 days and 5 years. The outcomes were stratified according to the presence or absence of DM.

A sub-analysis was conducted in the group of patients with DM to assess the mortality and MACCE rates at 30 days based on the anti-diabetic therapeutic regimen (patients on insulin vs. patients not on insulin).

Statistical analysis

Continuous variables are reported as means and standard deviations or as medians and interquartile ranges (IQR), as appropriate, whereas categorical variables are reported as numbers with percentages. A nonparametric test (Mann-Whitney-U-test) was used to compare continuous variables, whereas Pearson chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate. The survival estimates were assessed using Kaplan–Meier curves and the differences were tested with the log-rank test. The cut-off for statistical significance was set at $P<.05$. Analyses were performed with SPSS version 23.0 (IBM Corp, Armonk, NY, USA), whereas figures and graphs were compiled with Prism 7 software (GraphPad, La Jolla, CA, USA). The study is registered on clinicaltrials.gov with the record number NCT01947621.

RESULTS

Study population

Of 2,098 patients enrolled in the InterTAK registry when the study was conducted, 2,061 with known DM status were included. Overall, 316 (15.3%) patients exhibited DM. Most of the diabetic patients had type 2 DM; type 1 DM was only reported in 5 cases. The prevalence of DM was 14.5% among women and 23.1% among men (*P*=.001). In patients aged ≥65 years, the DM prevalence was greater (16.2%; 15.4% in women and 29.5% in men). The DM prevalence in the group, stratified by gender and age, is shown in **Table 1**.

The main features of the study population are reported in **Table 2**. Patients with DM were older and more frequently male, as compared to patients without DM. In addition, physical triggers and comorbidities (including cardiovascular risk factors and coronary artery disease) were more prevalent among DM patients. However, patients with DM presented with acute neurologic disorders less frequently. On admission, patients with DM exhibited a lower left ventricular ejection fraction (LVEF), higher left ventricular end diastolic pressure (LVEDP), and higher prevalence of atrial fibrillation (AF; 10.8% vs. 5.7%, *P*=.002). Patients with DM also had lower creatine kinase values and higher values of white blood cells, C-reactive protein, creatinine, and blood glucose on admission. Furthermore, patients with DM exhibited higher maximum values of B-natriuretic peptide during hospitalization.

Patient outcomes

Patients with DM developed cardiogenic shock more frequently (12.7% vs. 9.1%, *P*=.048) and required invasive or non-invasive ventilation more often (21.6% vs. 15.3%, *P*=.006) than patients without DM. Despite these differences, the rate of in-hospital death did not vary between patients with and without DM.

Patients with DM did not show different 30-day mortality, as compared to patients without DM (6.8% vs. 5.2%, *P*=.39; **Figure 1**); similar results were observed for the 30-day MACCE rate (7.6% vs. 6.4%, *P*=.55; **Figure 2**). At the long-term follow-up of 5-years,

patients with DM showed higher mortality (36.1% vs. 17.9%, *P*<.001; **Figure 1**) and MACCE rates, as compared to patients without DM (44.6% vs. 30.8%, *P*=.024; **Figure 2**).

Comparison of DM therapies

Among patients with data on DM therapy, those receiving insulin therapy (n=63) were compared with those receiving oral or diet therapy (n=135). As detailed in **Table 3**, patients receiving insulin were more likely to be male and have physical triggers. These patients also had a higher heart rate on admission. Interestingly, patients receiving insulin required catecholamine administration less frequently during hospitalization. Moreover, the rate of cardiogenic shock was lower in patients receiving insulin, although this difference was not significant.

Ten patients (7%) not receiving insulin died at 30 days compared to 2 patients (3%) in the insulin group (log-rank *P*=.23). No additional MACCE were observed in patients lacking insulin therapy beyond the 10 deaths reported, whereas 1 further MACCE event had occurred in the insulin group at 30 days (log-rank *P*=.45).

DISCUSSION

The main findings of the present studies are:

1. The prevalence of DM in TTS is 15.3%, with a higher prevalence observed in men
2. DM in TTS is associated with a higher burden of comorbidities and a higher frequency of physical triggers, but a lower prevalence of neurological triggers.
3. Patients with DM and TTS showed lower LVEF, higher LVEDP, and more frequent AF, as compared to patients without DM.
4. Despite presenting with cardiogenic shock more frequently, patients with DM and TTS did not show higher short-term mortality and MACCE rates, although the 5-year mortality and MACCE rates were higher in patients with DM.

The potential protective role of DM against TTS was first proposed by Madias based on the observation that DM prevalence reported in the literature for TTS patients was 16.8% (based on 1932 published articles and case reports), which is markedly lower than the prevalence (26.9%) reported in patients aged ≥65 years in the US by the National Health and Nutrition Examination Survey (NHANES).[1,15] This observation was based on a comparison with large national databases, whereas the range of DM prevalence in TTS widely varies in the literature. A systematic review reported a DM prevalence ranging between 4% and 34% (this range was 6–19% when only considering studies including ≥100 patients),[16] a recent study focusing on DM and TTS reported a prevalence of 21.1%,[6] and the SCAAR registry study described a relatively lower prevalence of 6.5%.[17] DM prevalence, however, presents regional variations[18] that should be considered when comparing the prevalence of DM in patients with and without TTS. Our analysis, which is based on the InterTAK registry and includes patients from three different continents, found a DM prevalence of 15.3%. In particular, the prevalence of DM in patients aged ≥65 years was 16.4%, whereas the value in the general population of the same age from Europe, North America, and Western Pacific (i.e. the 3 regions from which our patient data originated) has been reported as 19.4%, 20.0%, and 26.3%, respectively, by the International Diabetes Federation (IDF).[18] Of interest, when comparing our data with those reported by the IDF, female patients from our registry

consistently showed a lower prevalence of DM, as compared to the reference populations from Europe, Northern America and Western Pacific. In general, male patients reported a prevalence comparable to the one observed in Northern America—the region with the highest DM prevalence among the 3 considered.[18,19] When analyzing patients from the InterTAK registry separately based on geographic origin **(Table 1)**, females were confirmed to have lower DM prevalence compared to the respective general populations. Meanwhile, male patients aged ≥ 60 years had a slightly higher prevalence of DM compared to the respective reference population. Given that the majority of TTS patients are female, it appears that the overall TTS patient population has a lower prevalence of DM as compared to the global population, although this result may prove true only for female patients. Even though our study is not designed to adequately provide an answer regarding the potential role of DM in preventing TTS, our data suggest that a cautious approach should be taken towards the claim of a potential protective role of DM against the occurrence of TTS.

Patients with DM showed a higher burden of comorbidities, as compared to patients without DM. This finding is not surprising, as DM patients are often characterized by a high prevalence of comorbid conditions[20.21,22] Our study found that physical triggers were more common in TTS patients with DM, consistent with the previous reports of other studies.[4,6] A more surprising finding was the lower prevalence of acute neurological events in TTS patients with DM, including intracranial hemorrhage, ischemic stroke, and seizures. DM is a known risk factor for ischemic stroke and may possibly also increase the risk of hemorrhagic stroke.[23] Therefore these findings present an interesting contradiction.

On admission, patients with DM showed more critical TTS features, as compared to patients without DM. These patients had lower LVEF, higher LVEDP, and presented with AF more often on admission. Furthermore, the patients had a more severe acute clinical course, with a higher rate of cardiogenic shock and a higher need for invasive or non-invasive ventilation. However, patients with DM did not show higher short-term mortality or MACCE rate, as compared to patients without DM. These results are consistent with those recently reported in a study by Stiermaier et al. that similarly observed a higher rate of pulmonary

edema (but not of cardiogenic shock) in patients with DM, without any differences in short-term mortality between patients with and without DM.[6] It is possible that the tendency of patients with DM to have a more critical acute condition may be attributed to the higher rate of comorbidities observed in these patients. The fact that patients with DM have a short-term mortality similar to patients without DM, despite several features indicating a more severe acute clinical course, might be due to a protective role of DM in TTS. However, further data are needed to confirm such a hypothesis. Of note, the long-term prognosis of patients with DM was significantly poorer as compared to patients without DM. Therefore, even if a protective effect of DM on TTS exists, it is still important to consider the long-term negative systemic effects of DM.

Finally, we compared patients with DM receiving insulin therapy and patients with DM not receiving insulin. Insulin therapy has been associated with worse prognosis, as compared to oral or diabetic therapy, at least with regard to atherosclerotic cardiovascular disease.[25] In our analysis, patients receiving insulin had physical triggers more frequently and a markedly higher heart rate on admission, as compared to patients not receiving insulin. Moreover, a trend towards a higher prevalence of male gender in patients receiving insulin was observed. Although these factors are known predictors of adverse prognosis in TTS, [10,26,27] the patients receiving insulin had similar short-term outcomes and required significantly less catecholamine administrations. This analysis is based on a small sub-sample of the cohort and its results should be cautiously interpreted. However, these findings suggest that interactions between TTS and DM, and DM severity may actually exist, even if they are not completely understood.

Study limitations

The present study is partly of observational nature, hence, potential interference of unknown confounding factors should be considered. As the data were collected from “real-life” clinical setting, missing data can be encountered, particularly with regard to the anti-diabetic treatment of patients with DM.

CONCLUSIONS

The prevalence of DM in TTS is probably lower than in the general population, particularly among female patients. Patients with DM and TTS have a higher burden of comorbidities and present with physical triggers more often than TTS patients without DM. These patients also have a more severe acute clinical course, characterized by lower LVEF, a higher rate of cardiogenic shock, and a more frequent need for invasive or non-invasive ventilation. Despite these unfavorable features, the short-term mortality and MACCE rates were similar in patients with and without DM. At the long-term follow-up, patients with DM showed a worse prognosis as compared to patients without DM.

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CONFLICTS OF INTEREST

Nothing to declare

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FIGURE LEGENDS

Figure 1. Kaplan Meier curves describing mortality in patients with and without diabetes mellitus. While there were no differences in 30 day mortality between patients with and without diabetes mellitus (P=0.39, Panel A) patients with diabetes mellitus had a significantly higher 5-year mortality compared to patients without diabetes mellitus (P<0.001, Panel B).

TTS, takotsubo syndrome.

Figure 2. Kaplan Meier curves describing the rate of major adverse cardiovascular and cerebrovascular events (MACCE) in patients with and without diabetes mellitus. While there were no differences in 30 day MACCE between patients with and without diabetes mellitus (P=0.55, Panel A) patients with diabetes mellitus had a significantly higher 5-year MACCE compared to patients without diabetes mellitus (P=0.024, Panel B).

TTS, takotsubo syndrome.

Table 1 Prevalence of Diabetes Mellitus Stratified by Age Groups

Age - no./total no. (%)	Overall	Male	Female	P value
≤ 60 years	66 / 531 (12.2)	11 / 70 (15.7)	55 / 461 (11.6)	0.37
60-69 years	83 / 568 (14.5)	16 / 62 (25.4)	67 / 506 (13.1)	0.008
70-79 years	103 / 625 (16.2)	13 / 50 (26.0)	90 / 575 (15.4)	0.06
≥ 80 years	64 / 337 (18.6)	6 / 17 (33.3)	58 / 320 (17.7)	0.08

Table 2 Characteristics of Patients

Characteristic	Diabetes mellitus N=316	No Diabetes mellitus N=1745	P value
Demographics			
Female gender - no./total no. (%)	270 / 316 (85.4)	1592 / 1745 (91.2)	0.001
Age - yr	68.9 ± 11.6 (N=316)	66.6 ± 12.9 (N=1745)	0.010
Symptoms and triggers - no./total no. (%)			
Chest pain	199 / 278 (71.6)	1194 / 1592 (75.0)	0.23
Dyspnea	152 / 278 (54.7)	726 / 1590 (45.7)	0.005
Physical trigger	137 / 316 (43.4)	607 / 1745 (34.8)	0.004
Emotional trigger	77 / 316 (24.4)	541 / 1745 (31.0)	0.018
ECG on admission - no./total no. (%)			
Sinus rhythm	238 / 268 (88.8)	1448 / 1547 (93.6)	0.005
ST-segment elevation	122 / 268 (45.5)	661 / 1547 (42.7)	0.39
ST-segment depression	20 / 268 (7.5)	121 / 1547 (7.8)	0.84
T-wave inversion	108 / 268 (40.3)	640 / 1547 (41.4)	0.74
Corrected QT - ms - mean±SD	463.5 ± 52.7 (N=215)	457.7 ± 46.7 (N=1189)	0.28
Imaging and haemodynamic findings			
Apical type - no./total no. (%)	221 / 316 (69.9)	1248 / 1745 (71.6)	0.55
LVEF - % *	38.7 ± 11.8 (N=271)	41.1 ± 11.4 (N=1548)	0.001
Heart rate - beats/min.	88.8 ± 21.4 (N=232)	87.5 ± 21.5 (N=1369)	0.25
Systolic blood pressure - mmHg	132.7 ± 29.4 (N=241)	130.6 ± 28.8 (N=1394)	0.30
LVEDP - mmHg	23.2 ± 8.3 (N=172)	21.6 ± 8.3 (N=1018)	0.024
Comorbidities - no./total no. (%)			
Acute neurologic disorders	17 / 283 (6.0)	152 / 1567 (9.7)	0.047
Acute psychiatric disorders	27 / 283 (9.5)	146 / 1564 (9.3)	0.91
Hypertension	267 / 315 (84.8)	1071 / 1724 (62.1)	<0.001
Hypercholesterolemia	137 / 309 (44.3)	520 / 1699 (30.6)	<0.001
Coronary artery disease - no. (%) †	65 / 273 (23.8)	216 / 1566 (13.8)	<0.001
COPD/asthma exacerbation	16 / 310 (5.2)	99 / 1692 (5.9)	0.63
Malignancy	47 / 292 (16.1)	254 / 1595 (15.9)	0.94
Laboratory values on admission - median (IQR)			
Troponin - factor increase in ULN ‡	7.30 (2.21 - 20.18) N=246	8.10 (2.71 - 23.38) N=1341	0.16
Creatine kinase - factor increase in ULN	0.81 (0.47 - 1.25) N=200	0.89 (0.56 - 1.51) N=1182	0.017
BNP - factor increase in ULN §	8.29 (2.43 - 19.06) N=84	5.71 (2.11 - 16.62) N=463	0.14
CRP - mg/l	7.25 (2.0 - 22.38) N=184	4.00 (1.44 - 11.99) N=1102	<0.001
WBC - 10x 10^3 cells/µL	10.85 (8.00 - 14.67) N=274	9.60 (7.42 - 12.28) N=1465	<0.001
Creatinine - µmol/l	81.30 (61.90 - 110.00) N=167	70.70 (59.20 - 87.00) N=934	<0.001
Blood glucose - mmol/l	9.55 (7.70 - 13.16) N=134	6.70 (5.80 - 8.11) N=721	<0.001
In-hospital complications and management - no./total no. (%)			
Death	15 / 316 (4.7)	73 / 1745 (4.2)	0.65
Cardiogenic shock	40 / 316 (12.7)	157 / 1727 (9.1)	0.048
Catecholamine administration	47 / 315 (14.9)	201 / 1735 (11.6)	0.10
Invasive or non-invasive ventilation	68 / 315 (21.6)	266 / 1735 (15.3)	0.006

Values are counts per number of patients of whom data was available. Plus-minus values are means±SD.

BNP brain natriuretic peptide, COPD chronic obstructive pulmonary disease, CRP C-reactive protein, ECG electrocardiogram, IQR interquartile range, LVEDP left ventricular end diastolic pressure, LVEF left ventricular ejection fraction, ULN upper limit of the normal, WBC white blood cells.

* LVEF (%): information from catheterization or echocardiography, if both available: catheterization.

† coexisting coronary artery disease during acute hospitalization.

‡ including upper limits of of the normal range for troponin T, high sensitive troponin t, and troponin I.

§ including upper limits of the normal range for brain natriuretic peptide and the N-terminal of prohormone brain natriuretic peptide.

Table 3 Characteristics of Patients

Characteristic	Patients with DM and known therapy N=198	Patients with Insulin therapy N=63	Patients without Insulin therapy N=135	P value
Demographics				
Female gender - no./total no. (%)	172 / 198 (86.9)	51 / 63 (81.0)	121 / 135 (89.6)	0.09
Age - yr	68.9 ± 12.1 (N=198)	67.3 ± 13.3 (N=63)	69.7 ± 11.5 (N=135)	0.35
Symptoms and triggers - no./total no. (%)				
Chest pain	117 / 175 (66.9)	27 / 51 (52.9)	90 / 124 (72.6)	0.012
Dyspnea	99 /174 (56.9)	32 / 53 (60.4)	67 / 121 (55.4)	0.54
Physical trigger	95 / 198 (48.0)	37 / 63 (58.7)	58 / 135 (43.0)	0.039
Emotional trigger	41 / 198 (20.7)	8 / 63 (12.7)	33 / 135 (24.4)	0.057
ECG on admission - no./total no. (%)				
Sinus rhythm	154 / 169 (91.1)	53 / 56 (94.6)	101 / 113 (89.4)	0.26
ST-segment elevation	70 / 169 (41.4)	18 / 56 (32.1)	52 / 113 (46.0)	0.085
ST-segment depression	12 / 169 (7.1)	3 / 56 (5.4)	9 / 113 (8.0)	0.53
T-wave inversion	74 / 169 (43.8)	29 / 56 (51.8)	45 / 113 (39.8)	0.14
Corrected QT - ms - mean±SD	463.7 ± 52.6 (N=142)	468.4 ± 65.3 (N=48)	461.3 ± 45.0 (N=94)	0.85
Imaging and haemodynamic findings				
Apical type - no./total no. (%)	144 / 198 (72.7)	50 / 63 (79.4)	94 /135 (69.6)	0.15
LVEF - % *	38.3 ± 12.2 (N=170)	38.3 ± 13.3 (N=53)	38.3 ± 11.7 (N=117)	0.58
Heart rate - beats/min.	88.2 ± 20.5 (N=142)	97.8 ± 19.5 (N=46)	83.6 ± 19.4 (N=96)	<0.001
Systolic blood pressure - mmHg	130.8 ± 29.4 (N=146)	135.5 ± 33.7 (N=48)	128.6 ± 27.0 (N=98)	0.35
LVEDP - mmHg	23.0 ± 8.3 (N=112)	24.8 ± 8.6 (N=27)	22.5 ± 8.2 (N=85)	0.28
Comorbidities - no./total no. (%)				
Acute neurologic disorders	15 / 198 (7.6)	6 / 63 (9.5)	9 / 135 (6.7)	0.48
Acute psychiatric disorders	21 / 198 (10.6)	7 / 63 (11.1)	4 / 135 (10.4)	0.88
Hypertension	173 / 198 (87.4)	54 / 63 (85.7)	119 / 135 (88.1)	0.63
Hypercholesterolemia	88 / 195 (45.1)	27 / 61 (44.3)	61 / 134 (45.5)	0.87
Coronary artery disease - no. (%) †	39 / 164 (23.8)	12 / 50 (24.0)	27 / 114 (23.7)	0.97
COPD/asthma exacerbation	8 / 198 (4.0)	2 / 63 (3.2)	6 / 135 (4.4)	0.67
Malignancy	35 / 192 (18.2)	11 / 60 (18.3)	24 / 132 (18.2)	0.98
Laboratory values on admission - median (IQR)				
Troponin - factor increase in ULN ‡	7.20 (1.97 - 22.0) N=163	5.70 (1.70 - 14.51) N=45	8.57 (1.99 - 22.46) N=118	0.33
Creatine kinase - factor increase in ULN	0.74 (0.47 - 1.20) N=131	0.79 (0.46 - 1.30) N=38	0.71 (0.48 - 1.20) N=93	0.60
BNP - factor increase in ULN §	7.93 (2.27 - 15.71) N=54	6.33 (2.50 - 16.86) N=12	7.93 (2.16 - 15.71) N=42	0.90
CRP - mg/l	7.80 (2.00 - 18.38) N=108	11.00 (2.00 - 38.70) N=31	6.00 (2.00 - 14.15) N=77	0.08
WBC - 10x 10^3 cells/µL	10.89 (8.09 - 14.73) N=177	10.98 (8.78 - 13.10) N=55	10.80 (7.88 - 15.15) N=122	0.95
Creatinine - µmol/l	81.30 (61.90 - 108.50) N=141	83.10 (67.00 - 114.90) N=43	79.60 (61.68 - 106.10) N=98	0.32
Blood glucose - mmol/l	9.50 (7.80 - 12.60) N=115	9.90 (8.05 - 14.27) N=37	9.05 (7.68 - 11.93) N=78	0.11
In-hospital complications and management - no./total no. (%)				
Death	10 / 198 (5.1)	2 / 63 (3.2)	8 / 135 (5.9)	0.41
Cardiogenic shock	26 / 198 (13.1)	6 / 63 (9.5)	20 / 135 (14.8)	0.31
Catecholamine administration	27 / 198 (13.6)	3 / 63 (4.8)	24 / 135 (17.8)	0.013
Invasive or non-invasive ventilation	52 / 198 (26.3)	19 / 63 (30.2)	33 / 135 (24.4)	0.40

Values are counts per number of patients of whom data was available. Plus-minus values are means±SD.

BNP brain natriuretic peptide, COPD chronic obstructive pulmonary disease, CRP C-reactive protein, DM diabetes mellitus, ECG electrocardiogram, IQR interquartile range, LVEDP left ventricular end diastolic pressure, LVEF left ventricular ejection fraction, ULN upper limit of the normal, WBC white blood cells.

* LVEF (%): information from catheterization or echocardiography, if both available: catheterization.

† coexisting coronary artery disease during acute hospitalization.

‡ including upper limits of of the normal range for troponin T, high sensitive troponin t, and troponin I.

§ including upper limits of the normal range for brain natriuretic peptide and the N-terminal of prohormone brain natriuretic peptide.

Figure 1

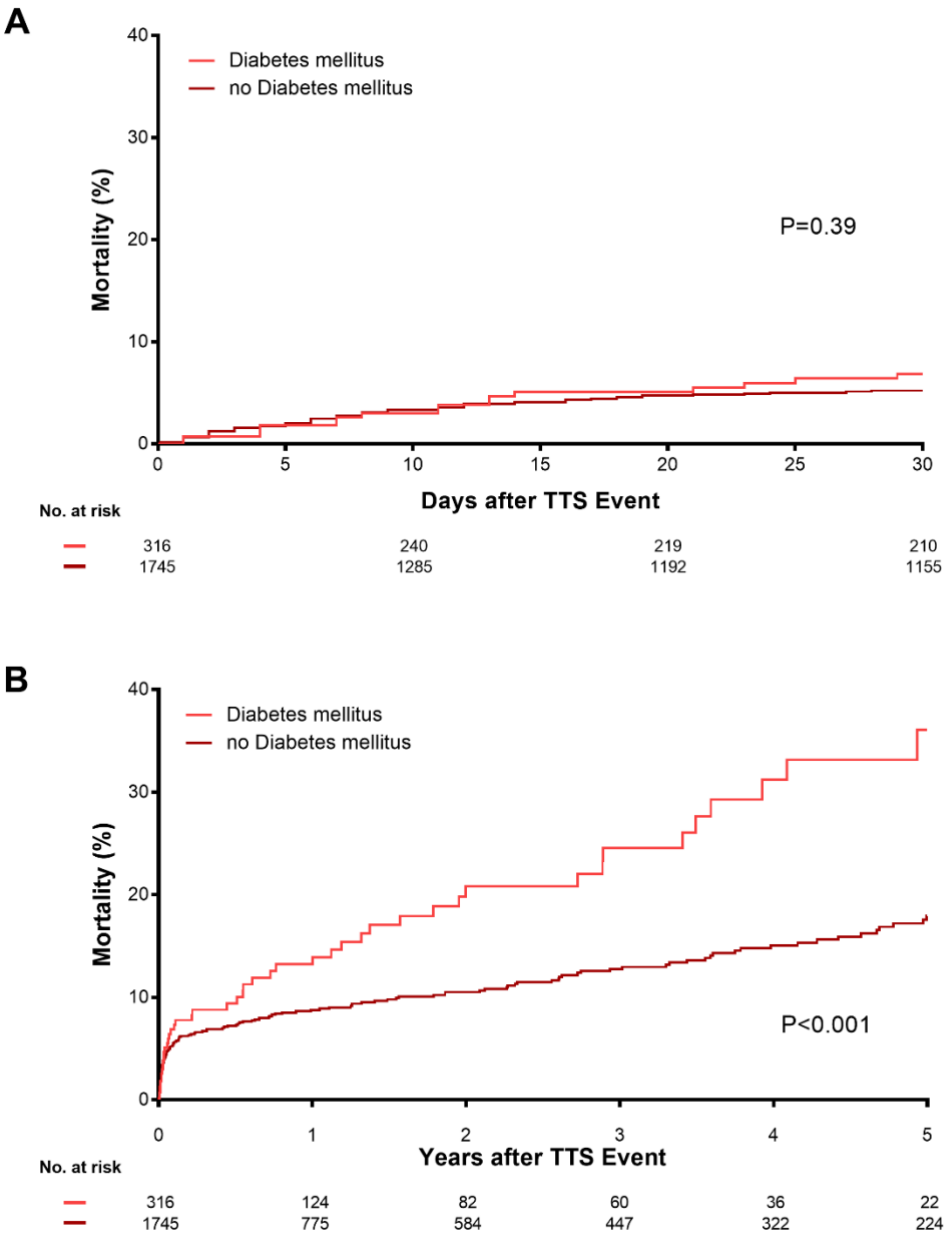
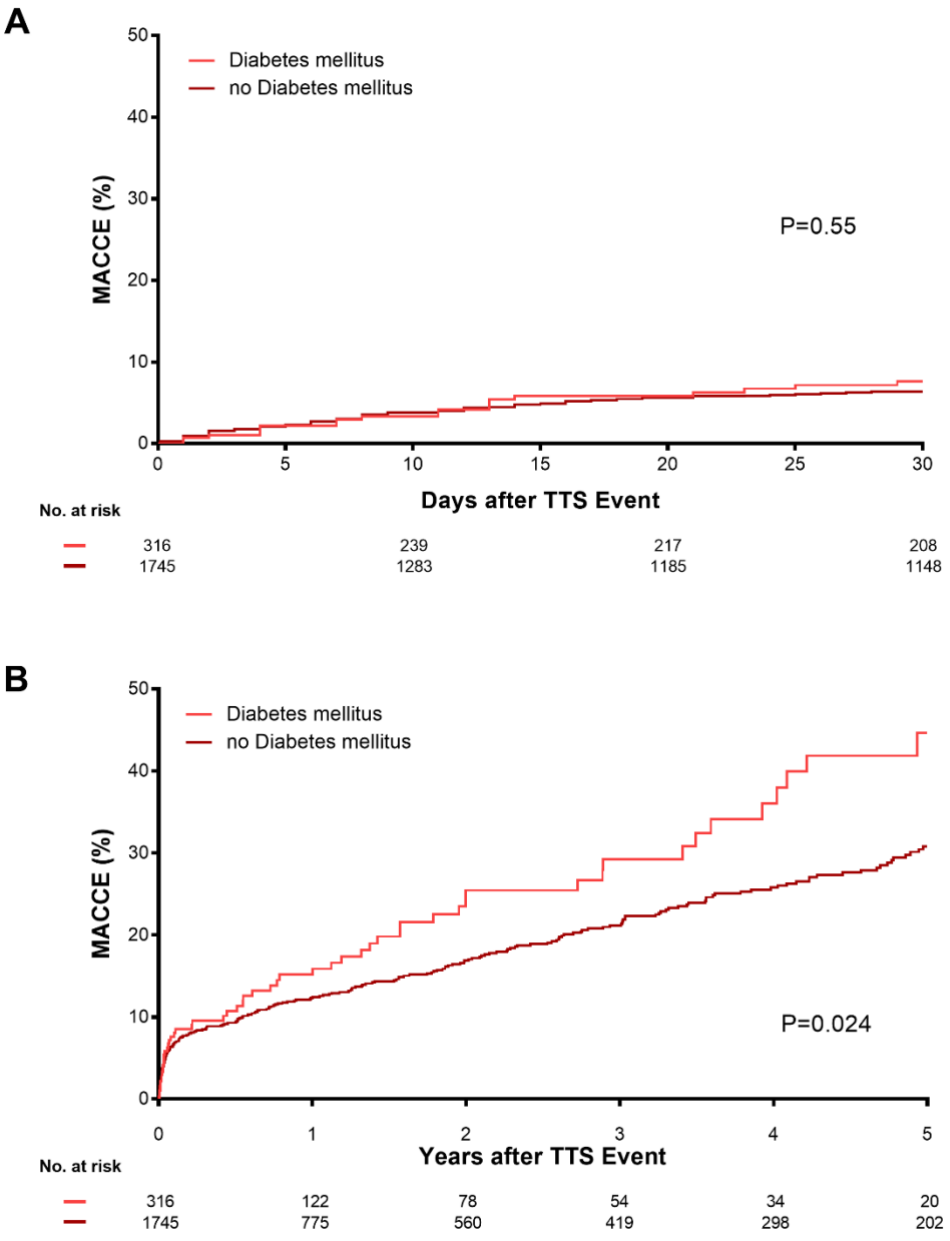

A
Diabetes mellitus
no Diabetes mellitus
Mortality (%)
40
30
20
10
0
P=0.39
0
5
10
15
20
25
30
Days after TTS Event
No. at risk
316
1745
240
1285
219
1192
210
1155
B
Diabetes mellitus
no Diabetes mellitus
Mortality (%)
40
30
20
10
0
P<0.001
0
1
2
3
4
5
Years after TTS Event
No. at risk
316
1745
124
775
82
584
60
447
36
322
22
224

Figure 2


A
Diabetes mellitus
no Diabetes mellitus
MACCE (%)
50
40
30
20
10
0
P=0.55
0
5
10
15
20
25
30
Days after TTS Event
No. at risk
316 239 217 208
1745 1283 1185 1148
B
Diabetes mellitus
no Diabetes mellitus
MACCE (%)
50
40
30
20
10
0
P=0.024
0
1
2
3
4
5
Years after TTS Event
No. at risk
316 122 78 54 34 20
1745 775 560 419 298 202

4. Danksagung

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5. Lebenslauf

Name, Vornamen	Famos Anna Flurina	
Geschlecht:	Weiblich	
Geburtsdatum:	01.02.1996	
Heimatort und Kanton:	Valsot, Graubünden	
Ausbildung:	2002 – 2005	Primarschule, Schule Niederuster, Uster
	2005 – 2007	Primarschule, Schule Hasenbühl, Uster
	2007 – 2009	Mittelschule, KS Glatttal, Dübendorf
	2009 – 2013	Mittelschule, Hohe Promenade, Zürich, Gymnasialer Maturitätsabschluss mit Schwerpunkt Englisch (Immersion) und Latein
	2014 – 2017	Bachelor Humanmedizin, Universität Zürich
	2017 – heute	Master Humanmedizin, Universität Zürich

6. Erklärung

Masterarbeit

Ich erkläre ausdrücklich, dass es sich bei der von mir im Rahmen des Studiengangs

Master of Medicine (M Med)

eingereichten schriftlichen Arbeit mit dem Titel

«Diabetes Mellitus In Takotsubo Syndrome»

um eine von mir selbst und ohne unerlaubte Beihilfe sowie *in eigenen Worten* verfasste Masterarbeit* handelt.

Ich bestätige überdies, dass die Arbeit als Ganzes oder in Teilen weder bereits einmal zur Abgeltung anderer Studienleistungen an der Universität Zürich oder an einer anderen Universität oder Ausbildungseinrichtung eingereicht worden ist.

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Sanktionen

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Ich bestätige mit meiner Unterschrift die Richtigkeit dieser Angaben.

Datum: 23.11.2019

Name: Famos Vorname: Anna Flurina

Unterschrift:……..*nur auf Printversion erforderlich*

* Falls die Masterarbeit eine Publikation enthält, bei der ich Erst- oder Koautor/-in bin, wird meine eigene Arbeitsleistung im Begleittext detailliert und strukturiert beschrieben.