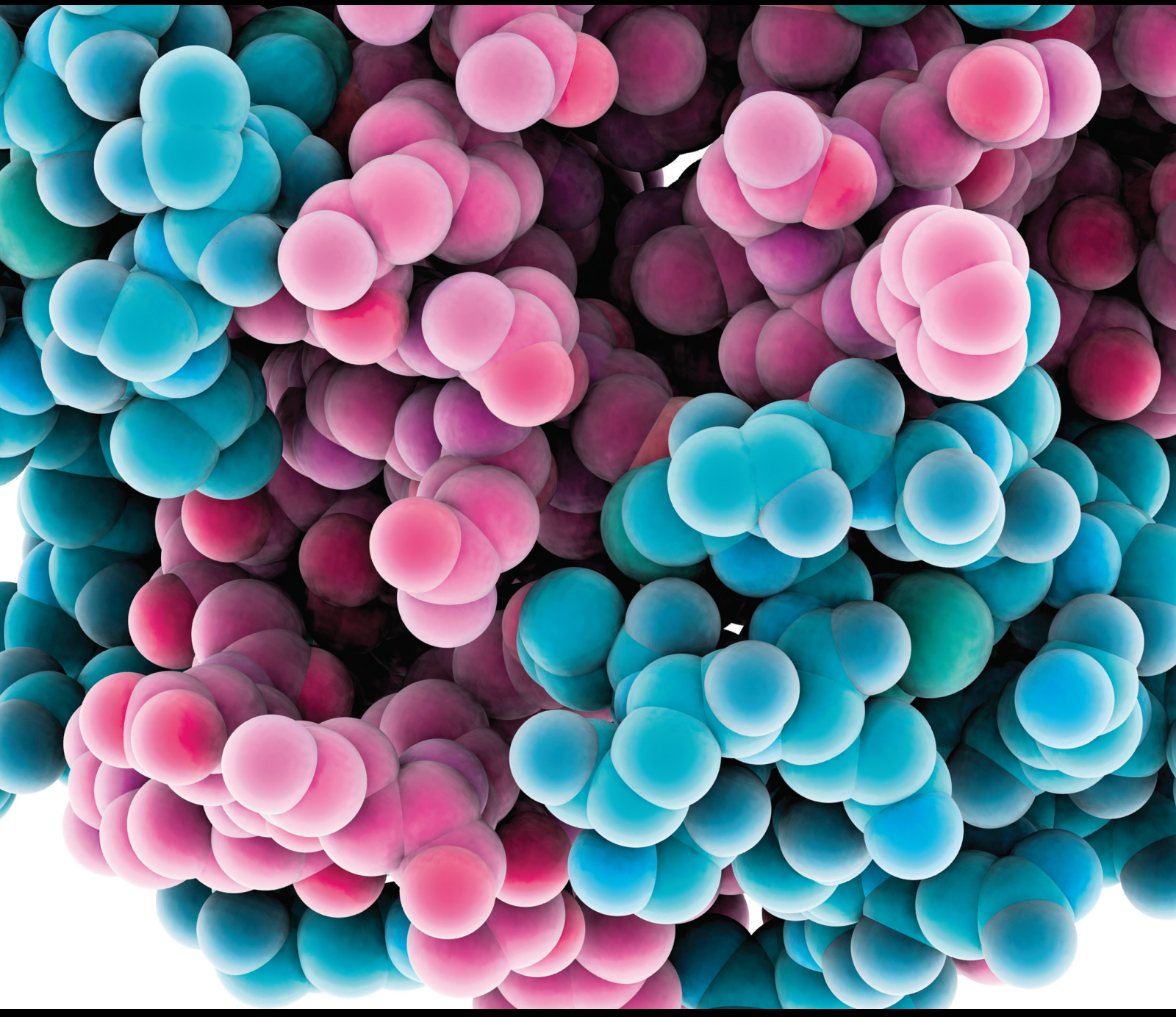
Journal of Diabetes Research

Impact of Diabetes on Different Clinical Cardiovascular Scenarios

Lead Guest Editor: Pawel Kleczynski
Guest Editors: Jacek Legutko, Krzysztof Zmudka, and Zoltan Ruzsa



Impact of Diabetes on Different Clinical Cardiovascular Scenarios

Journal of Diabetes Research

Impact of Diabetes on Different Clinical Cardiovascular Scenarios

Lead Guest Editor: Pawel Kleczynski
Guest Editors: Jacek Legutko, Krzysztof Zmudka, and Zoltan Ruzsa

Contents

Hindawi
Journal of Diabetes Research
Volume 2022, Article ID 8691842, 7 pages
https://doi.org/10.1155/2022/8691842

Research Article

Diabetes Mellitus and Clinical Outcomes in Carotid Artery Revascularization Using Second-Generation, MicroNet-Covered Stents: Analysis from the PARADIGM Study

Adam Mazurek,[1] Anna Borratynska,[2] Urszula Gancarczyk,[1] Lukasz Czyz,[1] Martyna Sikorska,[1] Lukasz Tekieli,[1,3] Bartosz Sobien,[1] Marcin Jakiel,[1] Mariusz Trystula,[4] Tomasz Drazkiewicz,[4] Piotr Podolec,[1] and Piotr Musialek[1]

[1]*Jagiellonian University, Department of Cardiac & Vascular Diseases, John Paul II Hospital, Krakow, Poland*
[2]*John Paul II Hospital, Neurology Outpatient Department, Krakow, Poland*
[3]*Jagiellonian University, Department of Interventional Cardiology, John Paul II Hospital, Krakow, Poland*
[4]*John Paul II Hospital, Department of Vascular Surgery, Krakow, Poland*

Correspondence should be addressed to Adam Mazurek; mazurekadam@yahoo.pl

Received 15 March 2022; Revised 16 June 2022; Accepted 12 August 2022; Published 26 September 2022

Academic Editor: Ike S. Okosun

Introduction. Carotid artery stenting (CAS) using conventional (single-layer) stents is associated with worse clinical outcomes in diabetes mellitus (DM) vs. non-DM patients: an effect driven largely by lesion-related adverse events. CAS outcomes with MicroNet-covered stents (MCS) in diabetic patients have not been evaluated. *Aim*. To compare short- and long-term clinical outcomes and restenosis rate in DM vs. non-DM patients with carotid stenosis treated using MCS. *Materials and Methods*. In a prospective study in all-comer symptomatic and increased-stroke-risk asymptomatic carotid stenosis, 101 consecutive patients (age 51-86 years, 41% diabetics) underwent 106 MCS-CAS. Clinical outcomes and duplex ultrasound velocities were assessed periprocedurally and at 30 days/12 months. *Results.* Baseline characteristics of DM vs. non-DM patients were similar except for a higher prevalence of recent cerebral symptoms in DM. Type 1 and type 1+2 plaques were more prevalent in DM patients (26.7% vs. 9.8%, $p = 0.02$; 62.2% vs. 37.7%, $p = 0.01$). Proximal embolic protection was more prevalent in DM (60% vs. 36%; $p = 0.015$). 30-day clinical complications were limited to a single periprocedural minor stroke in DM (2.4% vs. 0%, $p = 0.22$). 12-month in-stent velocities and clinical outcomes were not different (death rate 4.8% vs. 3.3%; $p = 0.69$; no new strokes). Restenosis rate was not different (0% vs. 1.7%, $p = 0.22$). *Conclusions.* MCS may offset the adverse impact of DM on periprocedural, 30-day, and 12-month clinical complications of CAS and minimize the risk of in-stent restenosis. In this increased-stroke-risk cohort, adverse event rate was low both in DM and non-DM. Further larger-scale clinical datasets including extended follow-ups are warranted.

1. Introduction

Diabetes mellitus type 2 (DM) not only significantly increases the risk of atherosclerotic cardiovascular disease but it is also associated with worse clinical outcomes in coronary artery disease and peripheral artery disease interventions, including interventional management of carotid artery stenosis [1]. With conventional carotid artery stenting (CAS), DM patients more frequently experience complications including peri- and postprocedural strokes [2]. Because of worse outcomes of conventional (single layer, also termed "first-generation" [3]) carotid stents in diabetic patients [2], DM has been considered, in some centers, a relative contraindication to using the endovascular route of carotid revascularization.

Regarding longer-term outcomes of atherosclerotic lesions treated with stents, DM is a major risk factor for in-stent restenosis both in the coronary tree and in the carotid arteries [4–6]. Recent evidence indicates that, in the coronaries, the

adverse impact of diabetes on postprocedural complications may be offset by using new-generation drug-eluting stents [7]. In CAS, MicroNet-covered stents (MCS) have been recently shown to effectively prevent periprocedural and long-term lesion-related cerebral embolism [8], and they may reduce clinical complications of CAS [9, 10], presenting a major improvement in the endovascular armentarium [11]. MCS outcomes in the diabetic population have not been evaluated.

We hypothesized that the dual-layer MicroNet-covered carotid stent use in CAS in primary and secondary stroke prevention in diabetic patients might offset—by plaque sealing with inhibition of cerebral embolism and the stented lumen optimization [8, 12]—the impact of DM on adverse clinical events and restenosis rate by 12 months.

2. Materials and Methods

PARADIGM (Prospective evaluation of All-comer peRcutaneous cArotiD revascularisation in symptomatic and Increased-risk asymptomatic carotid artery stenosis using CGuard™ MicroNet-covered embolic prevention stent system) is a prospective academic study in all-referral-tracked symptomatic and asymptomatic carotid stenosis, with a multispecialty neurovascular team (angiologist/cardiologist, vascular surgeon, neurologist) [13] decision-making on revascularization. Acute clinical presentation was defined as presentation within 14 days from symptoms of ipsilateral cerebral ischemia. The study enrolled unselected, consecutive patients with an independent neurologic evaluation at baseline, periprocedurally and at 1 and 12 months, and with event adjudication by an independent Clinical Events Committee (CEC) [13, 14]. CEC consisted of neurologist, cardiologist, and a vascular medicine specialist. Duplex ultrasound (DUS) was performed preprocedurally (lesions characteristics and velocities) and at 30 days and 12 months postprocedurally (in-stent material, velocities). Carotid plaque type [15] was routinely assessed on preprocedural DUS by consensus of two DUS analysts not performing interventions. Distal (filters) or proximal cerebral protection (transient flow reversal) was used in CAS [13]. The dual-layered study stent is 6F-compatible; thus, 6F sheaths were routinely used in case of filter-protected procedures. In proximal-protected cases, MoMa 9F or FlowGate 8F balloon catheters were typically used to ensure effective flow reversal to protect the brain against embolism. Stents were routinely "coronary-like" optimized, using appropriately sized balloons and high pressures [13]. The threshold for suspected restenosis on DUS follow-up was peak-systolic velocity of at least 175 cm/s [16]. Suspicion of in-stent restenosis (ISR) triggered invasive angiographic verification [12].

The PARADIGM study was registered with local Ethics Committee and has been conducted in accordance with the Declaration of Helsinki (1964). All study participants gave written consent form. The study record is registered and maintained at http://Clinicaltrial.gov (NCT04271033).

2.1. Study Outcomes. Clinical outcomes of interest included death, stroke, and myocardial infarction (MI), assessed periprocedurally, at 30 days and at 12 months). MI and stroke definitions were according to guidelines. The fundamental imaging-based outcome clinical relevance was the rate of ISR.

2.2. Study Data External Monitoring. Study data monitoring (100%) was performed, through an academic research grant, by an external clinical research organization (CRO).

2.3. Statistical Analysis. Continuous variables were compared using Student's *t*-test. Differences in proportions were evaluated with the chi-square test. The level of statistical significance was determined at $p < 0.05$. All numerical data were presented as mean and standard deviation, median and range, or as proportions. Statistical calculations were performed using STATISTICA data analysis software, version 10.0 (StatSoft, Inc., Tulsa, OK, USA).

3. Results

Baseline characteristics of DM vs. non-DM patients and lesions were similar and are depicted in Tables 1 and 2. Clinical presentation with recent symptoms (≤14 days) occurred more frequently in DM patients (20% vs. 2%; $p = 0.003$; data for DM vs. non-DM cohort). Increased-risk carotid plaque type (type 1 and type 1+2 according to Gray-Weale classification [15]) was more prevalent in DM patients (26.7% vs. 9.8%, $p = 0.02$ and 62.2% vs. 37.7%, $p = 0.01$). Combined prevalence of soft, highly-lipid carotid plaques on the one end of the spectrum, and highly calcific on the other [17], was also greater in the DM patients (82.2% % vs. 50.8%, $p < 0.001$). Consistent with the "tailored CAS" algorithm [18], the use of proximal embolic protection systems was significantly more frequent in DM patients (60.0% vs. 36.1%; $p = 0.015$).

In both study cohorts (i.e., DM and non-DM patients), most lesions were predilated (Table 2). There were no differences between the study cohorts in primary stenting rate (6.7% vs. 9.8% $p = 0.56$), mean stent diameters (8.13 mm vs. 8.21 mm, $p = 0.57$; range 7-9 mm for both), and stent length (32.2 mm vs. 33.6 mm, $p = 0.25$, range 30-40 mm in both groups). Postdilation balloon catheter diameters and pressures were also similar (maximal pressure 20.22 atm. vs. 19.31 atm, $p = 0.18$; balloon catheter diameter 5.12 mm vs. 5.24 mm, $p = 0.09$). Vascular closure device use was similar (53% vs. 57%, $p = 0.68$).

Periprocedural and 30-day outcomes were not different. There was a single periprocedural minor stroke (2.4% vs. 0%, $p = 0.22$) but no major stroke, no death, and no MI occurred. Access site closure device use rate was 55.7%, with no significant difference between DM and non-DM patients (53% vs. 57%, $p = 0.68$). The rate of access site complications requiring any intervention (such as false aneurysm thrombin injection or surgery) was 4.7% (4.4% vs. 4.9%, $p = 0.91$).

By 30 days, there were no new strokes, no postprocedural MIs, and no deaths. 12-month clinical outcomes were similar in both groups ($p = 0.70$), including 4.8% deaths in the DM cohort (mechanisms: urosepsis, chronic heart failure exacerbation) vs. 3.3% in non-DM (pulmonary embolism, pulmonary cancer). No new strokes or MIs occurred by 12 months in either group. Furthermore, restenosis rate was not different (0% vs. 1.7%, $p = 0.22$). The single in-stent restenosis (0.94%)

Table 1: Clinical characteristics of the study cohorts.

	DM ($n = 41$)	Non-DM ($n = 60$)	p value
Male (n, %)	30 (73.2)	41 (68.3)	0.60
Mean age ± SD (years, min-max)	70.54 ± 7.56 (51-86)	67.83 ± 7.23 (53-81)	0.08
Symptomatic (n, %)	25 (61)	30 (50)	0.27
Acute presentation (symptoms < 14 days) (n, %)	8 (19.5)	1 (1.7)	0.003
Prior stroke (n, %)	20 (48.8)	21 (35)	0.10
RTh (n, %)	1 (2.4)	5 (8.3)	0.22
AF (n, %)	4 (9.8)	5 (8.3)	0.81
Contralateral CAS/CEA (n, %)	2 (4.9)	10 (16.7)	0.07
CAD (n, %)	28 (68.3)	36 (60)	0.40
MI (n, %)	17 (41.5)	15 (25)	0.08
h/o CABG or PCI (n, %)	19 (46.3)	21 (35)	0.25
Arterial hypertension (n, %)	36 (87.8)	54 (90)	0.72

RTh: radiotherapy; AF: atrial fibrillation; CAS: carotid artery stenting; CEA: carotid endarterectomy; CAD: coronary artery disease; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; h/o: history of.

was effectively treated at 13 months with a drug-eluting balloon under IVUS control and distal embolic protection system use, and there was no relapse. At 12 months, a slight (though statistically significant) increase in in-stent velocities was noted in non-DM patients (peak-systolic velocity at 30 days 0.64 ± 0.24 m/s vs. 0.78 ± 0.31 m/s at 12 months; $p = 0.007$; end-diastolic velocity at 30 days 0.17 ± 0.07 m/s vs. 0.21 ± 0.09 m/s at 12 months; $p = 0.006$) but, interestingly, this did not reach statistical significance in DM patients (peak-systolic velocity at 30 days 0.73 ± 0.34 m/s vs. 0.87 ± 0.59 m/s at 12 months; $p = 0.16$; end-diastolic velocity at 30 days 0.18 ± 0.08 m/s vs. 0.22 ± 0.18 m/s at 12 months; $p = 0.14$). At each DUS time point, however, no significant differences occurred between the DM and non-DM patients (Tables 2 and 3).

4. Discussion

Our present analysis indicates that the MicroNet-covered stent use in CAS in diabetic patients (1) is associated with a low periprocedural complication rate in this otherwise high-risk population [19, 20] similar to that seen with this novel stent type in general/non-DM populations [9, 21, 22]; (2) there is absence of any signal of increased in-stent restenosis rate in MicroNet-covered stent implants in diabetic patients, and (3) the rate of 12-month adverse clinical events in DM patients treated with the use of MicroNet-covered stents is similar to that in non-DM patients.

Diabetes, independent from other risk factors, confers ≈2-fold excess risk for a wide range of atherosclerotic vascular diseases [1, 5]. Recent analysis of data for nearly 700 000 patients from 102 prospective studies showed, with diabetes, adjusted hazard ratio for ischemic stroke of 2.27 (95% CI 1.95-2.65) [5]. Women with diabetes may be at a particularly large risk [23]. In atherosclerotic carotid stenosis, luminal narrowing > 50% and diabetes duration significantly increase the risk of stroke ($p < 0.001$) [6]. This risk is not amenable to any sufficient control with classic optimized medical therapy (high-dose statin titrated to achieve guideline-indicated LDL-cholesterol level, antiplatelet agent, ACEI/ARB) [13], and it is also not reduced with gliflozines [24]. Thus, procedural low-risk carotid revascularization with plaque sealing [11] (on top of maximized medical therapy) might play an important role in durable stroke risk reduction [25] in diabetic patients with increased stroke-risk carotid stenosis. An important aspect of diabetes in the context of conventional cardiovascular interventions is that DM is associated with a permanent prothrombotic state that may importantly enhance the risk of stent thrombosis and restenosis [26]. The present study indicates that endovascular carotid revascularization using MCS is safe and effective also in diabetic patients who, with prior-generation CAS, are at increased risk of adverse events. This work expands our prior findings for patients with highly calcific carotid lesions [27] (a "classic" contraindication to conventional-stent CAS, similar to DM presenting, in view of some operators, a contraindication to conventional CAS), showing that CAS using a second-generation, MicroNet-covered stent can be performed safely and effectively also in increased-risk populations.

Our present work provides grounds for a hypothesis that the risk of lesion-related adverse events in CAS might be, at least in part, offset using MCS—similar to the role played by drug-eluting (rather than bare-metal) stents in coronary revascularization in diabetic patients [7, 28, 29]. This hypothesis requires further elucidation in larger patient cohorts.

First-generation (single-layer) carotid stents fail to sequestrate the atherosclerotic plaque [3, 30–32]. The unwanted phenomenon of plaque prolapse is not eliminated using closed-cell single-layer stents [31, 32]. In contrast, it can be effectively abolished with MCS use [11, 12]. This may be clinically important as a large proportion of peri- and postprocedural CAS complications is lesion-level based [11]. There is ample evidence that in CAS using conventional carotid stents, diabetes significantly increases the risk major adverse events including perioperative stroke (OR 1.38, 95% CI: 1.02-1.88, $p = 0.04$), death (OR 1.94, 95% CI: 1.36-2.75, $p = 0.0002$), the composite endpoint of perioperative stroke or death (OR 1.80, 95% CI: 1.32-2.47, $p = 0.0002$), and the risk of long-term death (OR 1.57, 95% CI: 1.22-2.03, $p = 0.0005$) [2]. DM patients with carotid disease suffer more frequently from symptoms of

Table 2: Study lesions and index procedure characteristics and in-stent velocities at follow-up.

	DM ($n = 45$)	Non-DM ($n = 61$)	p value
RICA (n, %)	25 (55.6)	32 (52.5)	0.75
Both sides (n, %)	4 (8.9)	1 (1.6)	0.08
Diameter stenosis; QCA (%)	84.1 ± 0.09	82.2 ± 0.10	0.34
Lesion length (mm)	18.7 ± 6.28	20.4 ± 5.60	0.15
Plaque type			
Type 1 (%)*	12 (26.7)	6 (9.8)	0.02
Type 2 (%)*	16 (35.6)	17 (27.9)	0.40
Type 3 (%)*	4 (8.9)	16 (26.2)	0.02
Type 4 (%)*	4 (8.9)	14 (22.9)	0.06
Type 5 (%)*	9 (20.0)	8 (13.1)	0.34
Type 1+2 (%)*	28 (62.2)	23 (37.7)	0.01
Type 1+2+5 (%)*	37 (82.2)	31 (50.8)	<0.001
Baseline PSV (m/s)	3.64 ± 1.06	3.75 ± 1.3	0.65
Baseline EDV (m/s)	1.21 ± 0.59	1.28 ± 0.72	0.58
Proximal EPD (n, %)	27 (60)	22 (36.1)	0.014
Distal EPD (n, %)	18 (40)	39 (63.9)	
Direct stenting (n, %)	3 (6.7)	6 (9.8)	0.56
Max. postdilatation pressure (mean ± SD; atm)	20.22 ± 3.44	19.31 ± 4.44	0.18
Postdilatation balloon catheter diameter (mean ± SD; mm)	5.12 ± 0.34	5.24 ± 0.34	0.09
Residual diameter stenosis; QCA (%)	6.1 ± 0.08	5.9 ± 0.05	0.84
Stent diameter (mean ± SD; mm)	8.13 ± 0.73	8.21 ± 0.69	0.57
Stent length (mean ± SD; mm)	32.22 ± 4.2	33.61 ± 7.97	0.25
Vascular closure device use (n, %)	24 (53)	35 (57)	0.68
30-day follow-up			
PSV (m/s ± SD)	0.73 ± 0.34	0.64 ± 0.24	0.17
EDV (m/s ± SD)	0.18 ± 0.08	0.17 ± 0.07	0.60
12-month follow-up			
PSV (m/s ± SD)	0.87 ± 0.59	0.78 ± 0.31	0.37
EDV (m/s ± SD)	0.22 ± 0.18	0.21 ± 0.09	0.74

RICA: right internal carotid artery; QCA: quantitative comparative analysis; PSV: peak systolic velocity; EDV: end diastolic velocity; EPD: embolic protection device. Note that continuous variables presented as mean ± SD; *DUS plaque type according to Gray-Weale classification (type 1: uniformly unechoic or hypoechoic; type 2: predominantly (>50%) hypoechoic; type 3: predominantly (>50%) hyperechoic; type 4: uniformly hyperechoic; type 5: uniformly echogenic with posterior shadowing (calcified plaque)) [14].

Table 3: In-stent velocity change in diabetes and non-diabetes patents.

30 days–12 months	p value
Δ PSV in DM	0.16
Δ PSV in non-DM	0.007
Δ EDV in DM	0.14
Δ EDV in non-DM	0.006

PSV: peak systolic velocity; EDV: end diastolic velocity for raw velocity values see Table 2.

cerebral ischemia, with DM-associated increased thrombotic activity as a leading potential mechanism [33].

In absence of plaque sequestration [11], diabetes significantly increases the risk of in-stent restenosis [34]. In conventional carotid stents, this mid/long-term complication may not be clinically benign [35], and it importantly contributes to CAS overall adverse events in relation to CEA [36]. Recent data suggest that a proportion of "in-stent restenoses" in single-layer (conventional) stents may represent plaque progression into the lumen [12]; an adverse phenomenon is amenable to elimination with MCS [11, 12]. This is important because "in-stent restenosis" is associated with an increased risk of recurrent stroke [24, 25], and it poses a significant management challenge [12, 37, 38].

Recent prospective analysis of conventional carotid stent CAS in 563 symptomatic patients (17.6% with DM) demonstrated a significant increase in the risk of ipsilateral stroke with diabetes (HR = 2.361; 95% CI: 1.052–5.302, $p = 0.037$, at 30 days) [19]. The single-layer stents used in that study included mainly Carotid Wallstent (77.9%) and Precise (6.7%) [19]. By 4 years, diabetes increased the risk of ipisilateral stroke by 69.3%, increased the risk of stroke or vascular death (HR = 2.091; 95% CI: 1.267–3.451, $p = 0.004$), and the risk of stroke or any death (HR = 1.921; 95% CI: 1.269–2.908, $p = 0.002$) [19]. Moreover, that study clearly demonstrated that "ISR" > 50% increased ipsilateral stroke during follow-up by >2-fold (HR = 2.187; 95% CI: 1.173–4.078, $p = 0.014$), a finding particularly important in view of the recent data that "ISR" in single-layer stents may represent in-stent atherosclerotic plaque progression [12]. Similarly, analysis of 946 consecutive (38.2% diabetic patients) [20] first-generation-stent CAS identified diabetes as a leading risk factor for in-stent restenosis (OR = 2.82; 95% CI: 1.13–7.15, $p = 0.025$). Single-layer carotid stents in that study included Carotid Wallstent (64.6%), Accu-link (14.8%), Xact (10.4%), Vivex (6.0%), Protegè (3.6%), Precise (1.4%), and Cristallo (0.3%) [20]. Normal in-stent velocities in MCS at 30 days and 12 months, similar in non-DM and DM patients (Table 2), reflect the device normal healing and are consistent with a low restenosis rate in MCS reported by other investigators [9, 22].

Our present work needs to be viewed in the context of other pivotal studies using "mesh-covered" stents, particularly those including second-generation stents other than the MCS [39–41]. In recent dual-metallic layer stent studies by Nerla and colleagues [39, 40], their 150 CAS patient population included 27% diabetics. In absence of CAS peri- and postprocedural events by 30 days, there were three deaths and three restenosis by 12 months [39, 40]. It is unclear, however, whether the affected patients were diabetic or nondiabetic, and evaluation of any potential impact of DM on ISR in dual-metallic layer stents is warranted. Regarding MCS, two large-scale Italian registries have been recently published: IRONGUARD-1 [42, 43] and IRONGUARD-2 [10, 44]. The IRONGUARD-1 study population of 200 patients included 28% diabetics. In 61 patients, postprocedural DW-MRI was performed, indicating no difference in new cerebral ischemic lesions between DM and non-DM patients. For the five periprocedural minor stroke patients, their DM status was unfortunately not given. Nevertheless, 12-month data showed no new ischemic strokes (suggesting lack of any diabetes impact on the postprocedural stroke rate) and a single ISR that required treatment. The IRONGUARD-2 study population (733 consecutive patents) had a larger proportion of DM patients (36%). Peri- and postprocedural adverse clinical outcomes (cumulative 30-day death/stroke/MI rate of 1.2%) showed no difference between DM and non-DM patients [10]; this corroborates the present findings in our study. Also 12-month data IRONGUARD-2 showed no difference in death/stroke/MI between DM vs. non-DM patients. There were 6 incidences of ISR; however, no DM status was provided for these patients [44]. Overall, the IRONGUARD-1 [42, 43] and IRONGUARD-2 [10, 44] clinical results are in concordance with our present findings. Long-term outcomes of dual-metallic layer stents in particular require further evaluation with respect to a potential role of DM [22].

Recent evidence shows that, in single-layer carotid stent CAS, plaque characteristics play a significant role in "ISR" [45, 46]. This is consistent with in-stent plaque progression as a clinically relevant mechanism of in-stent restenosis [12]; a phenomenon eliminated by plaque sealing [11] that may play a particularly important role in diabetic patients is known to be at increased risk of "ISR."

4.1. Limitations. This is an exploratory posthoc analysis from a single-center study, and further larger-scale prospective data are needed to corroborate our findings. Moreover, our present analysis is limited to transfemoral CAS using the MicroNet-covered stent. MCS may play an important role in reducing peri- and postprocedural events also in transcervical carotid revascularization [47]. With the use of a classic first-generation carotid stent in trans-cervical carotid revascularization under "dynamic" flow reversal, in a population including 37.4% diabetic patients, periprocedural stroke/death rate was increased 2-fold (odds ratio 1.99; 95% CI: 1.01–3.92; $p = 0.046$) in symptomatic vs. asymptomatic patients, and the restenosis rate remained high at ≈4% in ≈12months [48].

5. Conclusions

MicroNet-covered stent use may offset the adverse impact of DM on periprocedural, 30-day, and 12-month clinical complications of CAS as well as the adverse impact of DM on in-stent restenosis seen with conventional carotid stents in diabetic patients. In this increased stroke-risk cohort, 12-month death/stroke/myocardial infarction and restenosis risk was low both in DM and non-DM patients. Further, larger-scale multicentric clinical data are needed.

Data Availability

Inquiries for the study data can be directed to the corresponding author.

Conflicts of Interest

PM consulted for Abbot Vascular, InspireMD, and Medtronic and is a proctor for InspireMD and Medtronic. PM was Co-Principal Investigator in the CGuard CARENET study and is currently Co-Principal Investigator in the CGUARDIANS FDA-IDE Trial. Other authors have no conflicts of interest to declare.

Acknowledgments

This work was supported by the Jagiellonian University Medical College (K/ZDS/007819, N41/DBS/000822) and the John Paul II Hospital in Krakow Research Fund.

References

[1] L. M. Wei, Y. Q. Zhu, Y. Q. Bao et al., "Atherosclerosis in intracranial or extracranial vessels in diabetic patients and the association with stroke subtype," *Quantitative Imaging in Medicine and Surgery*, vol. 9, no. 6, pp. 960–967, 2019.

[2] M. A. Hussain, S. A. Bin-Ayeed, O. Q. Saeed, S. Verma, and M. Al-Omran, "Impact of diabetes on carotid artery revascularization," *Journal of Vascular Surgery*, vol. 63, no. 4, pp. 1099–1107.e4, 2016.

[3] I. Nakagawa, M. Kotsugi, H. S. Park et al., "Near-infrared spectroscopy carotid plaque characteristics and cerebral embolism in carotid artery stenting," *EuroIntervention*, vol. 17, no. 7, pp. 599–606, 2021.

[4] S. J. Hong, M. H. Kim, T. H. Ahn et al., "Multiple predictors of coronary restenosis after drug-eluting stent implantation in patients with diabetes," *Heart*, vol. 92, no. 8, pp. 1119–1124, 2006.

[5] N. Sarwar, P. Gao, S. R. Seshasai et al., "Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies," *The Lancet*, vol. 375, no. 9733, pp. 2215–2222, 2010.

[6] M. Noh, H. Kwon, C. H. Jung et al., "Impact of diabetes duration and degree of carotid artery stenosis on major adverse cardiovascular events: a single-center, retrospective, observational cohort study," *Cardiovascular Diabetology*, vol. 16, no. 1, p. 74, 2017.

[7] E. Paszek, W. Zajdel, P. Musiałek et al., "Percutaneous management of long and diffused coronary lesions using newer generation drug-eluting stents in routine clinical practice: long-term outcomes and complication predictors," *Polskie Archiwum Medycyny Wewnętrznej= Polish Archives of Internal Medicine*, vol. 129, no. 6, pp. 392–398, 2019.

[8] A. Karpenko, S. Bugurov, P. Ignatenko et al., "Randomized controlled trial of conventional versus MicroNet-covered stent in carotid artery revascularization," *JACC. Cardiovascular Interventions*, vol. 14, no. 21, pp. 2377–2387, 2021.

[9] E. Stabile, G. de Donato, P. Musialek et al., "Use of dual-layered stents in endovascular treatment of extracranial stenosis of the internal carotid artery: results of a patient-based meta-analysis of 4 clinical studies," *JACC. Cardiovascular Interventions*, vol. 11, no. 23, pp. 2405–2411, 2018.

[10] P. Sirignano, E. Stabile, W. Mansour et al., "1-month results from a prospective experience on CAS using CGuard stent system: the IRONGUARD 2 study," *JACC. Cardiovascular Interventions*, vol. 13, no. 18, pp. 2170–2177, 2020.

[11] P. Musialek and G. S. Roubin, "Commentary: Double-layer carotid stents: from the clinical need, through a stent-in-stent strategy, to effective plaque isolation… the journey toward safe carotid revascularization using the endovascular route," *Journal of Endovascular Therapy*, vol. 26, no. 4, pp. 572–577, 2019.

[12] L. Tekieli, A. Mazurek, P. Pieniazek, and P. Musialek, "Symptomatic atherosclerotic plaque progression in a first-generation carotid stent: management and 5-year clinical and imaging outcome-a case report," *European Heart Journal-Case Reports*, vol. 6, no. 1, p. 489, 2022.

[13] P. Musialek, A. Mazurek, M. Trystula et al., "Novel PARADIGM in carotid revascularisation: Prospective evaluation of All-comer peRcutaneous cArotiD revascularisation in symptomatic and Increased-risk asymptomatic carotid artery stenosis using CGuard™ MicroNet-covered embolic prevention stent system," *EuroIntervention*, vol. 12, no. 5, pp. e658–e670, 2016.

[14] A. Mazurek, A. Borratynska, K. P. Malinowski et al., "MicroNET-covered stents for embolic prevention in patients undergoing carotid revascularisation: twelve-month outcomes from the PARADIGM study," *EuroIntervention*, vol. 16, no. 11, pp. e950–e952, 2020.

[15] A. C. Gray-Weale, J. C. Graham, J. R. Burnett, K. Byrne, and R. J. Lusby, "Carotid artery atheroma: comparison of preoperative B-mode ultrasound appearance with carotid endarterectomy specimen pathology," *The Journal of Cardiovascular Surgery*, vol. 29, no. 6, pp. 676–681, 1988.

[16] C. Setacci, E. Chisci, F. Setacci, F. Iacoponi, and G. de Donato, "Grading carotid intrastent restenosis: a 6-year follow-up study," *Stroke*, vol. 39, no. 4, pp. 1189–1196, 2008.

[17] K. J. Paprottka, D. Saam, J. Rübenthaler et al., "Prevalence and distribution of calcified nodules in carotid arteries in correlation with clinical symptoms," *La Radiologia Medica*, vol. 122, no. 6, pp. 449–457, 2017.

[18] P. Pieniazek, P. Musialek, A. Kablak-Ziembicka et al., "Carotid artery stenting with patient- and lesion-tailored selection of the neuroprotection system and stent type: early and 5-year results from a prospective academic registry of 535 consecutive procedures (TARGET-CAS)," *Journal of Endovascular Therapy*, vol. 15, no. 3, pp. 249–262, 2008.

[19] M. S. Randall, M. F. McKevitt, S. Kumar et al., "Long-term results of carotid artery stents to manage symptomatic carotid artery stenosis and factors that affect outcome," *Circulation. Cardiovascular Interventions*, vol. 3, no. 1, pp. 50–56, 2010.

[20] G. Simonetti, R. Gandini, F. Versaci et al., "Carotid artery stenting: a single-Centre experience with up to 8 years' follow-up," *European Radiology*, vol. 19, no. 4, pp. 982–989, 2009.

[21] J. Schofer, P. Musiałek, K. Bijuklic et al., "A prospective, multicenter study of a novel mesh-covered carotid stent: the CGuard CARENET trial (carotid embolic protection using MicroNet)," *JACC. Cardiovascular Interventions*, vol. 8, no. 9, pp. 1229–1234, 2015.

[22] E. Stabile, G. de Donato, P. Musialek et al., "Use of dual-layered stents for carotid artery angioplasty: 1-year results of a patient-based meta-analysis," *JACC. Cardiovascular Interventions*, vol. 13, no. 14, pp. 1709–1715, 2020.

[23] S. A. Peters, R. R. Huxley, and M. Woodward, "Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes," *The Lancet*, vol. 383, no. 9933, pp. 1973–1980, 2014.

[24] D. K. McGuire, B. Zinman, S. E. Inzucchi et al., "Effects of empagliflozin on first and recurrent clinical events in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a secondary analysis of the EMPA-REG OUTCOME trial," *The Lancet Diabetes and Endocrinology*, vol. 8, no. 12, pp. 949–959, 2020.

[25] A. Mazurek, A. Borratynska, T. Tomaszewski et al., "Long-term outcomes of the MicroNetcovered stent system routine use for carotid revascularization in stroke prevention: PARADIGM-extend 5 year evidence—ESC best postervol. 41, Supplement 2, pp. ehaa946–eha2404.

[26] C. Cola, S. Brugaletta, V. Martín Yuste, B. Campos, D. J. Angiolillo, and M. Sabaté, "Diabetes mellitus: a prothrombotic state implications for outcomes after coronary revascularization," *Vascular Health and Risk Management*, vol. 5, no. 1, pp. 101–119, 2009.

[27] A. Mazurek, L. Partyka, M. Trystula et al., "Highly-calcific carotid lesions endovascular management in symptomatic and increased-stroke-risk asymptomatic patients using the CGuard™ dual-layer carotid stent system: analysis from the PARADIGM study," *Catheterization and Cardiovascular Interventions*, vol. 94, no. 1, pp. 149–156, 2019.

[28] D. J. Kumbhani, A. A. Bavry, A. R. Kamdar, T. J. Helton, and D. L. Bhatt, "The effect of drug-eluting stents on intermediate angiographic and clinical outcomes in diabetic patients: insights from randomized clinical trials," *American Heart Journal*, vol. 155, no. 4, pp. 640–647, 2008.

[29] K. K. W. Olesen, M. Pareek, M. Madsen et al., "Ten-year outcomes of sirolimus-eluting versus zotarolimus-eluting coronary stents in patients with versus without diabetes mellitus (SORT OUT III)," *The American Journal of Cardiology*, vol. 125, no. 3, pp. 349–353, 2020.

[30] H. Aikawa, T. Kodama, K. Nii et al., "Intraprocedural plaque protrusion resulting in cerebral embolism during carotid angioplasty with stenting," *Radiation Medicine*, vol. 26, no. 5, pp. 318–323, 2008.

[31] T. Okazaki, S. Sakamoto, K. Shinagawa et al., "Detection of in-stent protrusion (ISP) by intravascular ultrasound during carotid stenting: usefulness of stent-in-stent placement for ISP," *European Radiology*, vol. 29, no. 1, pp. 77–84, 2019.

[32] N. Shinozaki, N. Ogata, and Y. Ikari, "Plaque protrusion detected by intravascular ultrasound during carotid artery stenting," *Journal of Stroke and Cerebrovascular Diseases*, vol. 23, no. 10, pp. 2622–2625, 2014.

[33] J. A. Beckman, M. A. Creager, and P. Libby, "Diabetes and atherosclerosis," *Journal of the American Medical Association*, vol. 287, no. 19, pp. 2570–2581, 2002.

[34] L. H. Bonati, J. Gregson, J. Dobson et al., "Restenosis and risk of stroke after stenting or endarterectomy for symptomatic carotid stenosis in the International Carotid Stenting Study (ICSS): secondary analysis of a randomised trial," *Lancet Neurology*, vol. 17, no. 7, pp. 587–596, 2018.

[35] B. K. Lal, K. W. Beach, G. S. Roubin et al., "Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial," *Lancet Neurology*, vol. 11, no. 9, pp. 755–763, 2012.

[36] T. G. Brott, R. W. Hobson, G. Howard et al., "Stenting versus endarterectomy for treatment of carotid-artery stenosis," *The New England Journal of Medicine*, vol. 363, no. 1, pp. 11–23, 2010.

[37] L. Tekieli, P. Pieniazek, P. Musialek et al., "Zotarolimus-eluting stent for the treatment of recurrent, severe carotid artery in-stent stenosis in the TARGET-CAS population," *Journal of Endovascular Therapy*, vol. 19, no. 3, pp. 316–324, 2012.

[38] Ł. Tekieli, P. Musiałek, A. Kabłak-Ziembicka et al., "Severe, recurrent in-stent carotid restenosis: endovascular approach, risk factors. Results from a prospective academic registry of 2637 consecutive carotid artery stenting procedures (TARGET-CAS)," *Advances in Interventional Cardiology*, vol. 15, no. 4, pp. 465–471, 2019.

[39] R. Nerla, F. Castriota, A. Micari et al., "Carotid artery stenting with a new-generation double-mesh stent in three high-volume Italian centres: clinical results of a multidisciplinary approach," *EuroIntervention*, vol. 12, no. 5, pp. e677–e683, 2016.

[40] R. Nerla, A. Micari, F. Castriota et al., "Carotid artery stenting with a new-generation double-mesh stent in three high-volume Italian centres: 12-month follow-up results," *EuroIntervention*, vol. 14, no. 10, pp. 1147–1149, 2018.

[41] H. Imamura, N. Sakai, Y. Matsumoto et al., "Clinical trial of carotid artery stenting using dual-layer CASPER stent for carotid endarterectomy in patients at high and normal risk in the Japanese population," *Journal of neurointerventional surgery*, vol. 13, no. 6, pp. 524–529, 2021.

[42] F. Speziale, L. Capoccia, P. Sirignano et al., "Thirty-day results from prospective multi-specialty evaluation of carotid artery stenting using the CGuard MicroNet-covered Embolic Prevention System in real-world multicentre clinical practice: the IRON-guard study," *EuroIntervention*, vol. 13, no. 14, pp. 1714–1720, 2018.

[43] L. Capoccia, P. Sirignano, W. Mansour, E. Sbarigia, and F. Speziale, "Twelve-month results of the Italian registry on protected CAS with the mesh-covered CGuard stent: the IRON-Guard study," *EuroIntervention*, vol. 14, no. 10, pp. 1150–1152, 2018.

[44] P. Sirignano, E. Stabile, W. Mansour et al., "1-year results from a prospective experience on CAS using the CGuard stent system: the IRONGUARD 2 study," *JACC. Cardiovascular Interventions*, vol. 14, no. 17, pp. 1917–1923, 2021.

[45] S. Narumi, M. Sasaki, H. Ohba et al., "Prediction of carotid plaque characteristics using non-gated MR imaging: correlation with endarterectomy specimens," *American Journal of Neuroradiology*, vol. 34, no. 1, pp. 191–197, 2013.

[46] M. Kuwabara, S. Sakamoto, T. Okazaki et al., "Factors contributing to restenosis after carotid artery stenting and the usefulness of magnetic resonance plaque imaging: a study of 308 consecutive patients," *European Journal of Radiology*, vol. 154, article 110398, 2022.

[47] M. Trystuła and P. Musiałek, "Transient flow reversal combined with sustained embolic prevention in transcervical revascularization of symptomatic and highly-emboligenic carotid stenoses for optimized endovascular lumen reconstruction and improved peri- and post-procedural outcomes," *Advances in Interventional Cardiology*, vol. 16, no. 4, pp. 495–506, 2020.

[48] G. C. Galyfos, I. Tsoutsas, T. Konstantopoulos et al., "Editor's choice - early and late outcomes after transcarotid revascularisation for internal carotid artery stenosis: a systematic review and meta-analysis," *European Journal of Vascular and Endovascular Surgery*, vol. 61, no. 5, pp. 725–738, 2021.

Hindawi
Journal of Diabetes Research
Volume 2022, Article ID 4196195, 7 pages
https://doi.org/10.1155/2022/4196195

Research Article

Impact of Diabetes Mellitus on Early Clinical Outcome and Stent Restenosis after Carotid Artery Stenting

Alexandru Achim,[1,2] **Dávid Lackó**,[3] **Artúr Hüttl**,[3] **Csaba Csobay-Novák**,[3] **Ádám Csavajda**,[4] **Péter Sótonyi**,[3] **Béla Merkely**,[3] **Balázs Nemes**,[3] **and Zoltán Ruzsa**[2,3,4]

[1]*Department of Internal Medicine, Division of Invasive Cardiology, University of Szeged, Szeged, Hungary*
[2]*Department of Invasive Cardiology, Medicala 1 Clinic, University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania*
[3]*Semmelweis University, Cardiac and Vascular Center, Budapest, Hungary*
[4]*Bács-Kiskun County Hospital, Teaching Hospital of the Szent-Györgyi Albert Medical University, Kecskemét, Hungary*

Correspondence should be addressed to Zoltán Ruzsa; zruzsa25@gmail.com

Received 24 December 2021; Revised 28 January 2022; Accepted 9 June 2022; Published 11 July 2022

Academic Editor: Asirvatham Alwin Robert

Background. Diabetes mellitus is closely related to both the severity of carotid disease and its outcome after revascularization. Carotid artery stenting (CAS) has emerged as a viable alternative to surgical endarterectomy but little is known about the impact of diabetes after CAS. *Methods.* A consecutive cohort of 1940 patients undergoing CAS in two institutions was divided into two groups, diabetics and nondiabetics, and major cerebrovascular events (MACCEs) were analyzed at 30 days post-CAS and at 1 year follow-up. *Results.* There were 730 patients with diabetes, with significantly higher BMI, hypertension, chronic dialysis, and dyslipidemia frequency ($p < 0.05$). There was no significant difference between the two groups in terms of early and late MACCEs (composite of transient ischemic attack, major stroke, myocardial infarction, and death), with an early rate of 3.5% nondiabetics vs. 5.3%, $p = 0.08$ and 2.4 nondiabetics vs. 2.3% diabetics, $p = 0.1$ at 12 months. Overall stroke/death rate in the asymptomatic patients was 2.4%, and the restenosis rate was higher in the diabetes population (2.3% vs. 1%, $p = 0.04$). *Conclusion.* The presence of diabetes was associated with an acceptable increased periprocedural risk for CAS, but no further additional risk emerged during longer term follow-up. Diabetes may precipitate the rate of early in-stent restenosis.

1. Introduction

Diabetes mellitus (DM) has been associated with an increased prevalence and severity of carotid artery disease [1], with patients with diabetes having three times the risk of coronary disease or stroke compared to individuals without this condition [2]. Moreover, when compared with nondiabetics, diabetics have a worse outcome after cardiovascular interventions [3–6]. Internal carotid artery stenosis accounts for 10–15% of all strokes [7]. Carotid endarterectomy lowers the long-term risk of stroke in patients with symptomatic carotid stenosis [8]. Diabetes is a major risk factor for stroke, and diabetics make up 11%–40% of patients receiving carotid endarterectomy (CEA) [7]. There is inconsistent evidence regarding the correlation of DM with outcomes after CEA and little data regarding carotid artery stenting (CAS) [9]. CAS has emerged as a reliable alternative to endarterectomy because in randomized controlled trials (RCTs) comparing CAS with CEA for symptomatic carotid stenosis, stenting was associated with a higher risk of procedure-related stroke, particularly in elderly patients, but with lower risks of myocardial infarction, cranial nerve palsy, and access site hematoma [7, 10–12]. A closer look showed that the increase in procedure-related risk was powered by nondisabling stroke, with no evidence for a difference in rates of major or disabling stroke or mortality between the treatments [13, 14]. The impact of diabetes on the outcome of patients undergoing CAS remains unknown and because this procedure is expanding in both, prevalence and complexity, a rigorous

examination of its prognosis remains imperative. This prospective, multicenter, double-cohort, observational study, based on a large sample size, aimed to compare the effectiveness of percutaneous carotid revascularization in diabetic vs. nondiabetic patients and to evaluate the impact of DM on the outcomes of CAS.

2. Methods

2.1. Study Design and Patients. This retrospective two-center study was conducted on patients percutaneously treated for carotid artery stenosis during a 12-year period (January 2009-July 2021) at two high-volume Hungarian referral centers, Semmelweis University Heart and Vascular Center from Budapest and Bács-Kiskun County Teaching Hospital from Kecskemét. During this period, 1940 patients were treated due to either >50% symptomatic or >70% asymptomatic carotid stenosis, from which 730 had diabetes mellitus (37.6%) and 1210 patients were nondiabetics (62.3%). All data concerning these patients were prospectively collected in a dedicated database which contained preoperative and intraoperative data as well as perioperative results in terms of mortality and neurological and cardiac morbidity. Our Institutional Review Committee approved the study, and all patients provided written informed consent prior to study inclusion.

Inclusion criteria were as follows: (1) asymptomatic patients with carotid stenosis ≥ 70% and (2) symptomatic patients with carotid stenosis ≥ 50%, as detected by duplex ultrasound examination and confirmed by computer tomography angiography or magnetic resonance angiography using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [15]. The strategy for the revascularization method (i.e., CAS or CEA) was based on the current guideline recommendations e.g., ESVS (European Society Vascular Surgery), ACC/AHA (American College of Cardiology and American Heart Association), clinical judgment, and the desire of the patient [12, 16]. The following features excluded CAS: (1) history of acute or recent stroke (<2 weeks), (2) extreme deformity of the aortic arch or extremely tortuous carotid anatomy, or extreme calcification, (3) visible thrombus, and (4) known allergies to aspirin, clopidogrel, or contrast media.

As a further step, patients entered into the database were divided into two groups and analyzed. The first group included patients without diabetes while the second group included patients with diabetes. Patients with diabetes were considered as all those patients who had previously been diagnosed with diabetes mellitus (oral or insulin controlled glycaemia). Baseline demographic and clinical characteristics, interventional devices, stent type, procedural outcomes, and clinical complications were recorded.

Patient risk was also evaluated. Patients with a high risk of CEA were defined as those who met at least one of the following criteria: congestive heart failure (NYHA class III/IV), recent myocardial infarction (MI) in the last 4 weeks, severe angina (Canadian Cardiovascular Society class III/IV), multivessel coronary artery disease, severe COPD (GOLD III/IV), contralateral internal carotid artery occlusion; unstable carotid lesion, restenosis after CEA, unfavorable anatomy, and age ≥ 80 years.

2.2. CAS Procedures. Dual antiplatelet therapy was administered within 24 hours before the procedure. Intraoperative anticoagulation was achieved using 100 units/kg heparin. CAS was performed under local anesthesia without sedation. All aortic arch types were included. Majority of the cases were carried out via radial access, using Judkins-Right 3.5-4.0, 6.5, or 7.5-French sheathless guiding catheters (Asahi Intecc, Aichi, Japan) and in case of femoral access, the 7-French Guider-Softip XF (Boston Scientific, Marlborough, MA, USA) was preferred. CAS was performed according to the standard clinical practice, in the majority of cases using the Carotid WALLSTENT (Boston Scientific Corporation, Natick, MA, USA), Cristallo Ideale (Medtronic-Invatec, Frauenfeld, Switzerland), Roadsaver stent (Terumo, Tokyo, Japan), and Precise (Cordis Corporation, Bridgewater, NJ, USA) stents. In all procedures, we used either the EZ Filter wire (Boston Scientific, Marlborough, MA, USA) or Emboshield (Abbott Vascular, Santa Clara, CA, USA) cerebral protection device. Postdilation, to the diameter of the internal carotid artery ICA, was highly recommended (a more detailed procedural data is being presented in Table 1). Completion angiography was then performed, and a closure device was used to achieve hemostasis in all femoral cases. A successful angioplasty was defined as no more than 30 percent postintervention stenosis by the NASCET criteria.

2.3. Outcomes of Interest and Follow-Up. The primary outcome was the combined risk of any stroke, MI, or death within 30 days (perioperative). Secondary end points were the rate of stroke, death, and restenosis 1 year after the procedure. The relationship between the restenosis rate and other relevant factors such as stent design, postdilatation, antiplatelet, and/or statin therapy was also analyzed.

A major cerebrovascular clinical event (MACCE) was defined as any stroke, MI, or death. Any death, stroke, or MI < 30 days from the procedure was considered procedure-related. Stroke was defined as focal neurologic function acute disturbance that lasted over 24 h and resulted from intracranial vascular disturbance. The definition of minor strokes was neurologic deficits that resolved completely within 30 days or led to no functional impairment in daily activities. All other strokes were considered major strokes. MI was defined as the appearance of new pathologic *Q* waves on a standard electrocardiogram in two or more contiguous leads and/or a total creatinine kinase rise greater than twice the upper limit of normal with an elevated creatinine kinase myocardial band fraction. The short-term follow-up data were obtained through clinical visit or telephone. Patients were divided into the MACCE (+) group and the MACCE (–) group. Carotid restenosis was set at >50%, quantified by duplex ultrasound.

2.4. Statistical Analysis. Continuous variables with normal distribution are demonstrated as mean ± standard deviation, while categorical variables are demonstrated as number and percentage. The differences in categorical variables between the diabetic group and nondiabetic group were analyzed by

Table 1: Baseline characteristics in 1940 patients. PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; PTA: percutaneous transluminal angioplasty; COPD: chronic obstructive pulmonary disease.

	Nondiabetics ($n = 1210$)	Diabetics ($n = 730$)	p value
Age (years)	68.7 ± 12	67.4 ± 11	0.14
Male sex	547 (45%)	353 (48%)	0.17
Vascular risk factors			
Hypertension	42 (34%)	283 (39%)	0.03
Dyslipidemia	211 (17%)	136 (19%)	0.50
Chronic dialysis	114 (9%)	78 (10%)	0.36
Smoking	281 (23%)	159 (22%)	0.46
Family history	271 (22%)	166 (23%)	0.49
Previous PCI	289 (24%)	198 (27%)	0.11
Previous CABG	101 (8%)	79 (11%)	0.06
Previous carotid PTA	75 (6%)	59 (8%)	0.11
Peripheral artery disease	189 (15%)	134 (18%)	0.11
Atrial fibrillation	233 (19%)	134 (18%)	0.40
COPD	155 (12%)	89 (12%)	0.69
Degree of symptomatic carotid stenosis			
50–69%	44 (15%)	31 (16%)	0.96
70–99%	251 (85%)	175 (84%)	0.96
Indication for stenting			
Asymptomatic carotid stenosis	843 (69%)	480 (65%)	0.06
Symptomatic carotid stenosis	295 (24%)	206 (28%)	0.06
Acute carotid syndrome	72 (7%)	44 (7%)	0.94
Procedural data			
Radial access	883 (72%)	517 (70%)	0.30
Femoral access	281 (23%)	188 (25%)	0.20
Aortic arch type II/III	553 (45%)	312 (44%)	0.20
Postdilatation	1009 (83%)	602 (84%)	0.62
Predilatation	321 (26%)	201 (28%)	0.62
Closed-cell stent (WALLSTENT®)	784 (55%)	499 (54%)	0.10
Mesh-stent (Roadsaver ®)	129 (11%)	85 (12%)	0.50
Length-of-stay, days[a]	5 (3-8)	5 (3-9)	0.43

[a]Continuous variables are summarized using medians and interquartile ranges (IQR).

chi-squared test or Fisher exact test. The differences in continuous variables were analyzed by t-test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for 30-day postoperative MACCEs. SPSS version 19.0 (IBM, Chicago, IL, USA) was used for the data analysis. A $p < 0.05$ was considered statistically significant.

3. Results

In our study, 1940 patients were enrolled during the recruitment period, out of which 48 were lost to follow-up before 1 year.

Patients' characteristics at baseline were similar in the two groups (see Table 1). A total of 26.3% of patients were symptomatic. CAS was performed in symptomatic patients following ischemic stroke in 52 cases, TIA in 34 cases, and amaurosis fugax in 30 cases; 38.8% of them were in the high-risk group for CEA, and the remaining 61.2% were in the normal-risk group. There were no differences between these two groups in the terms of age ($p = 0.8$) and gender ($p = 0.2$), but the patients with diabetes had significantly higher BMI ($p < 0.002$). The frequency of hypertension ($p < 0.0001$), dyslipidemia ($p < 0.002$), and family history of cardiovascular disease ($p < 0.03$) was found to be significantly higher in the diabetic cohort. There was no difference found among these two groups in terms of coronary disease ($p = 0.2$) and smoking ($p = 0.2$). As expected, the history of previous carotid percutaneous transluminal angioplasty (PTA) was more prevalent in the diabetic group ($p < 0.0004$). Most of the patients with diabetes were on statin therapy ($n = 632$, $p < 0.01$) and had minimum an antiplatelet agent in their therapy ($n = 693$, $p < 0.01$).

3.1. Procedural Data. There were 1323 (68%) asymptomatic, 501 (25%) symptomatic carotid stenoses, and 116 (6%) acute carotid syndromes. Radial access was the most frequently

Table 2: Perioperative (< 30 days) and 1-year follow-up results among diabetic and nondiabetic patients. TIA: transient ischemic attack; MI: myocardial infarction.

	Nondiabetics ($n = 1210$)	Diabetics ($n = 730$) At 30 days	p value	Nondiabetics ($n = 1182$)	Diabetics ($n = 690$) At 12 months	p value
Minor TIA/stroke	27 (2.3%)	21 (2.8%)	0.37	33 (2.7%)	19 (2.7%)	0.96
Major stroke	14 (1.1%)	10 (1.3%)	0.68	20 (1.7%)	13 (1.8%)	0.76
MI	5 (0.4%)	5 (0.6%)	0.41	21 (1.7%)	16 (2.3%)	0.41
Death	2 (0.1%)	1 (0.1%)	0.88	25 (2.1%)	16 (2.3%)	0.77
Restenosis	0 (0%)	0 (0%)		12 (1%)	16 (2.3%)	0.04

used ($n = 1400$, 72%). The stent mostly used was Carotid WALLSTENT (Boston Scientific Corporation, Natick, MA, USA) ($n = 1284$, 66%), followed by Roadsaver stent (Terumo, Tokyo, Japan) ($n = 214$, 11%). Mean procedural duration was 35.1 ± 10.9 minutes, from which mean fluoroscopy time was 9.10 ± 6.9 minutes, generating an average radiation dose of 390 ± 32.2 mGy. The average dose of contrast administered was 109 ± 15 ml of iodinated agent. No difference in hospitalization duration was observed (nondiabetics 5 ± 2 vs. diabetics 5 ± 3 days).

3.2. Complications and Follow-Up (See Table 2). Minor procedural complications, such as bradycardia ($n = 39$, 2%) or asystole ($n = 3$, 0.1%), were more than double in the diabetic population (1.5% nondiabetics vs. 3.3% diabetics). Early (< 30 days) results showed 81 (4.1%) major cerebrovascular events. There was no statistically significant difference between the two groups (3.5% nondiabetics vs. 5.3%, $p = 0.08$). Rates of MI, transient ischemic attack (TIA), and cranial nerve injuries were also evenly distributed. A separate subanalysis showed a 2.4% stroke/death rate in the asymptomatic patients, with no difference between the two groups (2.38% nondiabetics vs. 2.43% diabetics, $p = 0.1$). Follow-up was at 12 months; during this period, 41 patients deaths (1.4%) and 85 (4.3%) ischemic strokes were reported. Overall, 163 additional MACCEs (8.7%) were recorded at 1-year follow-up, with no difference between the diabetic and nondiabetic population, 2.4% nondiabetics vs. 2.3% diabetics, $p = 0.1$ (Table 2).

At 1-year, patients with diabetes had a significantly higher restenosis rate comparing to nondiabetics (2.3% vs. 1%, $p = 0.04$). Further analysis (inverse probability treatment weighting) showed no difference between the two groups in terms of stent design (restenosis rate for WALLSTENT 54% vs. Roadsaver stent 46%, $p = 0.1$). The rate of postdilatation was significantly lower in the restenosis patients (71% vs. 86%, $p = 0.04$), with similar distribution across the diabetics and nondiabetics (diabetics 47% vs. nondiabetics 53%, $p = 0.8$).

4. Discussion

Our study showed that patients with diabetes and severe carotid stenosis share similar periprocedural stroke and death risks of nondiabetic patients when carotid stenting is applied for treatment (perioperative stroke and death rate: nondiabetics 1.7% vs. diabetics 2.0%; $p = 0.08$). Nevertheless, there is weak evidence towards a worse perioperative early outcome for patients with diabetes. Yet, according to our study, at one year follow-up, the rate of major cerebrovascular events is leveling, with similar outcomes between the two groups. Our findings are consistent with the conclusion of other previously published data [17–20]. Moreover, our early <30 days overall stroke/death rates fell under the 3% threshold in elective cases recommended by the American and European societies [12, 21]. The results of our study are of even greater relevance in the context in which the rates of 30-day stroke/death after CEA in asymptomatic patients with insulin-dependent DM exceeded international vascular societies' guideline thresholds for acceptable outcomes in asymptomatic patients, especially those with anatomic high-risk criteria [9]. General metabolic syndrome was also a risk for short-term MACCEs after CEA, but not CAS, in a 2000-chinese cohort reported by Jiao et al. [22]. However, it must be admitted that these data come from a retrospective, observational study, and our analysis did not differentiate between insulin-dependent diabetics and noninsulin-dependent diabetics.

It should be noted that the rate of early restenosis in the diabetic population was double (2.3% vs. 1%, $p = 0.04$). An important limitation of the present study is that it does not provide follow-up longer than 1 year, because diabetes could further increase risk for restenosis over time. However, this hypothesis comes from studies published more than 10 years ago, and it must be acknowledged that in the meantime, progress has been made in terms of endovascular treatment tools and new antiplatelet agents. Only Casana's study was published in 2018, showing the same trend, increased early periprocedural risk, but no further additional risk during longer term follow-up in the diabetic population undergoing CAS [23]. Restenosis rates reported by Casana et al. were also significantly higher among patients with diabetes (21.2% diabetes vs. 12.5% no diabetes at 36-months follow-up). Stent restenosis is presumed to be the result of neointimal hyperplasia, and this can be accelerated by diabetes [24], especially if the initial glycemic state, mirrored by HbA1c, is high during CAS. The early phase of stent healing seems to be influenced by the poor glycemic state rather than the diabetic condition, with good glycemic control, [25]; so, it is understandable that aiming for strict hyperglycemic optimization prior to the procedure is important. Another limitation of our study is that HbA1c was not followed; so, an in-depth analysis of the restenosis rate in association with

the baseline glycemic status could not be made. Similar mechanisms that demonstrate accelerated restenosis in diabetics have been described in other interventional fields [26–28]. It is assumed that the stenting of the coronary atherosclerotic plaque is different from the coronary plaque by the fact that in the case of CAS, the plaque is only pushed outwards, not cracked, and modified to the media, which would later stimulate intima proliferation [26].

In the literature, anatomical and technical risk factors for restenosis include the number of stents deployed, the presence of large and calcified plaques, and the existence of residual stenosis after the procedure or even the stent design used, to the detriment of stiffer stents with small cell sizes, but moderate radial force, such as WALLSTENT (Boston Scientific Corporation, Natick, MA, USA) [29, 30]. Dyslipidemia, statin therapy, female sex, and smoking were associated with CAS restenosis as well [31, 32]. Most likely, in our case, all types of stents performed well, due to the high postdilatation rate, avoiding residual lesions and metal recoil. A possible result bias could be the homogeneous population who received CAS in only 2 centers; on the other hand, the uniform skill experience of a few operators who have followed a fixed procedural protocol might have positively influenced the outcome of these patients. As diabetes appears to be an independent predictor of restenosis in several studies already, an optimal result in this subpopulation should be achieved, especially since, in the present study, the lack of postdilatation was correlated with repeat target lesion revascularization.

CAS has developed rapidly in recent years and has gradually become an alternative treatment for CEA [33, 34]. An increasing number of hospitals can carry out stent implantation, and an increasing number of patients receive stenting because it is a minimally invasive and efficient treatment; using radial access is also possible in CAS [34, 35]. Several large RCTs and meta-analyses have compared the efficacy and safety of CEA with CAS. However, to date, no RCTs have directly compared the effects of diabetes on the perioperative and long-term outcomes of patients with carotid artery stenosis after CEA or CAS surgery. Only a few observational studies have analyzed the effects of diabetes on CAS. Therefore, there is no consensus on which type of carotid revascularization should be performed in patients with DM. Our main findings provide evidence that CAS in diabetics can be performed under the same safety and feasibility conditions as CAS in general, with an emphasis on optimal control of this metabolic disease. A longer follow-up (minimum 5 years) is of great importance to validate this statement.

There are several limitations of our study that are worthy of mentioning. First, the study was retrospective, nonrandomized; although, patients were enrolled consecutively, receiving the same type of treatment, according to an internal procedural protocol. Second, the follow-up of patients is limited to 1 year; a definitive answer on clinical hard-endpoints will have to be provided at 5 and 10 years. Third, the severity of diabetes and the type of antidiabetic therapy were not known, and this could have an independent impact on MACCE.

5. Conclusion

The current study suggested that the presence of diabetes was associated with an acceptable increased periprocedural risk for CAS, but no further additional risk emerged during longer term follow-up. Diabetes may precipitate the rate of early in-stent restenosis.

Abbreviations

DM: Diabetes mellitus
CEA: Carotid endarterectomy
CAS: Carotid artery stenting
RCTs: Randomized controlled trials
MI: Myocardial infarction
MACCE: Major cerebrovascular clinical event
TIA: Transient ischemic attack.

Data Availability

Data is available upon request, and it is not deposited in a public repository due to patient personal data protection. Achim Alexandru can be contacted at dr.alex.achim@gmail.com or +40264597852 for this matter.

Disclosure

The abstract of this paper has been presented in a poster format at the Heart in Diabetes Conference, 24-26 June, Philadelphia, USA [36].

Conflicts of Interest

The authors report no financial relationships or conflicts of interest regarding the content herein. Current study received the proper ethical oversight.

References

[1] N. Katsiki and D. P. Mikhailidis, "Diabetes and carotid artery disease: a narrative review," *Ann Transl Med*, vol. 8, no. 19, p. 1280, 2020.

[2] P. Lacroix, V. Aboyans, M. H. Criqui et al., "Type-2 diabetes and carotid stenosis: a proposal for a screening strategy in asymptomatic patients," *Vascular Medicine*, vol. 11, no. 2, pp. 93–99, 2006.

[3] H. S. Gurm, I. J. Sarembock, D. J. Kereiakes et al., "Use of bivalirudin during percutaneous coronary intervention in patients with diabetes mellitus: an analysis from the randomized evaluation in percutaneous coronary intervention linking angiomax to reduced clinical events (REPLACE)-2 trial," *Journal of the American College of Cardiology*, vol. 45, no. 12, pp. 1932–1938, 2005.

[4] H. S. Gurm, A. M. Lincoff, D. Lee et al., "Outcome of acute ST-segment elevation myocardial infarction in diabetics treated with fibrinolytic or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: Lessons from the GUSTO V trial," *Journal of the American College of Cardiology*, vol. 43, no. 4, pp. 542–548, 2004.

[5] J. S. Weiss and B. E. Sumpio, "Review of prevalence and outcome of vascular disease in patients with diabetes mellitus,"

European Journal of Vascular and Endovascular Surgery, vol. 31, no. 2, pp. 143–150, 2006.

[6] S. S. Kanoun Schnur, A. Achim, and G. G. Toth, "Clinical application of results of the ISCHEMIA trial," *Trends in Cardiovascular Medicine*, vol. 2, pp. S1050–S1738, 2021.

[7] L. H. Bonati, J. Dobson, R. L. Featherstone et al., "Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial," *Lancet*, vol. 385, no. 9967, pp. 529–538, 2015.

[8] European Carotid Surgery Trialists' Collaborative Group, "Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST)," *Lancet*, vol. 351, no. 9113, pp. 1379–1387, 1998.

[9] A. B. Pothof, T. F. X. O'Donnell, N. J. Swerdlow et al., "Risk of insulin-dependent diabetes mellitus in patients undergoing carotid endarterectomy," *Journal of Vascular Surgery*, vol. 69, no. 3, pp. 814–823, 2019.

[10] T. G. Brott, R. W. Hobson, G. Howard et al., "Stenting versus endarterectomy for treatment of carotid-artery stenosis," *The New England Journal of Medicine*, vol. 363, no. 1, pp. 11–23, 2010.

[11] J. S. Yadav, M. Wholey, R. Kuntz et al., "Protected carotid-artery stenting versus endarterectomy in high-risk patients," *The New England Journal of Medicine*, vol. 351, no. 15, pp. 1493–1501, 2004.

[12] T. G. Brott, J. L. Halperin, S. Abbara et al., "2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease," *Stroke*, vol. 42, no. 8, pp. e464–e540, 2011.

[13] M. D. Müller, P. Lyrer, M. M. Brown, and L. H. Bonati, "Carotid artery stenting versus endarterectomy for treatment of carotid artery stenosis," *Cochrane Database of Systematic Reviews*, vol. 2, p. CD000515, 2020.

[14] A. Halliday, R. Bulbulia, L. H. Bonati et al., "Second asymptomatic carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy," *Lancet*, vol. 398, no. 10305, pp. 1065–1073, 2021.

[15] N. A. S. C. E. T. Collaborators, "Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis," *The New England Journal of Medicine*, vol. 325, no. 7, pp. 445–453, 1991.

[16] V. Aboyans, J. B. Ricco, M. E. L. Bartelink et al., "2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS)," *European Heart Journal*, vol. 39, no. 9, pp. 763–816, 2018.

[17] H. S. Gurm, V. Rajagopal, R. Sachar et al., "Impact of diabetes mellitus on outcome of patients undergoing carotid artery stenting: insights from a single center registry," *Catheterization and Cardiovascular Interventions*, vol. 69, no. 4, pp. 541–545, 2007.

[18] A. Lago, V. Parkhutik, J. I. Tembl et al., "Diabetes does not affect outcome of symptomatic carotid stenosis treated with endovascular techniques," *European Neurology*, vol. 69, no. 5, pp. 263–269, 2013.

[19] M. Schlüter, B. Reimers, F. Castriota et al., "Impact of diabetes, patient age, and gender on the 30-day incidence of stroke and death in patients undergoing carotid artery stenting with embolus protection: a post-hoc subanalysis of a prospective multicenter registry," *Journal of Endovascular Therapy*, vol. 14, no. 3, pp. 271–278, 2007.

[20] G. M. Parlani, P. de Rango, E. Cieri et al., "Diabetes is not a predictor of outcome for carotid revascularization with stenting as it may be for carotid endarterectomy," *Journal of Vascular Surgery*, vol. 55, no. 1, pp. 79–89, 2012.

[21] A. R. Naylor, J. B. Ricco, G. J. de Borst et al., "Editor's choice - management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelines of the European Society for Vascular Surgery (ESVS)," *European Journal of Vascular and Endovascular Surgery*, vol. 55, no. 1, pp. 3–81, 2018.

[22] X. S. Bai, Y. Feng, T. Wang et al., "Impact of metabolic syndrome on short-term outcome of carotid revascularization: a large sample size study in Chinese population," *Chinese Medical Journal*, vol. 133, no. 22, pp. 2688–2695, 2020.

[23] R. Casana, C. Malloggi, A. Odero Jr. et al., "Is diabetes a marker of higher risk after carotid revascularization? Experience from a single centre," *Diabetes & Vascular Disease Research*, vol. 15, no. 4, pp. 314–321, 2018.

[24] M. Cosottini, M. C. Michelassi, W. Bencivelli et al., "In stent restenosis predictors after carotid artery stenting," *Stroke Res Treat*, vol. 2010, article 864724, 2010.

[25] A. Willfort-Ehringer, R. Ahmadi, A. Gessl et al., "Neointimal proliferation within carotid stents is more pronounced in diabetic patients with initial poor glycaemic state," *Diabetologia*, vol. 47, no. 3, pp. 400–406, 2004.

[26] G. K. Jakubiak, N. Pawlas, G. Cieślar, and A. Stanek, "Pathogenesis and clinical significance of in-stent restenosis in patients with diabetes," *International Journal of Environmental Research and Public Health*, vol. 18, no. 22, p. 11970, 2021.

[27] A. Achim and G. Leibundgut, "FAME 3 fails to defame coronary artery bypass grafting: what went wrong in the percutaneous coronary intervention arm?," *European Journal of Cardio-Thoracic Surgery*, vol. 29, p. ezac 036, 2022.

[28] A. Achim, M. Marc, and Z. Ruzsa, "Surgical turned-downed CHIP cases-can PCI save the day?," *Front Cardiovasc Med.*, vol. 9, no. 9, article 872398, 2022.

[29] M. D. Müller, J. Gregson, D. J. H. McCabe et al., "Stent design, restenosis and recurrent stroke after carotid artery stenting in the international carotid stenting study," *Stroke*, vol. 50, no. 11, pp. 3013–3020, 2019.

[30] S. Ronchey, B. Praquin, M. Orrico et al., "Outcomes of 1000 carotid Wallstent implantations: single-center experience," *Journal of Endovascular Therapy*, vol. 23, no. 2, pp. 267–274, 2016.

[31] Ł. Tekieli, P. Musiałek, A. Kabłak-Ziembicka et al., "Severe, recurrent in-stent carotid restenosis: endovascular approach, risk factors. Results from a prospective academic registry of 2637 consecutive carotid artery stenting procedures (TARGET-CAS)," *Postepy Kardiol Interwencyjnej*, vol. 15, no. 4, pp. 465–471, 2019.

[32] B. K. Lal, K. W. Beach, G. S. Roubin et al., "Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial," *Lancet Neurology*, vol. 11, no. 9, pp. 755–763, 2012.

[33] J. Saw, "Carotid artery stenting for stroke prevention," *The Canadian Journal of Cardiology*, vol. 30, no. 1, pp. 22–34, 2014.

[34] Z. Ruzsa, B. Nemes, L. Pintér et al., "A randomised comparison of transradial and transfemoral approach for carotid artery stenting: RADCAR (RADial access for CARotid artery stenting) study," *Euro Intervention*, vol. 10, no. 3, pp. 381–391, 2014.

[35] A. Achim, K. Kákonyi, Z. Jambrik et al., "Distal radial artery access for coronary and peripheral procedures: a multicenter experience," *Journal of Clinical Medicine*, vol. 10, no. 24, p. 5974, 2021.

[36] University of Szeged, AA, "Impact of diabetes mellitus on early clinical outcome and stent restenosis after carotid artery stenting [poster session]," in *Heart in Diabetes 2022*, Philadelphia, USA, 2022.

Hindawi
Journal of Diabetes Research
Volume 2022, Article ID 2923291, 13 pages
https://doi.org/10.1155/2022/2923291

Research Article

UTP14A, DKC1, DDX10, PinX1, and ESF1 Modulate Cardiac Angiogenesis Leading to Obesity-Induced Cardiac Injury

Xiaoyu Pan,[1,2] Shuchun Chen,[1,2] Xing Chen,[1,2] Qingjuan Ren,[1,2] Lin Yue,[1,2] Shu Niu,[1,2] Zelin Li,[1,2] Ruiyi Zhu,[1,2] Xiaoyi Chen,[2] Zhuoya Jia,[1,2] Ruoxi Zhen,[1,2] and Jiangli Ban[2]

[1]*Department of Internal Medicine, Hebei Medical University, Shijiazhuang, China*
[2]*Department of Endocrinology, Hebei General Hospital, Shijiazhuang, China*

Correspondence should be addressed to Shuchun Chen; chenshuchunwork88@163.com

Received 9 January 2022; Accepted 28 May 2022; Published 13 June 2022

Academic Editor: Ali Sharif

Background. This study is aimed at exploring the key genes and the possible mechanism of heart damage caused by obesity. *Methods*. We analyzed the GSE98226 dataset. Firstly, differentially expressed genes (DEGs) were identified in heart tissues of obese and normal mice. Then, we analyzed DEGs using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. Thirdly, we constructed a protein-protein interaction (PPI) network and key modules and searched hub genes. Finally, we observed the pathological changes associated with obesity through histopathology. *Results*. A total of 763 DEGs were discovered, including 629 upregulated and 134 downregulated genes. GO enrichment analysis showed that these DEGs were mainly related to the regulation of transcription, DNA-templated, nucleic acid binding, and metal ion binding. KEGG pathway analysis revealed that the DEGs were enriched in long-term depression, gap junction, and sphingolipid signaling pathways. Finally, we identified UTP14A, DKC1, DDX10, PinX1, and ESF1 as the hub genes. Histopathologic analysis showed that obesity increased the number of collagen fibers and decreased the number of microvessels and proliferation of the endothelium and increased endothelial cell damage which further leads to dysfunction of cardiac microcirculation. *Conclusion*. UTP14A, DKC1, DDX10, PinX1, and ESF1 have been identified as hub genes in obesity-induced pathological changes in the heart and may be involved in obesity-induced cardiac injury by affecting cardiac microcirculatory function.

1. Introduction

Obesity is a metabolic disease with excessive accumulation of body fat. It is an independent risk factor for cardiovascular disease, metabolic disease, and type 2 diabetes [1]. With the improvement of the quality of life, the number of obese people in the world is increasing, especially in developed countries [2]. BMI is often used to measure obesity, which is defined by the World Health Organization as having a BMI ≥ 30 [3]. Obesity has been identified as an independent risk factor for cardiovascular diseases in the context of increasing morbidity and mortality [4, 5]. The essence of obesity is the abnormal accumulation of lipids and the increase in inflammatory factors in the body, which will inevitably augment the workload and impair the function of the heart and lungs. In addition, inflammatory factors affect the metabolism of the heart, impairing cardiac function [6]. For some obese patients, sleep apnea syndrome, elevated blood pressure, and blood sugar are risk factors for heart damage [7].

The mechanisms underlying obesity-induced cardiac dysfunction have not been fully elucidated [8]. Previous studies showed that obesity causes alterations in cardiac energy metabolism in cardiomyocytes, particularly fatty acid metabolism [9, 10], and analysis has revealed that acyl-CoA synthetase long-chain family member 1 (ACSL-1) and glucose transporter member 4 (GLUT-4) may be the key proteins responsible for heart damage [11]. Other studies discovered that obesity contributes to a chronic inflammatory state in the body and interferes with a variety of metabolic processes [12]. In this context, metabolic disorders will inevitably lead to abnormal metabolism of the heart, as

well as heart microcirculation dysfunction, which plays an important role in the occurrence and development of cardiovascular diseases [13, 14]. However, at present, the diagnosis and treatment of cardiac microcirculation are not mature.

Oxidative stress plays an important role in obesity and its complications and can interfere with angiogenesis, so oxidative stress, obesity, and angiogenesis are closely related. Angiogenesis is considered to be the most important change in the premorbid process of obesity [15]. Angiogenesis is a multistep process involved in the healing of damaged tissues, organ repair, and fetal development under physiological conditions, while under pathological conditions, it can promote the development of multiple cancers and multiple vascular complications [16, 17]. For the cardiovascular system, obesity significantly increases the likelihood of acute myocardial infarction and microcirculatory disturbance. Microcirculation dysfunction is one of the pathological changes of heart damage in obese patients, where the imbalance of the angiogenesis regulation mechanism plays a significant role.

In this study, we further revealed biomarkers of obesity-induced cardiac damage through the analysis of GSE98226 gene expression profiling and immunohistochemical analysis of cardiac tissue in obese mice. The identification of key genes and pathways is helpful to better understand the pathophysiological mechanisms of disease development, and it provides new ideas of cardiovascular protection for obese patients.

2. Materials and Methods

2.1. Microarray Data. The gene expression data utilized in this study (GSE98226) were downloaded from the NCBI Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/geo). The data was based on the GPL21163 Platform (Agilent-074809 SurePrint g 3mouse GE v 28x60k Microarray), and it came from heart tissues of three mice on a normal diet and three mice on a high-fat diet.

2.2. Screening of Differentially Expressed Genes. The GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/) online tool in the GEO database was applied to screen the differentially expressed genes (DEGs) in normal and hyperlipidemic mouse heart tissues. The determining criteria of the DEGs were adjusted P value < 0.01 and $|\log 2\text{foldchange(FC)}| \geq 2$. The Benjamini and Hochberg (false discovery rate) method is used to calculate the adjusted P value. The study deleted gene probes that do not correspond to gene names and replaced them with averages for multiple probes for one gene name. After initial processing, we input the DEG data into Excel for further analysis.

2.3. GO and KEGG Pathway Enrichment Analysis of DEGs. The study applied an online Database for Annotation, Visualization and Integrated Discovery (DAVID) (https://david.ncifcrf.gov) for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis. The data was collated, and the results were visualized using the online tool Bioinformatics (http://www.bioinformatics.com.cn/).

2.4. PPI Network Construction. We constructed a PPI network of DEGs through STRING (http://www.string-db.org), an online database, to determine protein-protein interactions. An interaction score that is equal to or greater than 0.7 is defined as having interaction between proteins, while the remaining options are set to default.

2.5. Module Analysis and Selection of Hub Genes. The PPI interaction map was imported into Cytoscape software, and the MCODE plug-in was used to extract and visualize major modules in the network. We screened the key genes in the network through three algorithms (Maximum Neighborhood Component (MNC), Density of Maximum Neighborhood Component (DMNC), and Maximal Clique Centrality (MCC)) in the plug-in CytoHubba.

2.6. Mice and Groups. Specific pathogen-free male C57BL/6 mice were purchased from Hebei Yiweiwo Biotechnology Co. Ltd. Six C57 mice were randomly divided into normal chow diet (NCD, $n = 3$) and high-fat diet (HFD, $n = 3$) after adaptive feeding for 1 week. The mice were fed for the next 24 weeks according to their groups, and their bodyweight was monitored weekly. We evaluated the results of obesity modeling by comparing the weight of mice in the high-fat group with that in the control group. The modeling would be considered successful if the body weight of mice in the high-fat group was 20% or higher than that in the control group. All mice were raised in a comfortable and sterile environment with specific conditions as follows: humidity 45%-65%, temperature 20-24°C, time ratio of night to day 1 : 1, adequate food and water supply, and bedding change twice a week. This experiment was subject to approval by the animal ethics association of Hebei General Hospital.

2.7. Preparation of Tissue Sample. The fully anesthetized and completed mice were placed on an icebox for blood collection. The chest cavity was opened, and the heart tissue was dissected. The blood vessels were cut off from the bottom of the heart, and the heart was harvested and flushed with saline. The excess blood was squeezed out with a filter paper and the surface fluid drained, and then, the heart tissue was fixed in 4% paraformaldehyde for later use.

2.8. HE and Masson Staining. Heart tissue soaked in paraformaldehyde was taken out and embedded in paraffin and sliced. Slices were placed in hematoxylin solution for 5 minutes, separated by 1% alcohol for 5 seconds, added 0.5% eosin for 30 seconds, and rinsed in running water. Then, dehydrate with 95% alcohol and 100% alcohol, respectively, for 5 minutes; then, soak in xylene and seal the tablets with neutral gum.

In Masson staining, conventional paraffin embedding and section treatment were performed. Sections were placed in hematoxylin for 5 minutes, Masson compound dyeing solution for 5 minutes, 1% phosphomolybdic acid for 5 minutes, 2% bright green dyeing solution for 5 minutes, and 1% phosphomolybdic acid for 5 minutes. Further treatment included alcohol dehydration, xylene treatment, and neutral gum sealing, and we observed the sections using a microscope.

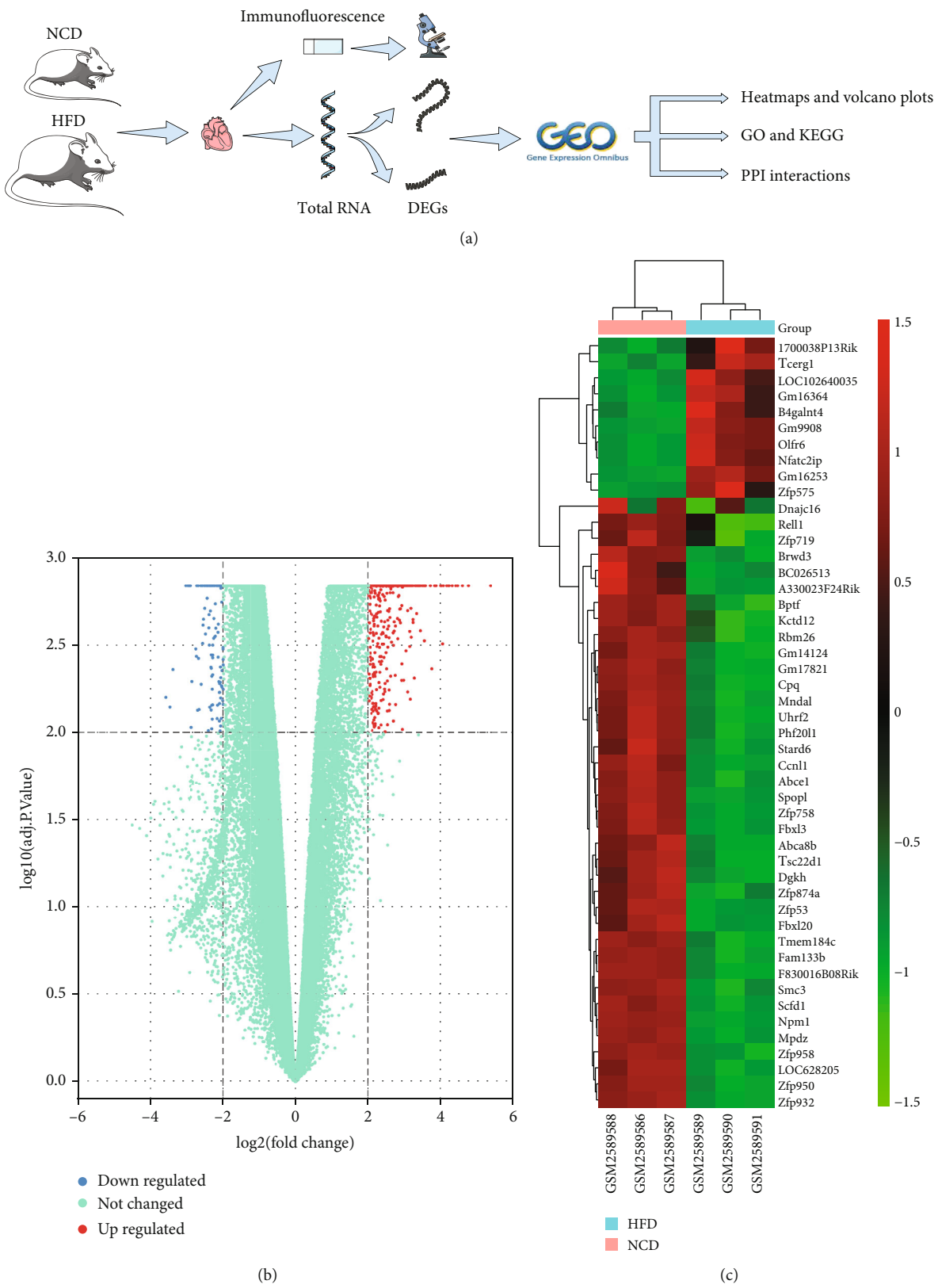
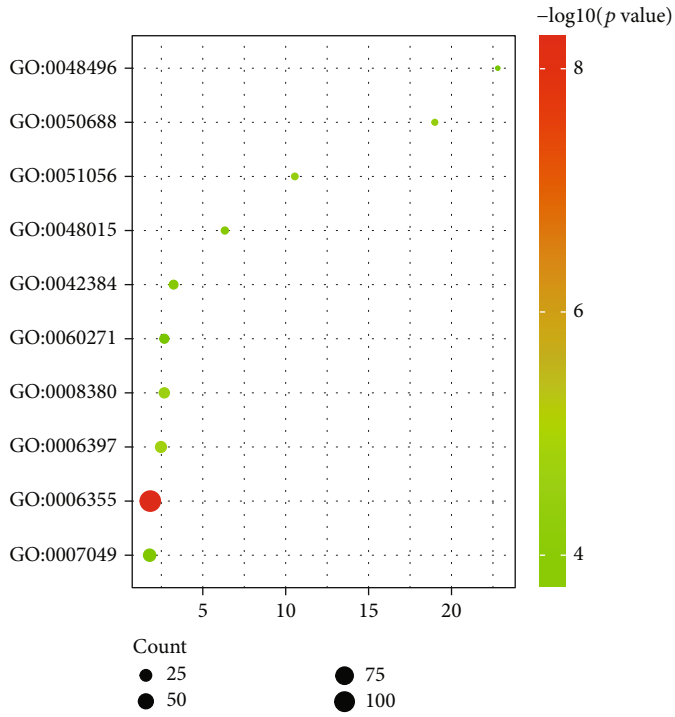
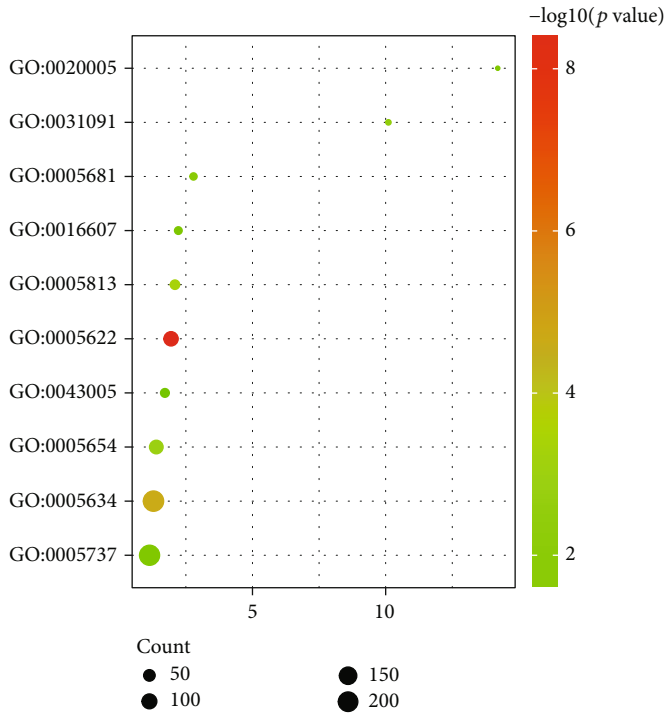


Figure 1: Screening and visualization of DEGs. (a) Experimental workflow. The hearts of NCD and HFD mice were harvested for DEGs analysis and pathological examination ($n = 3$). (b) The volcano plots of DEGs. The screening criteria for DEGs were adjusted P value < 0.01 and $|\log 2\text{foldchange(FC)}| \geq 2$. (c) The heatmaps of DEGs. Top 50 DEGs between NCD and HFD. Red: greater expression; blue: less expression; DEGs: differentially expressed genes; NCD: normal chow diet; HFD: high-fat diet; GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; PPI: protein-protein interaction.



(a)



(b)

Figure 2: Continued.

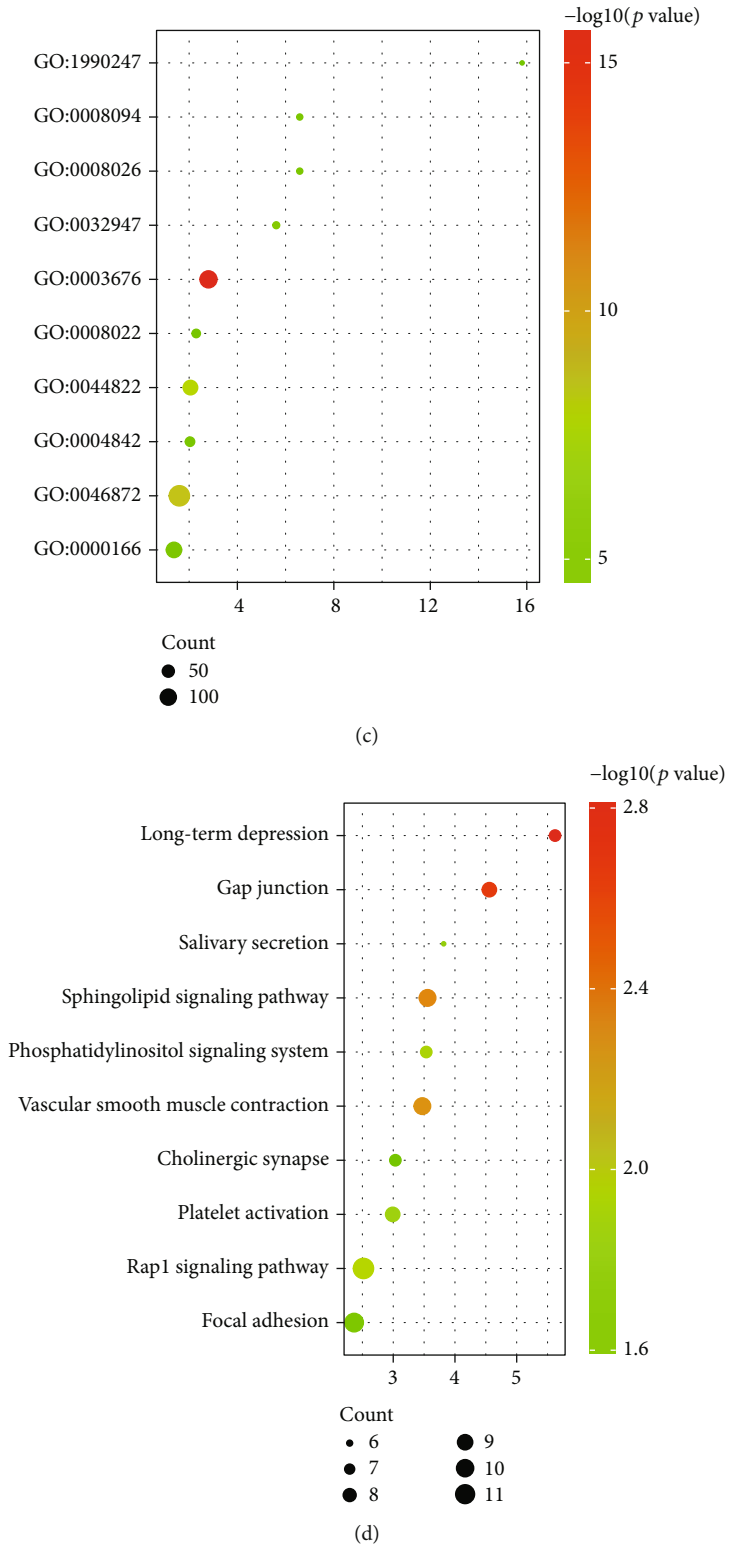


Figure 2: GO terms and KEGG pathway enrichment analysis. The x-axis represents the fold enrichment of each functional group gene. The y-axis represents the different functional groups. The size of the dots indicates the number of genes contained in different functional groups, and the color of the dots reflects the different range of $-\log 10(P \text{ value})$. The larger the number of genes, the larger the dot. The gradient from green to red represents a change in P value from large to small. GO analysis divided DEGs into three functional groups: BP (a), CC (b), and MC (c). (d) Top 10 KEGG pathway enrichment analysis of DEGs. GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; BP: biological processes; CC: cell composition; MF: molecular function; DEGs: differentially expressed genes.

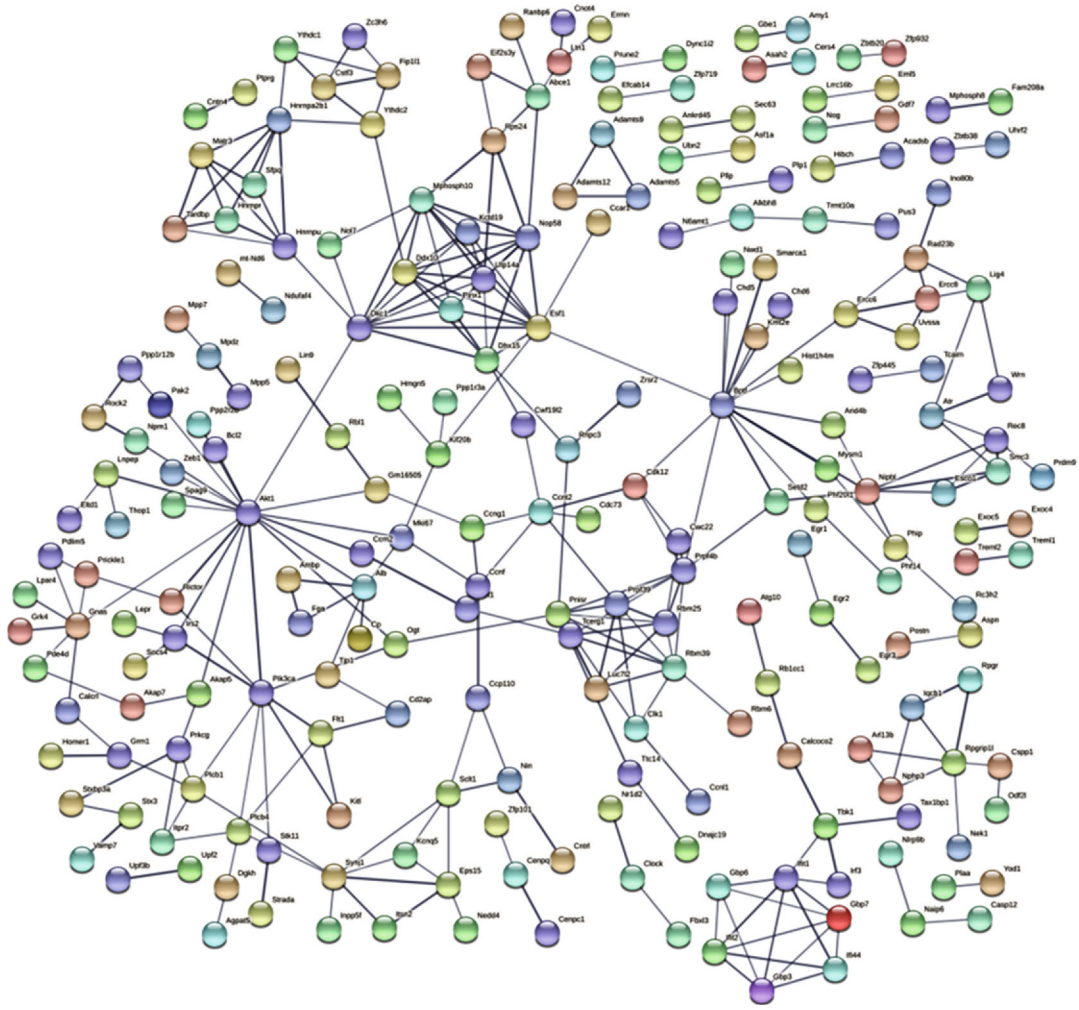


Figure 3: Results of PPI network analysis of DEGs. The circles represent genes; the lines represent the PPI between genes, and the images within the circles represent protein structures. The line color represents the PPI evidence level. PPI: protein-protein interaction; DEGs: differentially expressed genes.

Table 1: Hub genes based on cytoHubba.

Projects	Methods in cytoHubba		
	DMNC	MNC	MCC
Top 10 gene symbols	**Utp14a**	**Utp14a**	**Utp14a**
	Dkc1	**Dkc1**	**Dkc1**
	Ddx10	**Ddx10**	**Ddx10**
	Esf1	**Esf1**	**Esf1**
	Pinx1	Nop58	**Pinx1**
	Dhx15	**Pinx1**	Dhx15
	Kctd19	Mphosph10	Mphosph10
	Ifit1	Rbm39	Nop58
	Gbp3	Rbm25	Kctd19
	Gbp7	Prpf4b	Rbm39

Bold gene symbols were the overlap hub gene. MCC: Maximal Clique Centrality; DMNC: Density of Maximum Neighborhood Component; MNC: Maximum Neighborhood Component.

2.9. Immunofluorescence Analysis. The study examined cardiac tissue using CD34 immunochemistry to determine the density of blood vessels in the heart. The heart tissue was sectioned after conventional treatment and incubated with the first and secondary antibodies. The vessel density was calculated after observing under a microscope.

In order to identify changes in the cardiovascular function of obese mice, the study measured the vWF factor of heart tissue. The expression of vWF was observed by the microscope after the heart tissues were sectioned and incubated with the first and secondary antibodies, respectively.

The study identified the proliferation of cardiac endothelium cells by double immunofluorescence staining and applied CD31 and Ki-67 dual staining to detect the proliferation of cardiac endothelium cells. All operations were performed in strict accordance with the manufacturer's instructions and images were evaluated using Image-Pro Plus 6.0 software.

2.10. Statistical Analysis. All data are presented as mean ± standard deviation. Data were analyzed using GraphPad

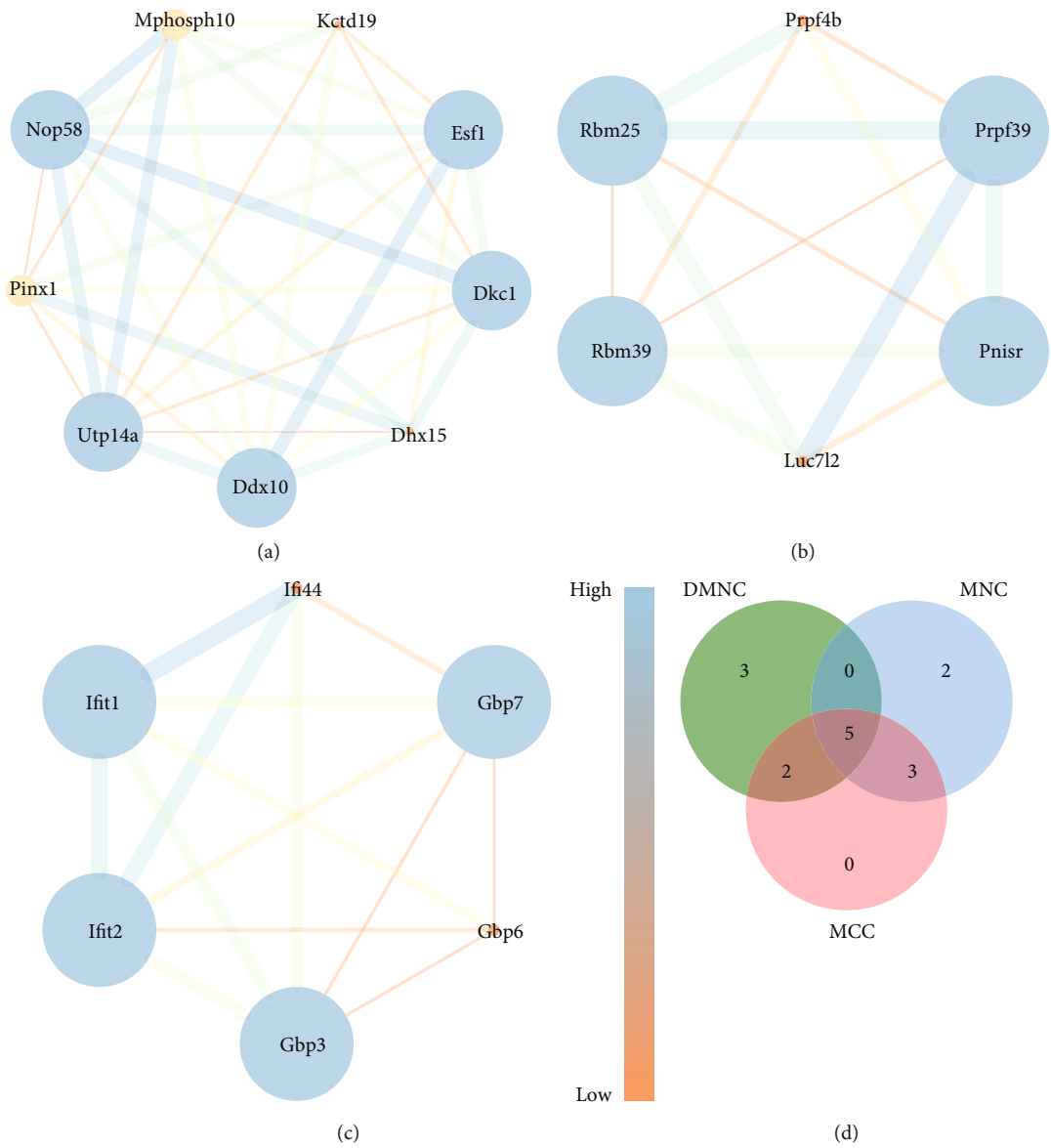


Figure 4: The protein-protein interaction module constructed based on the DEGs (a–c). The size of the circle and the thickness of the line represent the degree of importance; the larger the circle and the thicker the line, the more important it is. The color represents the degree value. Orange means the smallest degree value, while blue means the largest degree value. (d) Venn diagram of common hub genes based on three methods. DEGs: differentially expressed genes; DMNC: Density of Maximum Neighborhood Component; MCC: Maximal Clique Centrality; MNC: Maximum Neighborhood Component.

software, and independent samples t-tests were performed. $P < 0.05$ means the result is statistically significant, and $P < 0.01$ means the result is extremely statistically significant.

3. Results

3.1. Identification of DEGs. A total of 763 DEGs were identified in the heart tissue of the high-fat mice, including 629 upregulated genes and 134 downregulated genes. Figure 1 and Supplemental File 1 show the volcano plots of all DEGs and the heatmaps of the first 50 DEGs.

3.2. GO Enrichment Analysis. This study conducted the GO enrichment analysis of DEGs based on the DAVID database and screened out enrichment terms with adjusted P value < 0.05. As shown in Figure 2 and Supplemental File 2, the result contained 60 enrichment terms. Biological processes (BP) were mainly enriched in regulation of transcription, DNA-templated, mRNA processing, and RNA splicing; cellular component (CC) was mainly enriched in intracellular, nucleus, and centrosome; molecular function (MF) was mainly enriched in nucleic acid binding, metal ion binding, and poly(A) RNA binding.

3.3. KEGG Pathway Analysis. Figure 2 shows the top 10 KEGG enrichment pathways of DEGs, and Supplemental File 3 shows all pathway information. Main pathways

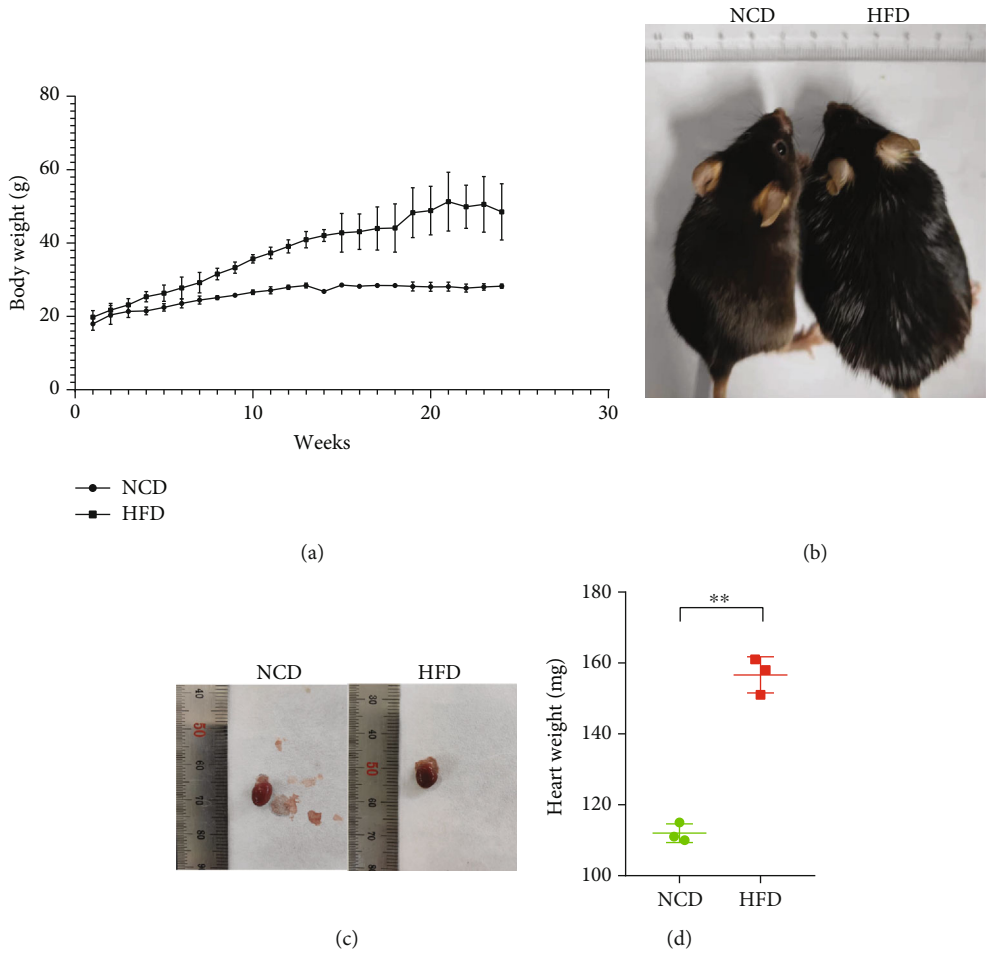


Figure 5: Effect of high-fat diet on mice. (a) Comparison of NCD and HFD mice. (b) Effect of high-fat diet on body weight of mice ($n = 3$). (c) A representative macroscopic image of the heart. (d) Comparison of heart weights between the two groups of mice ($n = 3$). Data were processed using independent samples t-test. ∗∗ represents $P < 0.01$. NCD: normal chow diet; HFD: high-fat diet.

include long-term depression, gap junction, and sphingolipid signaling pathway.

3.4. PPI Network Construction and Module Analysis. The study constructed a PPI network to better understand the biological characteristics of DEGs. Figure 3 shows the details of the PPI network and the corresponding modules. There are 584 nodes and 316 edges in this network. The three major modules were generated by importing the network into Cytoscape.

3.5. Hub Gene Selection and Analysis. Based on the key module, we screened out hub genes by applying the cytoHubba plug-in from Cytoscape. Three algorithms, MCC, DNMC, and MNC, were used to identify the top 10 hub genes, and five hub genes were identified in obese mice compared to controls: UTP14A, Dkc1, DDX10, PinX1, and ESF1, as shown in Table 1 and Figure 4.

3.6. General Conditions of Obese Mice. After 24 weeks of feeding, the weight of mice in the high-fat group was significantly higher than that in the control group. Compared with the high-fat group, the control group had faster movements, smoother and darker hair, smaller hearts, and less epicardial fat. For the HFD group, mice's heart weight was significantly higher compared with that of the NCD group ($P < 0.01$). The results are shown in Figure 5.

3.7. Myocardial Histopathology. The results of HE staining indicated that the cardiomyocytes from the control group were arranged compactly and orderly with less extracellular matrix, while the cardiomyocytes from the obese group were enlarged and slightly disordered with more extracellular matrix. Masson staining showed that the collagenous tissue in the control group was slender and orderly distributed, and the collagenous tissue in the obese group was obviously increased, disarranged, and unevenly distributed, and inflammatory cells were found around the vessels, as shown in Figure 6.

3.8. Effects of Obesity on Cardiac Angiogenesis, Proliferation, and Function. To determine the effect of obesity on cardiovascular angiogenesis, we measured the capillary density of mouse heart tissue. Compared to the control group, the cardiac capillary density was slightly decreased in obese mice,

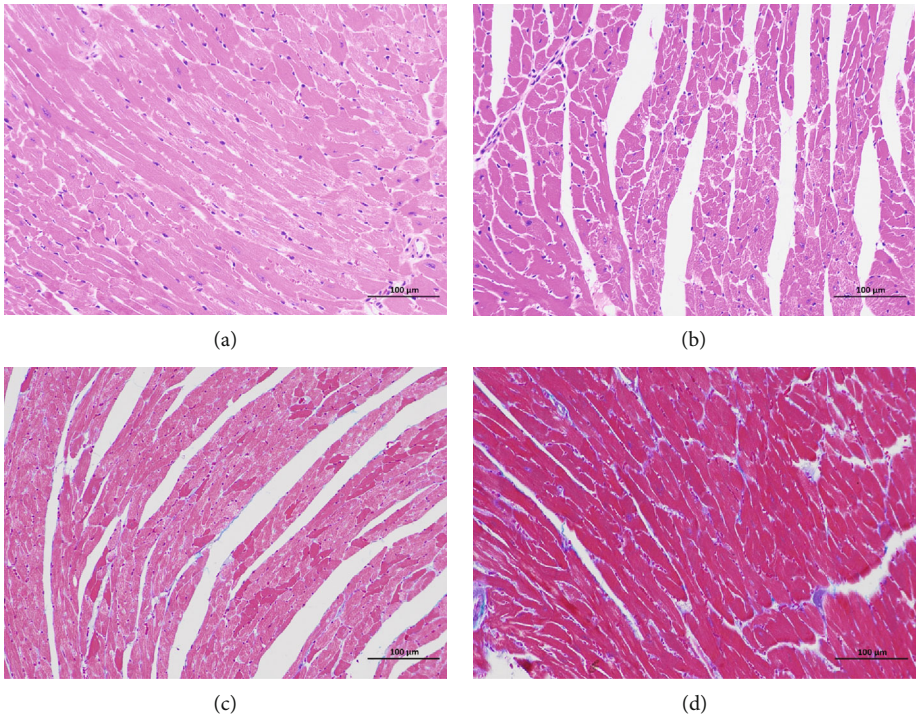


Figure 6: HE and Masson staining of rat myocardial tissue in each group (200x). HE staining of rat myocardial tissue in each group (a, b). Masson staining of rat myocardial tissue in each group (b, c). The left side of the graph represents the normal group, and the right side represents the high-fat group.

but not statistically significant ($P > 0.05$). Subsequently, we observed a slight increase in vWF factor expression in the hearts of obese mice. Double immunofluorescence staining showed that the proliferation capacity of endothelial cells in the hearts of obese mice was decreased compared with the control group, but there was no statistical difference between the two groups ($P > 0.05$), as shown in Figure 7. The expression levels of UTP14A, DKC1, DDX10, PinX1, and ESF1 were significantly associated with impaired cardiac angiogenesis (Supplemental File 4).

4. Discussion

Cardiovascular disease is the main cause of death worldwide, and its prevalence continues to increase. The main risk factors include dyslipidemia, insulin resistance, and type 2 diabetes. Obesity is closely linked to these risk factors [18, 19]. As a result, obese people are more apt to get cardiovascular disease and have higher mortality rates than people of normal weight. For obese patients, abnormal increases in adipose tissues can increase the release of cytokines and bioactive mediators, such as leptin, IL-6, and TNF, which can activate the inflammatory mechanism and impair the normal metabolism of the heart [20]. Cardiac microcirculation plays an important role in cardiac metabolism, and the endothelium is the major cell type in microcirculation. Therefore, when the microcirculation is in a state of low inflammation caused by obesity-related insulin resistance and cytokines released by fat cells, it inevitably leads to endothelial dysfunction [21, 22]. In this study, we demonstrated the effect of obesity on cardiac microcirculation by immunocytochemistry. The results showed that obesity can lead to vascular endothelial dysfunction, increase cell damage, and reduce cell proliferation.

Angiogenesis is essential for the maintenance of normal physiological functions. Numerous studies have shown that obesity promotes angiogenesis in various tumor and adipose tissues [23–25]. However, the pathophysiology of cardiac microvasculature in the obese state is still worth exploring. Studies have shown that cardiac microvessel density in obese mice is significantly higher than that in normal mice, but it decreases as the disease progresses. Another study of human heart tissue showed that obesity significantly reduced the number of microvessels [26–28]. In this study, the results of pathological examination showed that obesity can increase the diameter of myocardial cells, increase collagen fibers, and decrease the number of microvessels.

To determine the genetic mechanisms underlying the effects of obesity on cardiac microcirculation, we analyzed GSE98266 data and found 763 DEGs, including 629 upregulated genes and 134 downregulated genes. GO enrichment analysis showed that these DEGs were mainly associated with the regulation of transcription, DNA-templated, nucleic acid binding, and metal ion binding. KEGG pathway analysis revealed that the DEGs were enriched in long-term depression, gap junction, and sphingolipid signaling pathway. Finally, we identified UTP14A, DKC1, DDX10, PinX1, and ESF1 as the hub genes between the two groups.

U Three Protein 14A (UTP14A) is a small nucleolar RNA related to protein 14 homologue of U 3, belonging to

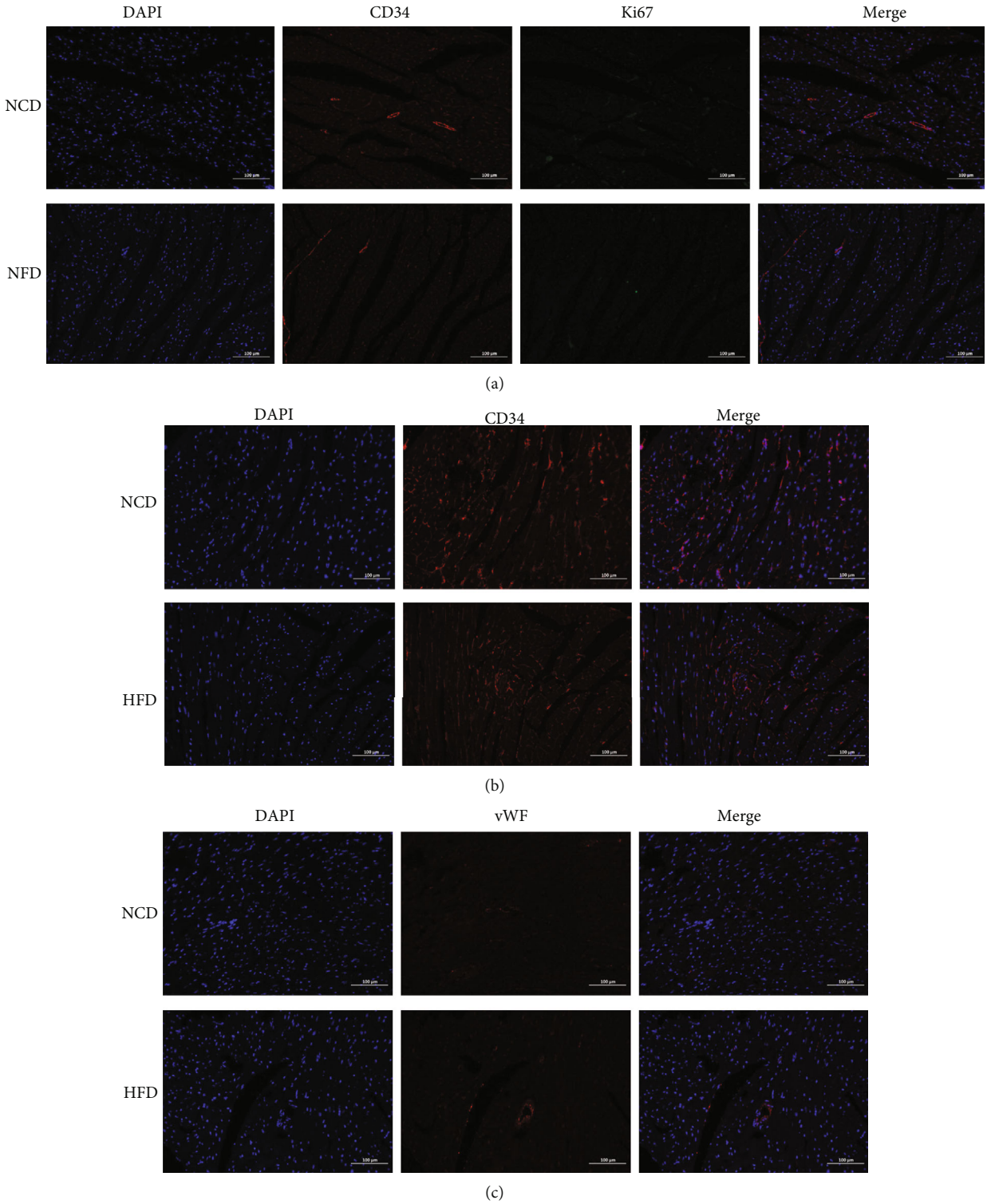


Figure 7: Continued.

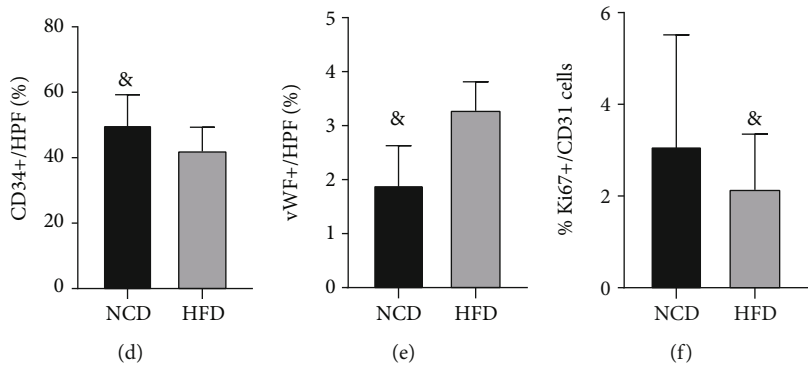


Figure 7: Comparison of cardiac angiogenesis, endothelial cell proliferation, and injury between NCD-heart and HFD-heart. (a) Immunofluorescent staining of Ki67 and CD31 to detect proliferative endothelial cells in NCD and HFD hearts; (b) CD34 immunofluorescence staining to determine the number of cardiac microvessels. (c) VWF immunofluorescence staining to determine the proportion of endothelial cell damage. (d) Comparison of CD34-positive cells per HPF between NCD and HFD hearts ($^{\&}P > 0.05$, $n = 3$). (e) Comparison of vWF-positive cells per HPF between NCD and HFD hearts ($^{\&}P > 0.05$, $n = 3$). (f) The comparison of the percentage of Ki67-positive cells between NCD and HFD hearts ($^{\&}P > 0.05$, $n = 3$). NCD: normal chow diet; HFD: high-fat diet; HPF: high-power field.

the UTP14 family, and plays a key role in the synthesis of ribosomes and 18s rRNA [29]. In a pathological state, UTP14A plays its role mainly by promoting angiogenesis. It has been noted that UTP14A is involved in the development of colorectal cancer by promoting angiogenesis, while the inhibition of UTP14A can improve the prognosis of patients [30, 31]. The upregulation of UTP14A was associated with the progression of esophageal cancer [32]. Similarly, PIN2/TRF1-interacting telomerase inhibitor 1 (PinX1) is involved in the development of cancer through angiogenesis [33]. In this study, UTP14A and PinX1 were identified as key genes in the heart of obese mice, which may be involved in the pathophysiology of obesity-related cardiac effects by regulating the balance of cardiac microvasculature, but there is no relevant research to verify this.

The dyskeratosis congenita 1 (DKC1) gene, located on the X chromosome xq28, was first discovered because of a mutation that causes dyskeratosis congenita [34], as well as a variety of cancers and pulmonary fibrosis [35, 36]. Studies have shown that DKC1 can be involved in cancer progression by promoting angiogenesis and is closely related to oxidative stress [37, 38]. DEAD/H box RNA helicase 10 (DDX10) is associated with a variety of cancers and diseases of the blood system [39, 40]. However, little research has been done on ESF1, and its role is still unclear.

This study found the key genes and related pathways of obesity-induced heart injury through gene chip. It is worth noting that UTP14A, DKC1, and PinX1 are all closely associated with angiogenesis in various diseases, so we speculate that all three may affect cardiac angiogenesis in obesity, but their angiogenic roles in cardiac tissue remain unclear. Moreover, we proved that obesity can increase the size of myocardial cells, increase the number of collagen fibers in the myocardial matrix, and decrease the number of microvessels in the heart and reduce endothelium proliferation which can affect the microcirculation of the heart, leading to impairment of cardiac function. This still needs further experimental verification.

5. Conclusions

UTP14A, DKC1, DDX10, PinX1, and ESF1 may be involved in obesity-induced cardiac injury by affecting angiogenesis in the heart.

Data Availability

The data used to support the results of this study are available from the first author upon request.

Ethical Approval

The animal experimental procedures were approved by the Animal Ethics Committee of Hebei General Hospital.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

This study was supported by the Hebei Provincial Central Leading Local Science and Technology Development Funds Project (206Z7702G).

Supplementary Materials

GSE98226 datasets were downloaded from GEO (http://www.ncbi.nlm.nih.gov/geo/). Supplemental File 1: DEGs. Supplemental File 2: GO enrichment analysis. Supplemental File 3: KEGG pathway analysis. Supplemental File 4: correlation between UTP14A, DKC1, DDX10, PinX1, and ESF1 expression and cardiac angiogenesis. *(Supplementary Materials)*

References

[1] M. P. Na Nongkhai, R. Yamprasert, and C. Punsawad, "Effects of continuous yoga on body composition in obese

adolescents," *Evidence-Based Complementary and Alternative Medicine*, vol. 2021, Article ID 6702767, 7 pages, 2021.

[2] N. Bian, X. Sun, B. Zhou et al., "Obese patients with higher TSH levels had an obvious metabolic improvement after bariatric surgery," *Endocrine Connections*, vol. 10, no. 10, pp. 1326–1336, 2021.

[3] S. Keihani, N. J. Alder, P. J. Cheng, G. J. Stoddard, A. W. Pastuszak, and J. M. Hotaling, "Obesity and baseline estradiol levels are independent predictors for initiation of anastrozole in hypogonadal men on clomiphene citrate," *The World Journal of Men's Health*, vol. 38, no. 4, pp. 582–590, 2020.

[4] K. Shirakawa and M. Sano, "T cell immunosenescence in aging, obesity, and cardiovascular disease," *Cell*, vol. 10, no. 9, p. 2435, 2021.

[5] T. Harada and M. Obokata, "Obesity-related heart failure with preserved ejection fraction: pathophysiology, diagnosis, and potential therapies," *Heart Failure Clinics*, vol. 16, no. 3, pp. 357–368, 2020.

[6] S. Yu, X. Guo, G. Li, H. Yang, L. Zheng, and Y. Sun, "Gender discrepancy in the predictive effect of metabolic syndrome and its components on newly onset cardiovascular disease in elderly from rural China," *BMC Geriatrics*, vol. 21, no. 1, p. 505, 2021.

[7] X. Guo, Z. Li, Y. Zhou et al., "The effects of transitions in metabolic health and obesity status on incident cardiovascular disease: insights from a general Chinese population," *European Journal of Preventive Cardiology*, vol. 28, no. 11, pp. 1250–1258, 2021.

[8] C. J. Lavie, M. A. Alpert, R. Arena, M. R. Mehra, R. V. Milani, and H. O. Ventura, "Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure," *JACC Heart Failure*, vol. 1, no. 2, pp. 93–102, 2013.

[9] D. F. Vileigas, V. M. Harman, P. P. Freire et al., "Landscape of heart proteome changes in a diet-induced obesity model," *Scientific Reports*, vol. 9, no. 1, article 18050, 2019.

[10] J. De la Cuesta-Zuluaga, N. T. Mueller, R. Álvarez-Quintero et al., "Higher fecal short-chain fatty acid levels are associated with gut microbiome dysbiosis, obesity, hypertension and cardiometabolic disease risk factors," *Nutrients*, vol. 11, no. 1, p. 51, 2019.

[11] A. D. Liśkiewicz, Ł. Marczak, K. Bogus, D. Liśkiewicz, M. Przybyła, and J. Lewin-Kowalik, "Proteomic and structural manifestations of cardiomyopathy in rat models of obesity and weight loss," *Front Endocrinol (Lausanne)*, vol. 12, article 568197, 2021.

[12] A. Ghosh, L. Gao, A. Thakur, P. M. Siu, and C. W. K. Lai, "Role of free fatty acids in endothelial dysfunction," *Journal of Biomedical Science*, vol. 24, no. 1, p. 50, 2017.

[13] M. Packer, "Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium," *Journal of the American College of Cardiology*, vol. 71, no. 20, pp. 2360–2372, 2018.

[14] N. Wiernsperger, P. Nivoit, and E. Bouskela, "Microcirculation in obesity: an unexplored domain," *Anais da Academia Brasileira de Ciências*, vol. 79, no. 4, pp. 617–638, 2007.

[15] P. Nijhawans, T. Behl, and S. Bhardwaj, "Angiogenesis in obesity," *Biomedicine & Pharmacotherapy*, vol. 126, article 110103, 2020.

[16] R. Cheng and J. X. Ma, "Angiogenesis in diabetes and obesity," *Reviews in Endocrine & Metabolic Disorders*, vol. 16, no. 1, pp. 67–75, 2015.

[17] R. Kolb, P. Kluz, Z. W. Tan et al., "Obesity-associated inflammation promotes angiogenesis and breast cancer via angiopoietin-like 4," *Oncogene*, vol. 38, no. 13, pp. 2351–2363, 2019.

[18] A. M. Rychter, A. E. Ratajczak, A. Zawada, A. Dobrowolska, and I. Krela-Kaźmierczak, "Non-systematic review of diet and nutritional risk factors of cardiovascular disease in obesity," *Nutrients*, vol. 12, no. 3, p. 814, 2020.

[19] M. E. Piché, A. Tchernof, and J. P. Després, "Obesity phenotypes, diabetes, and cardiovascular diseases," *Circulation Research*, vol. 126, no. 11, pp. 1477–3681500, 2020.

[20] L. F. Van Gaal, I. L. Mertens, and C. E. De Block, "Mechanisms linking obesity with cardiovascular disease," *Nature*, vol. 444, no. 7121, pp. 875–880, 2006.

[21] O. Sorop, T. D. Olver, J. van de Wouw et al., "The microcirculation: a key player in obesity-associated cardiovascular disease," *Cardiovascular Research*, vol. 113, no. 9, pp. 1035–1045, 2017.

[22] A. Virdis, S. Masi, R. Colucci et al., "Microvascular endothelial dysfunction in patients with obesity," *Current Hypertension Reports*, vol. 21, no. 4, p. 32, 2019.

[23] A. Y. Lemoine, S. Ledoux, and E. Larger, "Adipose tissue angiogenesis in obesity," *Thrombosis and Haemostasis*, vol. 110, no. 4, pp. 661–668, 2013.

[24] H. Wang, Y. Shi, and J. Gu, "A multitarget angiogenesis inhibitor, CTT peptide-endostatin mimic-kringle 5, prevents diet-induced obesity," *Journal of Molecular Medicine (Berlin, Germany)*, vol. 98, no. 12, pp. 1753–1765, 2020.

[25] K. M. Terlikowska, B. Dobrzycka, R. Terlikowski, A. Sienkiewicz, M. Kinalski, and S. J. Terlikowski, "Clinical value of selected markers of angiogenesis, inflammation, insulin resistance and obesity in type 1 endometrial cancer," *BMC Cancer*, vol. 20, no. 1, p. 921, 2020.

[26] M. Khazaei and Z. Tahergorabi, "Ghrelin did not change coronary angiogenesis in diet-induced obese mice," *Cellular and Molecular Biology (Noisy-le-Grand, France)*, vol. 63, no. 2, pp. 96–99, 2017.

[27] D. J. Campbell, J. B. Somaratne, D. L. Prior et al., "Obesity is associated with lower coronary microvascular density," *PLoS One*, vol. 8, no. 11, article E81798, 2013.

[28] T. Sugawara, S. Fujii, A. K. Zaman et al., "Coronary capillary network remodeling and hypofibrinolysis in aged obese diabetic rats: implications for increased myocardial vulnerability to ischemia," *Molecular and Cellular Biochemistry*, vol. 248, no. 1/2, pp. 165–170, 2003.

[29] K. K. Li, C. Y. Mao, J. G. Zhang et al., "Overexpression of U three protein 14a (UTP14a) is associated with poor prognosis of esophageal squamous cell carcinoma," *Thorac Cancer*, vol. 10, no. 11, pp. 2071–2080, 2019.

[30] P. Ren, X. Sun, C. Zhang, L. Wang, B. Xing, and X. Du, "Human UTP14a promotes angiogenesis through upregulating PDGFA expression in colorectal cancer," *Biochemical and Biophysical Research Communications*, vol. 512, no. 4, pp. 871–876, 2019.

[31] J. Zhang, P. Ren, D. Xu et al., "Human UTP14a promotes colorectal cancer progression by forming a positive regulation loop with c-Myc," *Cancer Letters*, vol. 440, pp. 106–115, 2019.

[32] K. K. Li, C. Y. Mao, Q. Ma et al., "U three protein 14a (UTP14A) promotes tumour proliferation and metastasis via the PERK/eIF2a/GRP78 signalling pathway in oesophageal

squamous cell carcinoma," *Journal of Cancer*, vol. 12, no. 1, pp. 134–140, 2021.

[33] P. Hou, H. Li, H. Yong et al., "PinX1 represses renal cancer angiogenesis via the mir-125a-3p/VEGF signaling pathway," *Angiogenesis*, vol. 22, no. 4, pp. 507–519, 2019.

[34] F. A. Miao, K. Chu, H. R. Chen et al., "Increased DKC1 expression in glioma and its significance in tumor cell proliferation, migration and invasion," *Investigational New Drugs*, vol. 37, no. 6, pp. 1177–1186, 2019.

[35] M. Penzo, L. Casoli, C. Ceccarelli et al., "DKC1 gene mutations in human sporadic cancer," *Histology and Histopathology*, vol. 28, no. 3, pp. 365–372, 2013.

[36] V. Gaysinskaya, S. E. Stanley, S. Adam, and M. Armanios, "Synonymous mutation in *DKC1* causes telomerase RNA insufficiency manifesting as familial pulmonary fibrosis," *Chest*, vol. 158, no. 6, pp. 2449–2457, 2020.

[37] P. Hou, P. Shi, T. Jiang et al., "DKC1 enhances angiogenesis by promoting HIF-1α transcription and facilitates metastasis in colorectal cancer," *British Journal of Cancer*, vol. 122, no. 5, pp. 668–679, 2020.

[38] J. S. Ibáñez-Cabellos, M. Seco-Cervera, C. Picher-Latorre, G. Pérez-Machado, J. L. García-Giménez, and F. V. Pallardó, "Acute depletion of telomerase components DKC1 and NOP10 induces oxidative stress and disrupts ribosomal biogenesis via NPM1 and activation of the P53 pathway," *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, vol. 1867, no. 12, article 118845, 2020.

[39] M. Gai, Q. Bo, and L. Qi, "Epigenetic down-regulated DDX10 promotes cell proliferation through Akt/NF-κB pathway in ovarian cancer," *Biochemical and Biophysical Research Communications*, vol. 469, no. 4, pp. 1000–1005, 2016.

[40] M. Yamamoto, K. Kakihana, T. Kurosu, N. Murakami, and O. Miura, "Clonal evolution with inv(11)(p15q22) and NUP98/DDX10 fusion gene in imatinib-resistant chronic myelogenous leukemia," *Cancer Genetics and Cytogenetics*, vol. 157, no. 2, pp. 104–108, 2005.

Hindawi
Journal of Diabetes Research
Volume 2022, Article ID 1531289, 17 pages
https://doi.org/10.1155/2022/1531289

Review Article

The Impact of Diabetes on Vascular Disease: Progress from the Perspective of Epidemics and Treatments

Runyang Liu,[1] Lihua Li,[2] Chen Shao,[1] Honghua Cai,[3] and Zhongqun Wang[1]

[1]*Department of Cardiology, Affiliated Hospital of Jiangsu University, Zhenjiang, China*
[2]*Department of Pathology, Affiliated Hospital of Jiangsu University, Zhenjiang, China*
[3]*Department of Burn Surgery, Affiliated Hospital of Jiangsu University, Zhenjiang, China*

Correspondence should be addressed to Zhongqun Wang; wangtsmc@126.com

Received 17 January 2022; Revised 10 March 2022; Accepted 23 March 2022; Published 8 April 2022

Academic Editor: Pawel Kleczynski

At present, the global incidence of diabetes has increased in countries with large populations, and the changes in developing regions are particularly worthy of attention. In the past 40 years or so, the income situation in China, India, and other countries has exploded, leading to changes in the way of life and work as well as an increase in the prevalence of diabetes. Metabolic disorders caused by diabetes can lead to secondary vascular complications, which have long-term malignant effects on the heart, kidneys, brain, and other vital organs of patients. Adequate primary prevention measures are needed to reduce the incidence of diabetic vascular complications, and more attention should be given to treatment after the disease. To this end, it is necessary to determine a standardized drug and physical therapy system and to build a more efficient and low-cost chronic disease management system.

1. Introduction

Diabetes can cause vascular complications directly or indirectly through a variety of mechanisms. Vascular lesions caused by diabetes include macrovascular and microvascular lesions. Macrovascular lesions may lead to cerebrovascular disease, cardiovascular disease, and peripheral vascular disease. Microvascular diseases can cause specific complications, such as renal failure, retinopathy, and neuropathy. In recent decades, the global incidence of diabetes has been on the rise, and coupled with the growth of the population base, the number of people with diabetes has gradually increased. Different from diabetes itself, the complications of diabetes are closely related to the region. In the past 30 years, the incidence of diabetes in traditional developed countries has been relatively high, but thanks to better diagnosis, treatment, and nursing processes, the incidence of diabetes complications has been low. However, in developing countries and regions, poor diagnosis and a general lack of nursing awareness has led to a high incidence of both diabetes and diabetes complications. Healthcare systems around the world carry an enormous financial burden to treat these complications. In this review, based on populations in different regions of the world, we analyzed the risk factors affecting diabetes and vascular complications and the prevalence of representative complications. We also summarized the prevention and treatment experience in many countries as well as reasonable prevention, treatment, and chronic disease management measures.

2. Epidemiology

According to estimates from the 9th edition of the IDF Diabetes Atlas in 2019, there are already approximately 463 million people with diabetes in the world, including estimated undiagnosed people, and based on risk factors, the prevalence of diabetes will continue to rise in the future. By 2030, an estimated 10.2% of the total population or 578 million people is expected to have diabetes. By 2045, this proportion will rise to 10.9%, and the total number of patients will reach 700 million, and increase of 51.9% compared to 2019 [1]. Similar incidence changes can also be found in smaller areas. A study evaluating the subsequent impact of diabetes in the United States noted that between 1990 and

2010, adults with diabetes increased 3.1-fold to 20.7 million people [2]. Similar to the United States, as of 2013, seven nationwide spot checks on the prevalence of diabetes in China showed that the number of patients diagnosed with diabetes in the past 40 years had exploded. On the one hand, this is due to the large population base in China. On the other hand, it has a strong relationship with the rising prevalence of diabetes [3–7].

The real scary thing about diabetes is not the disease itself but the complications it brings. Among adults with diabetes worldwide (20-79 years), the leading cause of death can be attributed to diabetic vascular complications [8]. Interestingly, there are large regional differences in the incidence of the vascular complications of diabetes. Researchers in the United States have pointed out that the prevalence of diabetic vascular complications, especially cardiovascular diseases, is experiencing a downward trend. Similar conclusions were also found in studies of cerebrovascular diseases, peripheral vascular diseases, and retinopathy [2, 9, 10]. Numerous European studies have shown similar conclusions, i.e., improvements in the prevalence of vascular complications as well as cardiovascular mortality [11, 12]. In some Asian countries, such as Japan and South Korea, whose economic situation is similar to that of Europe and the United States, the number of patients receiving drug treatment for diabetes is high, and nursing care for diabetes is also better than that in developing countries [13–15]. In relatively underdeveloped regions such as China, there is a relative lack of aggregated epidemiological reports on diabetic vascular complications, and most of them are regional sample surveys. Seven national surveys in China have also tended to focus on blood samples. Pooled surveys of vascular complications are typically cross-sectional, making it difficult to summarize trends in complications [16]. In India, surveys have also focused on the prevalence of diabetes, showing a growth trend similar to that in China. Surveys on vascular complications have also tended to focus on a specific time, and there is a lack of cohort studies and follow-up studies [17].

Therefore, it is difficult to draw direct and clear conclusions on the incidence of diabetic vascular complications in these developing countries.

3. The Influencing Factors of Diabetic Vascular Complications

3.1. External Factors

3.1.1. Diet. The current popular modern diet features American fast food with good taste [18]. The diet of many developing countries has also undergone tremendous changes, with many Asian countries gradually shifting to a Western diet [19, 20]. This change in dietary trends will increase the incidence of obesity and, in turn, the incidence of type 2 diabetes globally. A prospective cohort study in the United States found that a Western dietary pattern was positively associated with cardiovascular disease, with the highest risk group having a nearly 2-fold increase in the incidence of CHD [21].

The reason modern diets have such an effect on the body is that they cause individuals to consume more carbohydrates, which plays a crucial role in the pathogenesis of diabetes. The original staple food in many parts of China is mainly coarsely processed grains other than rice. However, currently, Chinese consumers often refuse to eat coarse grains because of their higher price and poor taste. Refined grains have become the mainstream. This staple food has a higher glycemic index and less fiber, potentially increasing the risk of type 2 diabetes [22]. The role of added sugars, especially fructose, in beverages in the pathogenesis of diabetes has been increasingly emphasized [23]. A national survey conducted in the United States showed a linear correlation between fructose intake and the incidence of diabetes. The main reason for this change can be attributed to sugar-sweetened beverages, which account for an astonishing 50% of added sugar in the United States, a trend that has also spread to developing countries such as China and India [22, 24–26].

Western diets also consist of higher fat and protein intake, with protein intake tending to be dominated by red and processed meat [19]. Some Asian countries that are in transition also show a higher intake of fat, while the proportion of high-quality protein intake is relatively low [24]. Although there is little research on the subject, taking China as an example, the ratio of fat to protein in local food and beverages has also changed, and there is also a trend toward high-fat and highly processed meat. Among them, the contents of sodium glutamate and sodium chloride are high, such as in hot pot and Sichuan dishes. All of these factors increase the risk of diabetes and cardiovascular disease.

In addition, the effect of alcohol intake on macrovascular and microvascular complications has also been widely discussed. A Chinese study on hospitalized patients with type 2 diabetes noted a clear dose–response relationship between alcohol consumption and lower extremity aortic lesions, and the group that had drank alcohol for more than 20 years was 3.5 times more likely to develop the disease [27]. However, a case study in Singapore also showed that alcohol intake can reduce the incidence of diabetic retinopathy, suggesting that certain amounts of alcohol could have a protective effect on microvascular function [28].

3.1.2. Physical Activity. Due to changes in production methods in developing countries, the proportion of manual labor in social production has declined. The continuous increase in motor vehicle usage has reduced the use commuting methods that require exercise, such as walking and cycling, as has relatively extended working hours and increases in sedentary time. Generally, people, especially urban residents, have less time for exercise [29].

In addition, sedentary activities such as watching TV account for a large proportion of the current entertainment patterns of urban residents in various countries. Such changes in work and play increase the risk of type 2 diabetes and even have a certain correlation with the genetics of obesity [30, 31].

3.1.3. Other Lifestyle Factors. Smoking is an important risk factor for diabetes. At the beginning of the 21st century, a

sample survey in China showed that up to 70% of men smoked. The prevalence of diabetes in smokers is approximately 20% higher compared with nonsmokers, with higher risk for those who started smoking earlier and those who have smoked longer. Older people are more likely to be at risk of developing diabetes [32]. At the same time, increases in environmental pollutants such as air pollutants and some harmful metal elements may also be correlated with increases in cerebrovascular complications, but whether air pollutants are related to type 2 diabetes remains to be confirmed [33].

3.2. Internal Factors

3.2.1. Blood Sugar. In diabetic patients with poor glycemic control, some arteries in the body are more likely to have increased calcification and medial thickness and dilation, which ultimately leads to complete disease of the enlarged vessels. Worsening macrovascular disease is positively correlated with blood glucose levels, and the glucotoxicity and lipotoxicity caused by hyperglycemia and metabolic disorder, respectively, can lead to accelerated arteriosclerosis [18]. In T1DM patients, HbA1c (glycosylated glycemic protein) plays a crucial role in the assessment of blood glucose and is a leading risk factor for CVD in addition to age [27]. Rawshani's research also pointed out that the HbA1c level of diabetic patients is the strongest risk factor for stroke among many other factors [34].

However, lower blood sugar is not always better, and the effect of hypoglycemia on blood vessels has also been mentioned in many studies. From a mechanistic point of view, a small-scale blood glucose test study of 121 T2DM patients conducted by the University of Malta found a correlation between hypoglycemia and macrovascular disease stress or a series of inflammatory cytokine responses [35]. From an epidemiological point of view, a study that aggregated data from 109 countries showed that some countries in the Americas had the highest proportion of hypoglycemia-related mortality [12]. This suggests that large fluctuations in blood sugar and the impact of hypoglycemia on vascular complications among diabetic patients should not be ignored.

3.2.2. Blood Lipids. It is well known that vascular fat deposition is a basic feature of macrovascular disease, and this also applies to macrovascular disease secondary to diabetes. Experiments based on LDL receptor-deficient mice have shown that blood lipids can actually mediate vascular lesions; the mechanism may be that lipids can induce downstream vascular-related signaling pathways [36]. The main components of atherosclerotic plaques are free cholesterol and cholesterol esters. The DCCT/EDIC study in Pittsburgh, USA, also found that vascular complications were associated with triglyceride (TG) levels. If TG/high-density lipoprotein cholesterol $(\mathrm{HDL}-\mathrm{C}) > 2$, the patient's cardiovascular risk is increased [37]. In addition to blood lipids, perivascular adipose tissue (PAT) can cause chemotaxis among inflammatory cells through a variety of inflammatory factors and can destroy the normal tension of blood vessels through the insulin signaling pathway, thereby impairing vascular function, aggravating insulin resistance, and increasing the occurrence of vascular complications [38].

3.2.3. Blood Pressure. Both Eastern and Western scholars have found a positive correlation between hypertension and diabetic vascular complications. A prospective cohort study in Finland found that from 1995 to 2008, patients with type 1 diabetes were more likely to suffer from coronary heart disease and stroke and have a higher mortality rate due to complications [39]. The China Stroke Primary Prevention Trial (CSPPT) conducted in China found that during the 4.5-year survey period, subjects with a systolic blood pressure between 130 and 140 mmHg had a 1.37-fold higher risk of developing diabetes than the 120-130 mmHg group, and hypertension reduced the probability of the former group returning to a normal fasting blood sugar by approximately 30% [40].

3.2.4. BMI/Waist Circumference. A high BMI is often accompanied by a higher risk of diabetes. A prospective study conducted by Wang showed that a higher BMI was the most important factor related to the onset of diabetes. The prevalence of diabetes among Chinese individuals with a higher BMI can reach nearly twice than that among individuals with a normal BMI in the same period [41]. Cohort studies conducted in the United States from 2007 to 2012 pointed out that the onset of diabetes may not be related to body mass index alone and that a larger waist circumference may be more closely related to the onset of diabetes [42]. This point may be more applicable in Asian populations. A study conducted in southern China found that the obesity rate among 15,364 respondents was 7.9% but the rate of abdominal obesity was up to 1.3% among people with a low BMI. This is because, for many individuals in China, obesity typically manifests as central obesity characterized by fat accumulation in the abdomen, and because BMI cannot indicate local fat distribution, it is often lower in Asian diabetic patients [43].

However, a BMI that is too low does not play a protective role against the onset of diabetic complications. A study conducted by Zhang in China with 3,224 patients showed that although diabetic retinopathy (DR) and atherosclerotic plaques were positively correlated with BMI, the incidence of diabetic neuropathy presented a U-shaped curve with increased BMI, indicating that a BMI that is too low or too high may increase the possibility of diabetes onset [23].

3.3. New Challenges

3.3.1. Regional and Ethnic Differences. Many countries are relatively ethnically diverse, and interindividual differences in diabetes prevalence may be partly attributable to ethnic differences. The U.S. has many immigrants, so studies can compare genetic differences in diabetes prevalence in the same environment. A study of 49,574 subjects showed that between 1997 and 2004, racial differences in diabetes prevalence were found among different BMI groups, with the largest racial differences among the normal BMI groups, and this gap shows a widening trend [44]. The prevalence of

diabetes among different ethnic groups in China has also been mentioned by many scholars. For example, the prevalence of diabetes in Tibetans is significantly lower than that in Han Chinese people. Apart from the differences in economic and lifestyle factors analyzed previously, Tibetans are more likely to have diabetes. High exercise levels may prevent the vascular complications of diabetes [3, 45]. Racial differences can also be reflected in specific complications. A study comparing different ethnic groups in Singapore showed that Singaporeans of Indian descent had a higher risk of developing diabetic eye disease than those of Chinese and Malayan descent (Indian 30.7%, Chinese 26.2%, Malayan 25.5%, $p = 0.012$) [46]. Gupta and Misra's study also found that South Asians had a higher incidence of retinopathy than Caucasians [47].

In addition to differences between races and countries, differences in prevalence within the same country are also worthy of attention. A Chinese study that aggregated data from 31 items showed that the prevalence of diabetes was 1.73 times higher in eastern regions compared with western regions [48]. An urban-rural disparity in diabetes in Asian countries is also increasingly evident. Urban areas have a higher incidence and better medical standards. In contrast, the incidence of diabetes in rural areas is lower, but medical care is less optimum, resulting in a greater incidence of vascular complications. Postmortem mortality is also higher [17, 49, 50].

3.3.2. Juvenile Onset. Diabetes, especially type 2 diabetes, shows a trend of younger onset, and it is more characteristic for adolescents to have an increased incidence of diabetes [51]. Because young diabetic patients suffer from early disease onset, the course of diabetes is greatly prolonged, and the possibility of cardiovascular complications is greatly increased. This trend creates a huge burden in terms of the diagnosis and treatment of vascular complications [52].

3.3.3. Aging Worsens Diabetic Complications. Due to various factors, such as improvement in medical standards, the global population with diabetes complications shows the characteristics of aging [11]. Aging may have two influences on diabetes complications. On the one hand, there is a higher prevalence of diabetes with age. On the other hand, the prolonged course of diabetes in aging patients often leads to a greater possibility of vascular complications. The multi-country results of diabetes complications compiled by Beckman showed that the prevalence of various diseases, including the peripheral vascular complications PAD and DM retinopathy, increases with aging [53]. A study of risk factors in China also found that increasing age greatly increases the incidence of PAD: 2.81% (95% CI = 1.77 – 4.43) and 3.84% (95% CI = 2.44 – 5.98), respectively, in men and women aged 25-29 compared with 21.95% (95% CI = 15.39 – 30.31) and 27.95% (95% CI = 20.14 – 37.37) in men and women aged 95-99 years [54].

3.3.4. Gestational Diabetes. In developing regions, the follow-up impact of gestational diabetes (GDM) has gradually received attention because the disease may not only affect the pregnant women themselves but also have a profound impact on fetal diabetes metabolism and disease [55]. Indian research has pointed out that the prevalence of type 2 diabetes for mothers with GDM is increased 7-fold and that the fetus will be more likely to have obesity or T2DM [17]. A pooled study in China showed that in a group of 7-year-old children, the offspring of mothers with GDM were twice as likely to be obese [16]. Because this disease needs to be prevented between generations, the number of affected groups is large, the age of onset is often earlier, and the cost of treatment can be double; therefore, special attention should be paid.

Figure 1 shows a comparison of risk factors for diabetes in different regions, the incidence of diabetes, and the decline in diabetic vascular complications in Europe (Figure 1).

4. Macrovascular Complications

Diabetic macrovascular disease is the main way that diabetes reduces the life of diabetic patients. Macrovascular disease of important organs is likely to cause disability and even death in patients. The lesions of macrovascular disease can be mainly divided into cardiovascular, cerebrovascular, and peripheral arterial lesions [8]. A pooled study of 57 reports worldwide found an overall macrovascular complication rate of 32.2% among 4,549,481 patients with T2DM who were systematically reviewed [56].

A comparison of the risk for different diabetic vascular complications is shown in Table 1.

4.1. Cerebrovascular Disease. An important manifestation of diabetic cerebrovascular disease is stroke. In addition to vascular disease in the brain, it may also be related to insufficient blood supply to the brain caused by carotid artery disease. The INTERSTROKE study, which included stroke-related data from 32 countries, showed that compared with the nondiabetic population, the risk of stroke in diabetic patients was increased by 16% [57]. Guo et al. also found that among diabetic patients in Zhejiang Province, China, from 2007 to 2013, the risk of stroke in both male and female type 2 diabetic patients was more than three times greater than that in the nondiabetic population. Among them, women (OR = 3.87, 95%; CI = 3.76 – 3.99) had an obviously higher risk than men (OR = 3.38, 95%; CI = 3.27 – 3.48) [58].

Compared with normal patients, diabetic patients have poorer outcomes from stroke because diabetes mediates both vascular disease and neuropathy, exacerbating neurological sequelae, such as recurrence and death [59]. A follow-up study conducted in China showed that among the 143 people surveyed, patients with uncomplicated diabetes were more likely to have stroke recurrence than nondiabetic individuals. The risk was increased by 2.77 times (HR = 2.77, 95% CI = 1.66 – 4.63) [60]. A study combining the Emerging Risk Factors Collaboration (ERFC) and the British Biobank showed that compared with stroke alone (mortality per 1,000 person-years = 15.6), diabetes significantly increased the mortality rate of stroke (diabetes and

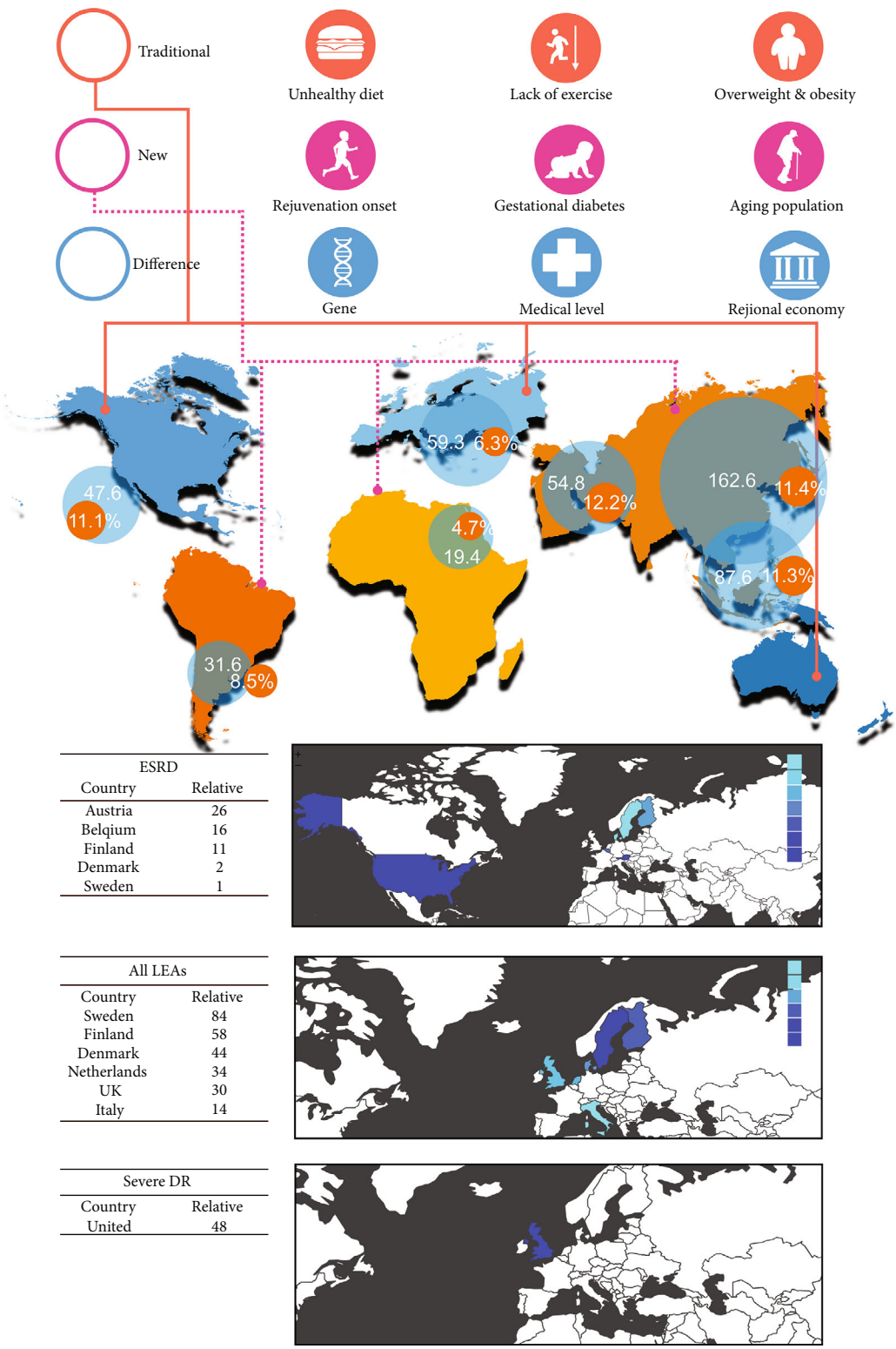


Figure 1: The risk factors for diabetic vascular complications and the decrease in morbidity caused by treatment. Worldwide, the incidence of diabetes has shown an overall upward trend. It is worth noting that there are obvious differences in the incidence of diabetes between different regions, which are presumably caused by differences in economic development, medical care levels, and genetics between regions. Due to an unhealthy diet and lack of exercise, which leads to obesity, current diabetes prevention also needs to pay attention to the effects of dietary changes in some areas, childhood obesity, gestational diabetes, and population aging. Fortunately, better medical treatment can bring about improvements in the incidence of diabetic vascular complications. (For the convenience of observation, the connection between Europe and Asia is split. The data in the picture come from an article that analyzes the changes in IDF and vascular complications [1, 11].)

Table 1: Comparison of the risk of different diabetic vascular complications.

Event	Country/ region	Research time period	Number of overall research participants	Specific event	Evaluation parameters	95% CI
Cerebrovascular disease	China [70]	2003~2004	1,087	Stroke recurrence	HR = 2.77	1.66-4.63
	Worldwide [63]	2007~2015.8.8	40,391	All stroke	OR = 1.16	1.05-1.30
	Worldwide [67]	1966~2013	787,924	Diabetes-related stroke	Females RR = 2.28; males RR = 1.83	1·93-2·69; 1·60-2·08
	China [64]	2007~2013	635,252	Stroke and stroke subtypes	Females SIR = 3.87; males SIR = 3.38	3.76-3.99; 3.27-3.48
	Iran [65]	1976~2002	116,316	All stroke	T1DM females RR = 4.7; T2DM females RR = 1.8	3.3-6.6; 1.7-2.0
	Japan [66]	1990~2004	35,747	Ischemic stroke	HR = 4.64	1.76-12.2
	Germany [69]	2005~ 2007	5,757	Risk of death after stroke (30 days, 1-2 years, 3-5 years)	Mortality rate: HR = 0.67; HR = 1.42; HR = 1.00	0.53-0.84; 1.09-1.85; 0.67-1.41
Cerebrovascular disease	China [72]	2007~ 2008	22,216	Death 6 months after ischemic stroke	OR = 1.23	1.10-1.37
	Worldwide [73]	1966~2013	886,710	Coronary heart disease	Females RR = 2.82; males RR = 2.16; females vs. males RRR = 1.44	2.35-3.38; 1.82-2.56; 1.27-1.63
	China [74]	1986~ 2009	110,660	Cardiovascular death	Females HR = 6.9; males HR = 3.5	—
Cardiovascular disease	Finland [77]	1982~ 1984	—	Myocardial infarction	HR of death due to coronary heart disease among non-DM patients with a previous MI history vs. DM patients without a previous MI history = 1.0	0.7-2.6
	Denmark [79]	1997-2002	—	Cardiovascular death	HR of DM males without a previous MI history = 2.42; HR of non-DM males with a previous MI history = 2.44	2.35-2.49; 2.39-2.49
	Sweden [83]	—	18,624	Primary composite endpoint; all-cause mortality; stent thrombosis; and major bleeding	DM patients: HR = 0.88; HR = 0.82; HR = 0.65; HR = 0.95	0.76-1.03; 0.66-1.01; 0.36-1.17; 0.81-1.12
Peripheral vascular disease	China [85]	1990-2000	—	PAD	OR = 1.71	1.45-2.01
	Worldwide [86]		13,885	PAD	ARD = 5.5%; OR = 1.43	1.28-1.61

stroke deaths per 1,000 person-years rate = 32.5) [61]. Among them, the course of disease may be an important factor affecting the prognosis. A study analyzing German medical insurance pointed out that between 2005 and 2009, the malignant degree of stroke increased in the 5,757 patients under investigation due to the prolonged course of diabetes. Ultimately, 1/3 of the patients died of cerebrovascular disease within 5 years [62].

Fortunately, the control of cerebrovascular disease in developed areas may have a relatively good effect on the incidence of stroke. Many countries have shown a certain downward trend, but similar conclusions may not be applicable in India and China [11, 16, 17].

4.2. Cardiovascular Disease. Diabetes patients are prone to secondary heart-related vascular complications. The main manifestations are CHD, myocardial infarction (MI), and sudden cardiac death (SCD). A systematic study by Einarson and colleagues that aggregated 57 data points from all over the world pointed out that 32.2% (53 studies, $n = 4{,}289{,}140$) of more than 450,000 patients with type 2 diabetes had diabetic macrovascular disease, of which CVD accounted for 21.2%, followed by heart failure (14.9%), angina pectoris (14.6%), and MI (10.0%), and the probability of occurrence of these cardiovascular diseases was much larger than that of cerebrovascular lesions [56].

In cardiovascular disease, one of the more serious consequences is heart failure. In earlier studies, the impact of diabetes was thought to be similar to that of MI. A Finnish-based population study conducted by Haffner et al. showed that patients with diabetes but no previous MI had the same risk of MI in the future as patients with MI without diabetes;

thus, a history of type 2 diabetes can be considered to be equivalent to a previous MI [63]. However, the Finnish study at the time adopted the 1980 diagnostic criteria, which includes a higher blood glucose threshold than the new standard; thus, the degree of diabetes was more serious, which may have exaggerated the effect of general diabetes on cardiovascular disease. A study conducted by Schramm and collaborators in Denmark based on 3.3 million people found that diabetes can indeed increase the risk of neovascular disease (males OR = 2.42, 95% CI = 2.35 − 2.49; females OR = 2.45, 95% CI = 2.38 − 2.51), but this effect was weak in patients with coronary heart disease (males OR = 2.44, 95% CI = 2.35 − 2.49; females OR = 2.62, 95% CI = 2.38 − 2.51) [64]. However, there are also experiments showing that the level of blood glucose control seems to be independent of severe cardiovascular results. A cohort study of 2,740 patients in the United States conducted by de Simone et al. showed that HbA1c levels were higher in patients without heart failure than in those with heart failure (7.92 ± 2.47% vs. 6.78 ± 2.39%, $p < 0.04$); the products of abnormal metabolism in diabetic patients are suspected to be able to directly provide energy for myocardial contractions [64].

According to Beckman, in addition to increasing the risk of cardiovascular disease, diabetes also worsens its consequences [65]. An investigation into frequently occurring cardiometabolic diseases indicated that diabetes may lead to myocardial apoptosis through cell oxidation or endoplasmic reticulum stress. As a result, among patients with diabetes, those with MI (32.0 per 1,000 person-years) are more likely to experience cardiovascular death than those with MI alone (16.8 per 1,000 person-years) [61, 66]. A plasma phospholipid transfer protein knockout (PLTPO) experiment further pointed out that in patients who have undergone PCI treatment, the severity of diabetes may be positively correlated with cardiovascular death because the risk of cardiovascular death was 50% higher in patients with diabetes who received insulin treatment than in those who did not; moreover, the prognosis is worse after normal blood flow is restored by stent placement [67].

Due to genetic differences, cardiovascular disease in Asian populations is different from that in Caucasian populations. A pooled study from India pointed out that from the perspective of the time of onset of the disease, the course of CAD occurs earlier in some Asian populations than in Caucasian populations, and the mortality rate caused by acute macrovascular events is also higher. The main reason may be that Asian people have higher levels of insulin and blood lipids after the onset of type 2 diabetes than Caucasian people, which likely causes more serious insulin resistance and endothelial disorders, further accelerating the course of vascular disease and causing more serious disease [17]. However, on a global scale, due to improvements in medical care in most developed countries, the risk of diabetic cardiovascular disease has gradually decreased. This may be due, in part, to improved blood sugar control in diabetic patients, but it may also be related to a decline in the incidence of CVD itself [11].

4.3. Peripheral Vascular Disease and Diabetic Foot. In addition to cerebrovascular and cardiovascular diseases, another important effect of diabetic macrovascular disease is peripheral vascular disease. The main cause of the pathological changes is atherosclerosis of the large blood vessels of the lower extremities, leading to blood circulation disorders. One of the characteristic secondary pathological changes is diabetic foot. A study by Song et al. compiled 37 PAD-related parameters in China and showed that diabetes is the third leading cause of PAD after smoking and hypertension. Patients with diabetes are nearly 1.71 times (95% CI = 1.45 − 2.01) more likely to develop PAD than nondiabetic patients [54].

Diabetes also increases the consequences of PAD because it involves more distant acral vessels and may cause medial sclerosis and accelerate vascular hardening through mechanisms such as oxidative stress, genetic damage, and vascular damage [68]. In addition to vascular disease, diabetes itself can also cause lower limb neuropathy, microvascular disease, and changes in foot dynamics. These factors work together with PAD to cause diabetic foot [69]. For patients, diabetes can worsen the quality of life after PAD onset. Studies have pointed out that compared with the general population, diabetic patients tend to be more prone to lower extremity pain, hypoesthesia, and other sensory changes. This is because the correlation between diabetic vascular disease and neuropathy is approximately 2-fold higher [70].

At present, the control of diabetic peripheral vascular disease remains mixed. A study summarizing lower limb amputation in many European countries showed that the current control situation is still mixed. In Ireland and Spain, among other places, the rates of major amputation among diabetic patients have increased from 0.0479% and 0.00712% to 0.0480% and 0.00747%, respectively, in different time periods; the rates of minor amputations in the corresponding regions increased from 96.2/100,000 and 9.23/100,000 to 127/100,000 and 10.970/100,000, respectively. In addition, the rate of minor amputations in Finland also increased from 11.0/100,000 to 13.5/100,000 [71]. However, a study conducted by Kurowski and others in Western Australia showed that from 2000 to 2010, among a total of 5,981 amputations, as many as 71% of the patients had peripheral arterial disease. Under the premise that the lower extremity amputation rate has dropped overall, diabetic patients (6.2% per year) have shown a smaller decline in the amputation rate than nondiabetic individuals (6.7% per year) [72].

5. Microvascular Complications

In addition to macrovascular lesions, microvascular lesions also play an important role in mediating later complications, but microvascular lesions are often easily overlooked. From a diabetes nursing perspective, the degree of microvascular disease is commonly used today to reflect the degree of care.

5.1. Kidney Disease. Diabetes is the main cause of diabetic nephropathy, and the end-stage renal disease (ESRD) population is dominated by diabetic patients [73]. Similar to those of retinopathy, the histological manifestations of diabetic nephropathy include thickening of the basement membrane

and aneurysms. Along with an increase in glomerular filtration, expansion of the adjacent cell matrix and progression of partial sclerosis of the nephron, the original filtration barrier is destroyed [53].

Zhang et al. compiled reports from 30 studies conducted in China and showed that among the 79,364 participants surveyed, up to 21.8% of diabetic patients (95% CI = 18.5 – 25.4%) had diabetic nephropathy and that the prevalence rate in the region (41.3%) was significantly higher than that in Western countries (22.3%) [74]. In some areas, as many as 7% of initially diagnosed diabetic patients have ESRD, and a survey showed that the prevalence of kidney disease in type 2 diabetic patients reached 25% after 10 follow-up visits [75, 76]. A study conducted by Yeung in Hong Kong showed that among hospitalized patients, the proportions of type 2 diabetic patients with microalbuminuria and macroalbuminuria were 24.9% (95% CI = 22.9 – 27.0%) and 18.3% (95% CI = 16.5 – 20.2%), respectively, showing that nearly 60% of patients with type 2 diabetes may have some degree of kidney disease. In contrast, the prevalence of kidney disease in patients with type 1 diabetes is less than 12% at 7 years after diagnosis [77].

Similar to other vascular diseases, ESRD shows a downward trend in developed areas but has a worsening trend in economically underdeveloped areas. A study of several databases in the United States showed that over 20 years (1990-2010), the incidence of ESRD in diabetic patients decreased by 28% and that the incidence of ESRD in all age groups decreased significantly after 2000 [2]. During the same period, the incidence of diabetes-related ESRD in some Western European countries and Nordic countries declined to varying degrees. In contrast, however, diabetic nephropathy in parts of Russia, East Asia, and South Asia increased rather than decreased [49]. A study by Huang et al. obtained data from 878 hospitals in China and showed that diabetic nephropathy among chronic kidney disease (CKD) patients increased from 19.5% in 2010 to 24.3% in 2015, with an average annual growth rate of 0.96% during the period; this trend was most significant in the populations living in cities in the northern region [78].

5.2. Retinopathy. Diabetic patients affected by retinopathy account for 30% of the total retinopathy population, and some patients with retinopathy have a high probability of eventually becoming blind. In different follow-up studies, the incidence of diabetic retinopathy has developed in different directions in people worldwide [11]. At present, retinopathy is usually divided into proliferative and nonproliferative. The main difference between the two is whether there is retinal vascular renewal. However, both types of retinopathy are accompanied by the destruction of the pericytes that wrap the retina, which results in the blood vessels of the retina losing the ability to maintain normal vascular tension, growing unstable, and becoming easily damaged by oxides, ultimately leading to the destruction of the retinal barrier to cause microangiopathy [11]. Song et al. conducted a pooled study in China and showed that the incidence rates of proliferative diabetic retinopathy (PDR) and nonproliferative diabetic retinopathy (NPDR) reached 0.99% (95% CI = 0.40 – 1.80) and 15.06% (95% CI = 11.59 – 18.88) and that the aggregated changes in any type of diabetic retinopathy reached 18.45% (95% CI = 14.77 – 22.43) [79].

From an optimistic point of view, studies from 2000 to 2017 show that the incidence of diabetic retinopathy (STDR) in many regions has dropped significantly, with the highest decline reaching an astonishing 91% (1.7% to 0.16%). In some countries, such as the United Kingdom, the incidence of several different types of retinopathy increased by more than twofold (2.0% to 4.7%) from 1991 to 2006. These declining trends may largely be attributed to better treatment levels and the use of better care measures [80]. However, European studies on future predictions show that the incidence of diabetes in Europe is expected to increase by 2 million people over the next 30 years; approximately 50% of patients with type 1 diabetes and approximately 25% of patients with type 2 diabetes will continue to suffer from diabetic eye disease [81].

5.3. Neuropathy. Diabetic neuropathy is related to the mechanism of microvascular disease. Due to the hardening and thickening of the basement membrane of the capillaries, the blood flow of the capillaries that nourish the nerves is reduced, and along with damage to the surrounding cells, leads to continuous hypoxia, oxidative stress, and other complexities. The downstream mechanisms jointly destroy the nervous tissue [82, 83]. Specific types of diabetic neuropathy can be divided into two categories. The first category, which is more common, is called typical diabetic peripheral neuropathy (DPN), also known as length-dependent sensorimotor polyneuropathy (DSPN); the second category is atypical DPN, also called polyneuropathy [84]. The risk factors caused by high blood sugar levels may be more clinically significant in typical DPN, while atypical DPN is rarer and has a less predictable disease course, so it is more difficult to make inferences from risk factors [53]. A study by Lu and colleagues in Shanghai showed that among 2,035 individuals with abnormal blood glucose regulation, including diabetes, impaired glucose regulation (IGR) and normal glucose tolerance (NGT), the incidence of peripheral neuropathy (PN) in patients with known diabetes reached 13.1%, and the incidence in the IGR population was also increased by approximately 1.8 times compared with that of the normal population (2.8% vs. 1.5%) [85]. However, few studies on diabetic vascular complications alone exist because neuropathy is often considered to be an auxiliary cause of diabetes and is analyzed together with microvascular disease.

6. Countermeasures for Diabetic Vascular Complications

In view of the above risk factors and morbidity, we roughly put forward some preventive suggestions at the level of the individual and explored the treatment plan. In response to the needs of patients with diabetic vascular complications, a whole management process from prevention, diagnosis, and treatment to chronic disease care should be established.

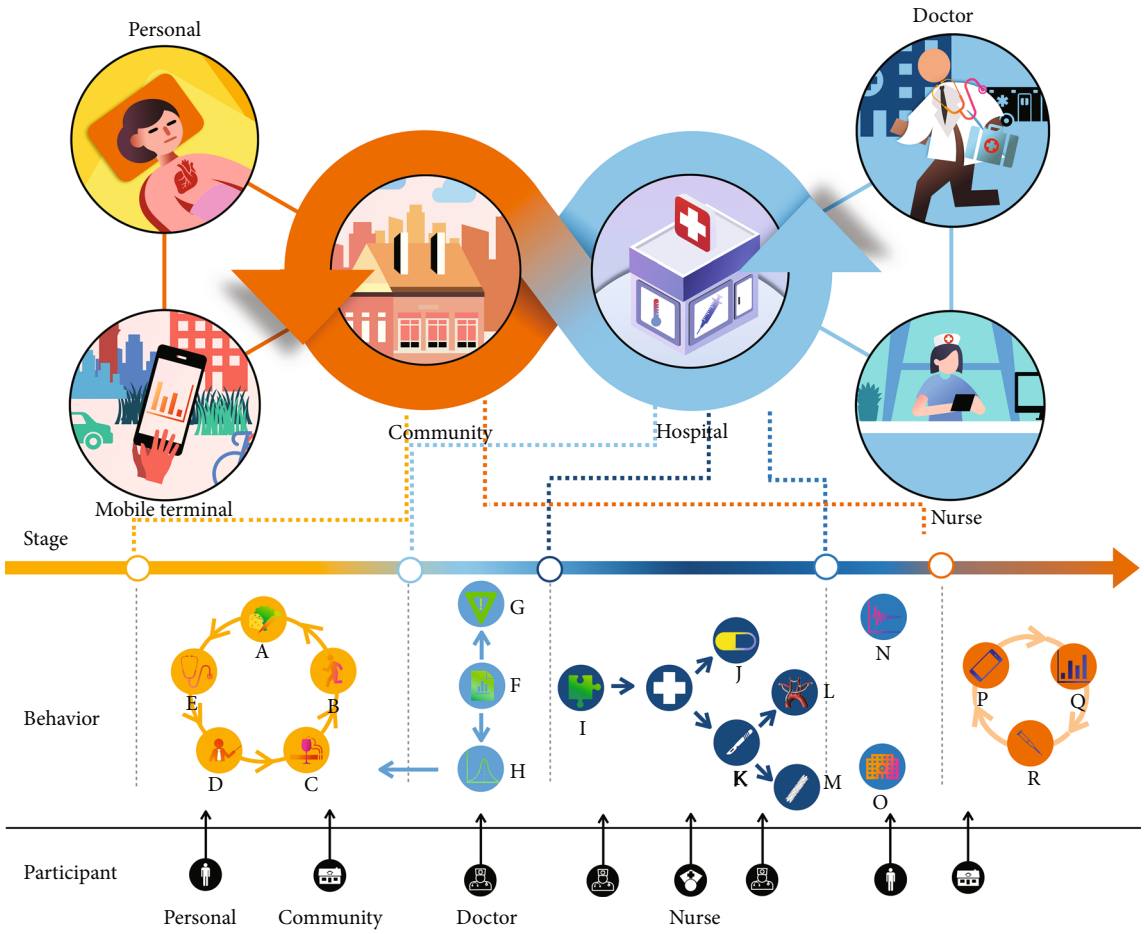


Figure 2: The prevention, treatment, and management of diabetic vascular complications. A: Diet; B: sport; C: quitting smoking and alcohol; D: health knowledge information; E: regular health examinations; F: diagnostic results; G: report individual risk factors; H: aggregate data analyses; I: treatment plans; J: drugs; K: surgery; L: bypass surgery; M: percutaneous coronary intervention; N: index detection; O: hospital care; P: mobile terminals; Q: cloud database analyses; and R: data-based treatment changes. Before the onset of diabetic vascular complications, diabetic patients can reduce their chances of onset by adjusting their diet, increasing exercise, and abstaining from bad habits. At the same time, they can actively participate in physical examinations and health education lectures. Doctors can actively use mobile phone data during the diagnosis and treatment of diabetic vascular complications to obtain accurate risk factors and help prevent them. At the same time, after the treatment is completed, a low-cost and timely chronic disease management system can be established through mobile devices to reduce the risk of recurrence of vascular complications and improve prevention.

In this process, patients, communities, and medical staff must participate together (Figure 2).

6.1. Lifestyle-Level Prevention

6.1.1. Diet

(1) Ensure a Reasonable Total Food Intake. Taking China as an example, the relative intake of the traditional diet should be reduced; this traditional eating pattern can reduce the possibility of obesity [25].

(2) Maintain a Balanced Nutrient Intake Ratio. In developed countries, the proportion of coarse grains and vegetables should be increased, thereby increasing the intake of cellulose, maintaining the intake of protein, and reducing the intake of fat. In developing regions, the intake of certain vegetables should be increased to reduce the intake of refined grains, and by consuming affordable meats such as eggs and chicken, the intake of protein should be increased and the intake of fat should be maintained to a certain amount. In some developing countries, the original diet consists of mainly carbohydrates and plants, and therefore, protein accounts for a low proportion of the overall energy intake and grains account for more than 60% of total energy intake [25, 86]. In addition, healthy foods such as vegetables are relatively low priced in China, and thus, it is more feasible to promote a diet that has protective functions against diabetes and cardiovascular diseases [87].

(3) Reduce the Intake of Sugar-Sweetened Beverages. Malik and others have pointed out that it is possible to replace sugary beverages with beverages that do not contain fructose, such as those containing new sugar substitutes and conventional beverages such as water, coffee, and fruit juice. However, a prospective study on beverages found that the consumption of

fruit juice and beverages containing sugar substitutes increased by 7% (1% to 14%, $I(2) = 51\%$) and 8% (2% to 15%, $I(2) = 64\%$), respectively. Although there may be some offset factors, these two beverages are still not recommended as alternatives to sugary beverages [88].

(4) Moderate Alcohol Intake. A study by Gupta in Singapore found that occasional and frequent drinkers in the group had a lower likelihood of retinopathy, although the generalizability of this conclusion is debatable, as some scholars have pointed out that long-term alcohol consumption can lead to retinopathy and impair the function of large blood vessels [28].

6.1.2. Physical Activity

(1) If You Already Have Diabetes, Do Planned Exercise. A pooled study by Kumar et al. clearly pointed out that planned exercise can be used to treat insulin resistance in type 2 diabetes and can reduce HbA1c levels by 0.27 (-0.82 to 2.08), which is very important for vascular complications; thus, exercise may have a considerable protective effect against the complications of diabetes [89]. Taking into account a decline in physical function among diabetic patients, recommended exercise methods should be reasonable and regular.

(2) Everyone Should Develop Exercise Habits as Soon as Possible to Improve Their Sports Ability. A study conducted by the U.S. Veterans' Medical Center among elderly patients showed that exercise capacity is negatively correlated with the mortality of type 2 diabetes patients and that people who do not exercise have relatively poor control over the vascular complications of type 2 diabetes and are more likely to develop vascular complications. Thus, exercise can be used to improve an individual's exercise ability and prevent the vascular complications of diabetes [90].

6.1.3. Smoking and Environmental Pollution

(1) Quit Smoking as Soon as Possible and Reduce Exposure to Air Pollutants through Reasonable Protective Equipment Such as Masks. Reducing the amount of smoking or quitting smoking has been proven by many studies to have an important effect on the cardiovascular complications of diabetes. It can also have a certain protective effect against nondiabetic vascular complications. At the same time, the isolation of pollutants and some heavy metal elements in the air by necessary means has also been proven to be related to the prevention of cerebrovascular disease in patients with diabetes (the risk factors for air pollution and lead exposure were found to affect 33.4% of diabetic patients) [32].

6.2. Prevention, Diagnosis, and Treatment at the Medical Level

6.2.1. Infer Possible Complications, Choose a Reasonable Inspection Method, and Find Undiagnosed Patients as Soon as Possible. Researchers in China found in the latest national survey that among 170,287 participants, the unknown rate of patients was more than 3/5, and more than 1/3 of the population had abnormal glucose homeostasis, indicating a large number of potentially undiagnosed diabetic patients [91]. Due to the longer actual course of disease, this group may have a higher risk of vascular complications than patients with diagnosed diabetes; therefore, it is necessary to diagnose patients with hidden diabetes in a timely manner.

In terms of macrovascular complications, diabetes also causes certain difficulties in the diagnosis of concomitant blood vessel complications, so it is necessary to choose an appropriate diagnostic method. Approximately 20-30% of patients with type 2 diabetes will experience "silent ischemia," causing the initial diagnosis of cardiovascular disease to be made after a longer disease duration. Moreover, the disease progression of diabetic patients is also relatively rapid, which worsens the outcome and prognosis of complications [92]. However, some scholars believe that asymptomatic coronary artery disease does not necessarily bring serious consequences based on the screening results of ischemia detection in diabetic patients (DIAD) and CT angiography [93]. In addition, taking PAD as an example, the ankle-brachial index is usually used to measure the degree of peripheral arterial disease. Generally, the critical value of the ankle-brachial index is 0.90. Diabetic patients with an ankle-brachial index less than this value may have a greater risk of peripheral arterial disease. Diagnostic medical ultrasound (CDU) and multidetector computed tomography (CTA) are also commonly used diagnostic methods [94].

Microvascular complications also have many specific effects. Currently, diabetic nephropathy is often diagnosed by proteinuria, but newly discovered specific markers should also be considered. Mannose-binding lectin (MBL) can trigger downstream inflammation and complement pathways, and it has been experimentally proven that after correcting for these factors, MBL is strongly correlated with type 2 ($OR = 7.55$; 95% $CI = 3.44 - 19.04$) and type 1 ($OR = 6.99$; 95% $CI = 2.83 - 17.15$) diabetes. It is speculated that the MBL level can also be used to predict the possibility of nephropathy [95, 96]. There are also a variety of diagnostic methods for neuropathy, most commonly reflex tests, symptom score tables, and skin puncture. Because neuropathy can also bring pain, convulsions, and other neurological symptoms, these symptoms also need targeted treatment [83].

6.2.2. Control Blood Sugar, Blood Lipids, and Blood Pressure within a Reasonable Range. Manuscripts should make recommendations for glycemic control, blood pressure, and lipid control to prevent cardiovascular complications in diabetic patients. Many scholars have demonstrated that well-controlled blood glucose levels can prevent vascular complications and reduce consequences. A study by Low Wang et al. found that better control of blood glucose levels was associated with less malignant outcomes in peripheral vascular disease, with each percentage point reduction in HbA1c reducing the likelihood of adverse cardiovascular events by 14.2% [97]. Similarly, optimal glycemic control may prevent the development of diabetic nephropathy. A study on multifactor intensive blood glucose treatment showed that after strict blood glucose control and treatment with renal active

drugs, the incidence of different kidney diseases in type 2 diabetic patients decreased to various degrees, and the risks of ESRD, microalbuminuria, and macroproteinuria were reduced by 65% (20 events vs. 7 events), 9% (1298 patients vs. 1410 patients), and 30% (162 patients vs. 231 patients), respectively [98]. Lower blood sugar levels are also an important protective factor for retinopathy. Chronic but well-controlled blood sugar levels have been found to reduce the likelihood of retinopathy by 11 times compared to approximately 2 times for coronary artery disease [99]. Additionally, similar to other pathologies, strict blood sugar control and a good lifestyle have also been shown to be effective in preventing neuropathy [100].

Similarly, lowering blood lipids is associated with the prevention of vascular complications, but the specific protective effect of these complications remains controversial. A study conducted in Shanghai, China, showed that diabetic patients with lower blood lipid levels had a lower prevalence of diabetic nephropathy (DKD) but no significant difference in the prevalence of diabetic retinopathy (DR). Of these, TG, TG/HDL-C, and non-HDL-C/HDL-C values were independently associated with diabetes [101].

Numerous studies have also reported that good blood pressure control can reduce the consequences of vascular complications. For example, control of high blood pressure has some benefit in the prognosis of cerebrovascular disease. In a preventive study of cardiovascular complications in more than 3,500 diabetic patients, the incidence of stroke decreased by 33% in patients treated with ACEIs [102].

In summary, although there are certain controversies in clinical trials, the study by Hewitt et al. still recommends controlling blood sugar, blood lipids, and blood pressure as a means to prevent specific complications of diabetes [103].

6.2.3. Appropriate Treatment for Specific Complications

(1) For the Onset of Cerebrovascular Disease, the First Priority Is to Control Blood Sugar, and at the Same Time, Thrombolytic Drugs Must Be Reasonably Selected According to the Indications. The prevailing view is that blood supply to the brain can be improved with thrombolytic drugs, but some current research suggests that restoring blood flow to the brain may bring about worse outcomes. A study of thrombolytic drugs showed that among 389 male patients, higher admission blood glucose levels were associated with a poorer prognosis and could cause intracranial hemorrhage. This indicates that ischemia–reperfusion may have a certain destructive effect on cerebrovascular diseases; therefore, the cerebrovascular complications of diabetes should be treated with blood sugar improvements and more conservative strategies [104].

(2) For Cardiovascular Disease, Drugs Are Recommended for Mild Cases, and Coronary Artery Bypass Graft Therapy Is Recommended for Severe Cases Rather than Interventional Therapy. Schmidt's review presents the current glucagon-like peptide 1 receptor agonists (GLP-1 RAs), sodium glucose cotransporter-2 (SGLT-2) inhibitors, proprotein convertase subtilisin type 9 (PCKSK9), and other new drugs for the treatment of CVD diseases. In addition, gene-level treatment via RNA-based therapies is awaiting research [105]. In addition, more mainstream CVD treatment can be achieved through vascular stents or bypass surgery. However, due to the presence of diabetes, the measures taken to revascularize may need to be changed. Experiments have proven that the ideal treatment should be vascular bypass surgery rather than implantation of percutaneous stents. Based on research in British Columbia, CABG has a better prognosis than PCI, and the advantage of CABG is more obvious in patients with major adverse cardiac or cerebrovascular events (MACCEs) (0.4995%, 95% CI = 0.34 – 0.71) [106]. Similar findings were found in Ishihara et al.'s study in Japan. After implantation of drug-eluting stents (DES) and dual antiplatelet therapy (DAPT), diabetic patients had more uncovered struts in the short term, and the treatment was not ideal [107]. A study conducted by Ramanathan from 1982 to 2011 proved that cardiac bypass has a considerable effect on survival. At 1, 5, 10, and 20 years, the survival rates could reach 97%, 97%, 96%, and 96%, respectively, all exceeding 95% [108].

(3) For Peripheral Vascular Disease, Especially Lower Extremity Vascular Disease, Drug Therapy Is Recommended, Followed by Vascular Surgery, and New Treatments Such as Endovascular Lithotripsy Should Be Selected According to the Situation. Similar to the treatment of cardiovascular diseases, there are studies on improving the blood supply of the lower extremities through surgery in the field of diabetes PAD treatment, such as percutaneous stents or vascular bypass. On the premise, PCI is less invasive and has a good prognosis, while the perioperative mortality rate of bypass surgery is as high as 3% [109]. A study by Arvela et al. on the single-segment great saphenous vein (ssGSV) showed that even if bypass angiogenesis of an autologous vein graft (AAVG) is used, there is a higher possibility of vascular stenosis after blood flow is restored (occlusive transplantation failure AAVG vs. ssGSV RR = 2.00, 95%CI = 1.39 – 2.88, $p < 0.0001$) [110]. Taylor et al.'s study in the United States of patients with severe PAD showed that after percutaneous transluminal angioplasty (PTA) in 314 subjects, the loss of walking function and the loss of independence of the lower limbs were improved (HR = 0.53; $p = 0.025$; HR = 0.53; $p = 0.025$); however, the mortality rate was higher than that of conventional amputation (HR = 1.62, $p = 0.006$) [111]. We speculate that because vascular lesions of the lower extremities involve mixed lesions of large and microvessels, interventional surgery may not be ideal for curing microvascular lesions. Therefore, for the treatment of diabetic foot, bypass is not the mainstream treatment. We recommend nonvascular therapy for injured patients, which mainly refers to nursing care, debridement, and taking certain thrombolytic drugs [53]. A study on thrombolytic drugs by Olinic et al. showed that after the use of clopidogrel and aspirin DAPT or aspirin single antiplatelet therapy (SAPT), thrombin receptor antagonists (vorapaxar) can improve the prognosis of PAD, but the risk of bleeding will increase as long as the drug is taken. If patients have undergone surgery, DAPT should also be used for a period of time; patients

implanted with transinguinal stents should use DAPT for at least 4 weeks, while those with transknee stents should take DAPT for a longer period [112]. Compared with conventional medical treatment, intravascular lithotripsy (IVL) has also been proven to be more effective. The Disrupt PAD III study conducted in the United States showed that between 2017 and 2018, the prognosis of patients with IVL did not worsen, so this therapy may become a direction for PAD treatment in the future [113].

6.2.4. Good Nursing Care Should Be Provided for Diabetic Patients with Complications. Thankfully, the incidence of CVD events has declined in the developed world as a whole due to better care and revascularization techniques. A survey of vascular complications conducted by Wu in Hong Kong showed that between 2001 and 2016, the incidence of heart failure in diabetic patients decreased by approximately 63.6% (-6.4, 95% CI = −8.0 – −4.7) [114]. Furthermore, a study comparing the clinical experience in the United Kingdom and Sweden also proved that during the period from 2004 to 2010, good treatment had a protective effect against the consequences of cardiovascular complications [115].

6.3. Chronic Disease Management. The onset prevention and prevention of diabetes complications is relatively long. Therefore, only treating the initial disease cannot completely control it. Diabetes must be managed after the initial onset, and vascular complications must be promptly targeted as they occur by monitoring risk factors. Among developing countries, India has relatively rich experience in the use of low-cost methods for chronic disease management, such as text messages to provide advice on lifestyle habits for diabetes protection (HR = 0.64, 95% CI = 0.45 – 0.9, $p = 0.015$) [17]. Similarly, in China, where smart mobile terminals are more popular, medical staff use mobile phone applications to monitor diseases. In a study conducted by Zhang, compared with the control group, the groups using the chronic disease management system had lower levels of glycosylated hemoglobin at the 3rd and 6th months (both $p < 0.05$), and interactive procedures had better results at the 6th month ($p = 0.04$) [116]. In addition, in Europe and the United States, where the field of diabetes management is relatively advanced, digital health technology and related equipment are widely used. The more common methods are continuous blood glucose monitoring systems for testing and insulin pumps or delivery systems that focus on treatment. The popularity of emerging mobile terminals in these regions and the importance of health-related applications are also worthy of attention [117]. The future goals of the management of diabetic vascular complications are the realization of remote diagnosis of disease through computer-related technology, and for the purpose of disease prevention, data sharing can be achieved in hospitals and communities in different urban areas.

7. Conclusion and Outlook

This manuscript focused on the macro and microvascular complications of diabetes, and a summary analysis was used to draw some key conclusions: the high prevalence of diabetes in emerging economies and the relative lack of treatment technologies make diabetic patients more prone to vascular complications. Further, the relatively low awareness and compliance among the patients make the prevention of vascular complications even more difficult. A sample survey found that there is a large number of undiagnosed diabetic patients in the population. Although the prevalence of diabetic vascular complications in developed countries and regions has shown a trend of relative improvement, the resources consumed by the corresponding better medical technology will place a heavy burden on society. There are also many new challenges in the prevention of diabetic vascular complications. For example, a younger generation of diabetic patients has increased the incidences of related diseases. At the same time, the aging of the global population makes it difficult to reduce the prevalence of diabetes, and many studies have reported an expansion in the impact of gestational diabetes. To prevent and control the occurrence and development of diabetes complications, multistep cooperation from medical workers to patients is needed. At the same time, actions should be taken by the government and other relevant departments for disease prevention. The onset of diabetes itself and its vascular complications can be additionally controlled through the following measures: (1) In terms of lifestyle factors, diabetic patients are encouraged to reduce their total caloric intake, decrease the proportions of oil and salt and increase the proportions of fiber-rich foods and high-quality protein in their diet, participate in appropriate physical exercise, and reduce the frequency of smoking and alcohol consumption. (2) In terms of treatment, patients with milder illness should strictly control their blood sugar, blood lipids, and blood pressure. Those with severe vascular complications should actively receive drug treatment, necessary surgical treatment, and better diabetes care practices. (3) Clinicians should adopt a chronic disease management system for timely follow-up and monitoring of disease and provide personalized control plans based on the principles of precision medicine.

Data Availability

All relevant data are available in this paper.

Additional Points

New and Noteworthy. This manuscript focused on the macro and microvascular complications of diabetes, and a summary analysis was used to draw some key conclusions: the high prevalence of diabetes in emerging economies and the relative lack of treatment technologies make diabetic patients more prone to vascular complications, and the relatively low awareness and compliance among the patients make the prevention of vascular complications even more difficult. The resources consumed by the corresponding better medical technology will place a heavy burden on society in developed countries. There are also many new challenges, such as gestational diabetes, juvenile onset, and aging that worsen diabetic complications. To prevent and control the

occurrence and development of diabetes complications, multistep cooperation from medical workers to patients is needed.

Conflicts of Interest

The authors declare that there is no duality of interest associated with this manuscript.

Authors' Contributions

R.L. drafted the manuscript. R.L., L.L., C.S., and H.C. prepared the figures. R.L., L.L., C.S., H.C. and Z.W. edited and revised the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgments

This work was supported by as follows: the National Natural Science Foundation of China (82070455); the Related Foundation of Jiangsu Province (BK20201225, M2020016); the Open Project Program of Guangxi Key Laboratory of Centre of Diabetic Systems Medicine (GKLCDSM-20210101-02); and the Medical Innovation Team Project of Jiangsu Province (CXTDA2017010).

References

[1] P. Saeedi, I. Petersohn, P. Salpea et al., "Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9 edition," *Diabetes Research and Clinical Practice*, vol. 157, p. 107843, 2019.

[2] E. W. Gregg, Y. Li, J. Wang et al., "Changes in diabetes-related complications in the United States, 1990-2010," *The New England Journal of Medicine*, vol. 370, no. 16, pp. 1514–1523, 2014.

[3] L. Wang, P. Gao, M. Zhang et al., "Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013," *JAMA*, vol. 317, no. 24, pp. 2515–2523, 2017.

[4] J. Mathew, "Diabetes in China," *The Medical Journal of Australia*, vol. 1, no. 6, p. 320, 1981.

[5] X. R. Pan, W. Y. Yang, G. W. Li, J. Liu, and National Diabetes Prevention and Control Cooperative Group, "Prevalence of diabetes and Its Risk Factors in China, 1994," *Diabetes Care*, vol. 20, no. 11, pp. 1664–1669, 1997.

[6] D. Gu, K. Reynolds, X. Duan et al., "Prevalence of diabetes and impaired fasting glucose in the Chinese adult population: international collaborative study of cardiovascular disease in Asia (InterASIA)," *Diabetologia*, vol. 46, no. 9, pp. 1190–1198, 2003.

[7] Y. Xu, L. Wang, J. He et al., "Prevalence and control of diabetes in Chinese adults," *JAMA*, vol. 310, no. 9, pp. 948–959, 2013.

[8] E. Dal Canto, A. Ceriello, L. Rydén et al., "Diabetes as a cardiovascular risk factor: an overview of global trends of macro and micro vascular complications," *European Journal of Preventive Cardiology*, vol. 26, 2_suppl, pp. 25–32, 2019.

[9] H.-Y. Li, Y. D. Jiang, C. H. Chang, C. H. Chung, B. J. Lin, and L. M. Chuang, "Mortality trends in patients with diabetes in Taiwan: a nationwide survey in 2000-2009," *Taiwan yi zhi*, vol. 111, no. 11, pp. 645–650, 2012.

[10] V. L. Rowe, W. Lee, F. A. Weaver, and D. Etzioni, "Patterns of treatment for peripheral arterial disease in the United States: 1996-2005," *Journal of Vascular Surgery*, vol. 49, no. 4, pp. 910–917, 2009.

[11] J. L. Harding, M. E. Pavkov, D. J. Magliano, J. E. Shaw, and E. W. Gregg, "Global trends in diabetes complications: a review of current evidence," *Diabetologia*, vol. 62, no. 1, pp. 3–16, 2019.

[12] F. Zaccardi, N. N. Dhalwani, D. R. Webb, M. J. Davies, and K. Khunti, "Global burden of hypoglycaemia-related mortality in 109 countries, from 2000 to 2014: an analysis of death certificates," *Diabetologia*, vol. 61, no. 7, pp. 1592–1602, 2018.

[13] J. C. Won, J. H. Lee, J. H. Kim et al., "Diabetes fact sheet in Korea, 2016: an appraisal of current status," *Diabetes & Metabolism Journal*, vol. 42, no. 5, pp. 415–424, 2018.

[14] T. Urakami, R. Kuwabara, and K. Yoshida, "Economic impact of diabetes in Japan," *Current Diabetes Reports*, vol. 19, no. 1, p. 2, 2019.

[15] Y. Nishioka, T. Noda, S. Okada et al., "Incidence and seasonality of type 1 diabetes: a population-based 3-year cohort study using the National Database in Japan," *BMJ Open Diabetes Research & Care*, vol. 8, no. 1, p. e001262, 2020.

[16] B. Zhang, F. Y. Zhai, S. F. du, and B. M. Popkin, "The China Health and Nutrition Survey, 1989–2011," *Obesity Reviews : An Official Journal of the International Association for the Study of Obesity*, vol. 15, Suppl 1, pp. 2–7, 2014.

[17] R. Unnikrishnan, R. M. Anjana, and V. Mohan, "Diabetes mellitus and its complications in India," *Nature Reviews. Endocrinology*, vol. 12, no. 6, pp. 357–370, 2016.

[18] M. Stolar, "Glycemic control and complications in type 2 diabetes mellitus," *The American Journal of Medicine*, vol. 123, no. 3, pp. S3–11, 2010.

[19] Y. Cao, X. Xu, and Z. Shi, "Trajectories of dietary patterns, sleep duration, and body mass index in china: a population-based longitudinal study from China nutrition and health survey, 1991-2009," *Nutrients*, vol. 12, no. 8, p. 2245, 2020.

[20] R. M. van Dam, E. B. Rimm, W. C. Willett, M. J. Stampfer, and F. B. Hu, "Dietary patterns and risk for type 2 diabetes mellitus in U.S. men," *Annals of Internal Medicine*, vol. 136, no. 3, pp. 201–209, 2002.

[21] F. B. Hu, E. B. Rimm, M. J. Stampfer, A. Ascherio, D. Spiegelman, and W. C. Willett, "Prospective study of major dietary patterns and risk of coronary heart disease in men," *The American Journal of Clinical Nutrition*, vol. 72, no. 4, pp. 912–921, 2000.

[22] G. Zhang, V. S. Malik, A. Pan et al., "Substituting brown rice for white rice to lower diabetes risk: a focus-group study in Chinese adults," *Journal of the American Dietetic Association*, vol. 110, no. 8, pp. 1216–1221, 2010.

[23] Y. Zhang, Y. Guo, X. Shen, F. Zhao, and S. Yan, "Lower body mass index is not of more benefit for diabetic complications," *Journal of diabetes investigation*, vol. 10, no. 5, pp. 1307–1317, 2019.

[24] M. Deepa, R. M. Anjana, and V. Mohan, "Role of lifestyle factors in the epidemic of diabetes: lessons learnt from India," *European Journal of Clinical Nutrition*, vol. 71, no. 7, pp. 825–831, 2017.

[25] Y. Li, D. D. Wang, S. H. Ley et al., "Time trends of dietary and lifestyle factors and their potential impact on diabetes burden

in China," *Diabetes Care*, vol. 40, no. 12, pp. 1685–1694, 2017.

[26] D. A. Barrière, C. Noll, G. Roussy et al., "Combination of high-fat/high-fructose diet and low-dose streptozotocin to model long-term type-2 diabetes complications," *Scientific Reports*, vol. 8, no. 1, p. 424, 2018.

[27] S. Yang, S. Wang, B. Yang, J. Zheng, Y. Cai, and Z. Yang, "Alcohol consumption is a risk factor for lower extremity arterial disease in Chinese patients with T2DM," *Journal of Diabetes Research*, vol. 2017, 2017.

[28] P. Gupta, E. K. Fenwick, C. Sabanayagam et al., "Association of alcohol intake with incidence and progression of diabetic retinopathy," *The British Journal of Ophthalmology*, vol. 105, no. 4, pp. 538–542, 2021.

[29] L. Wang, J. Fan, J. Wang, Y. Zhao, Z. Li, and R. Guo, "Spatio-temporal characteristics of the relationship between carbon emissions and economic growth in China's transportation industry," *Environmental Science and Pollution Research International*, vol. 27, no. 26, pp. 32962–32979, 2020.

[30] F. B. Hu, T. Y. Li, G. A. Colditz, W. C. Willett, and J. E. Manson, "Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women," *JAMA*, vol. 289, no. 14, pp. 1785–1791, 2003.

[31] Q. Qi, Y. Li, A. K. Chomistek et al., "Television watching, leisure time physical activity, and the genetic predisposition in relation to body mass index in women and men," *Circulation*, vol. 126, no. 15, pp. 1821–1827, 2012.

[32] X. Liu, F. Bragg, L. Yang et al., "Smoking and smoking cessation in relation to risk of diabetes in Chinese men and women: a 9-year prospective study of 0∗5 million people," *The Lancet. Public health*, vol. 3, no. 4, pp. e167–e176, 2018.

[33] P. Balakumar, K. Maung-U, and G. Jagadeesh, "Prevalence and prevention of cardiovascular disease and diabetes mellitus," *Pharmacological Research*, vol. 113, pp. 600–609, 2016.

[34] S. Yan, S. Liu, Y. Zhao et al., "Diagnostic accuracy of HbA1c in diabetes between Eastern and Western," *European Journal of Clinical Investigation*, vol. 43, no. 7, pp. 716–726, 2013.

[35] C. J. Magri, D. Mintoff, L. Camilleri, R. G. Xuereb, J. Galea, and S. Fava, "Relationship of hyperglycaemia, hypoglycaemia, and glucose variability to atherosclerotic disease in type 2 diabetes," *Journal of Diabetes Research*, vol. 2018, 2018.

[36] J. E. Kanter, F. Johansson, R. C. LeBoeuf, and K. E. Bornfeldt, "Do glucose and lipids exert independent effects on atherosclerotic lesion initiation or progression to advanced plaques?," *Circulation Research*, vol. 100, no. 6, pp. 769–781, 2007.

[37] V. N. Shah, R. Bailey, M. Wu et al., "Risk factors for cardiovascular disease (CVD) in adults with type 1 diabetes: findings from prospective real-life T1D exchange registry," *The Journal of Clinical Endocrinology and Metabolism*, vol. 105, no. 5, pp. e2032–e2038, 2020.

[38] R. I. Meijer, E. H. Serne, Y. M. Smulders, V. W. M. van Hinsbergh, J. S. Yudkin, and E. C. Eringa, "Perivascular adipose tissue and its role in type 2 diabetes and cardiovascular disease," *Current Diabetes Reports*, vol. 11, no. 3, pp. 211–217, 2011.

[39] R. Lithovius, V. Harjutsalo, S. Mutter et al., "Resistant hypertension and risk of adverse events in individuals with type 1 diabetes: a nationwide prospective study," *Diabetes Care*, vol. 43, no. 8, pp. 1885–1892, 2020.

[40] Y. Zhang, J. Nie, Y. Zhang et al., "Degree of blood pressure control and incident diabetes mellitus in Chinese adults with hypertension," *Journal of the American Heart Association*, vol. 9, no. 16, article e017015, 2020.

[41] T. Wang, J. Lu, L. Shi et al., "Association of insulin resistance and β-cell dysfunction with incident diabetes among adults in China: a nationwide, population-based, prospective cohort study," *The lancet. Diabetes & endocrinology*, vol. 8, no. 2, pp. 115–124, 2020.

[42] S. S. Albrecht, E. Mayer-Davis, and B. M. Popkin, "Secular and race/ethnic trends in glycemic outcomes by BMI in US adults: the role of waist circumference," *Diabetes/Metabolism Research and Reviews*, vol. 33, no. 5, 2017.

[43] L. Hu, X. Huang, C. You et al., "Prevalence of overweight, obesity, abdominal obesity and obesity-related risk factors in southern China," *PLoS One*, vol. 12, no. 9, article e0183934, 2017.

[44] Q. Zhang, Y. Wang, and E. S. Huang, "Changes in racial/ethnic disparities in the prevalence of type 2 diabetes by obesity level among US adults," *Ethnicity & Health*, vol. 14, no. 5, pp. 439–457, 2009.

[45] S. L. Stewart, J. Dang, and M. S. Chen, "Diabetes prevalence and risk factors in four Asian American communities," *Journal of Community Health*, vol. 41, no. 6, pp. 1264–1273, 2016.

[46] G. S. Tan, A. Gan, C. Sabanayagam et al., "Ethnic differences in the prevalence and risk factors of diabetic retinopathy: the Singapore epidemiology of eye diseases study," *Ophthalmology*, vol. 125, no. 4, pp. 529–536, 2018.

[47] R. Gupta and A. Misra, "Epidemiology of microvascular complications of diabetes in South Asians and comparison with other ethnicities," *Journal of Diabetes*, vol. 8, no. 4, pp. 470–482, 2016.

[48] H. Zuo, Z. Shi, and A. Hussain, "Prevalence, trends and risk factors for the diabetes epidemic in China: a systematic review and meta-analysis," *Diabetes Research and Clinical Practice*, vol. 104, no. 1, pp. 63–72, 2014.

[49] H. Wu, K. N. Eggleston, J. Zhong et al., "How do type 2 diabetes mellitus (T2DM)-related complications and socioeconomic factors impact direct medical costs? A cross-sectional study in rural Southeast China," *BMJ Open*, vol. 8, no. 11, article e020647, 2018.

[50] W. Yang, J. Lu, J. Weng et al., "Prevalence of diabetes among men and women in China," *The New England Journal of Medicine*, vol. 362, no. 12, pp. 1090–1101, 2010.

[51] N. Lascar, J. Brown, H. Pattison, A. H. Barnett, C. J. Bailey, and S. Bellary, "Type 2 diabetes in adolescents and young adults," *The lancet. Diabetes & endocrinology*, vol. 6, no. 1, pp. 69–80, 2018.

[52] R. O. Yeung, Y. Zhang, A. Luk et al., "Metabolic profiles and treatment gaps in young-onset type 2 diabetes in Asia (the JADE programme): a cross-sectional study of a prospective cohort," *The lancet. Diabetes & endocrinology*, vol. 2, no. 12, pp. 935–943, 2014.

[53] J. A. Beckman and M. A. Creager, "Vascular complications of diabetes," *Circulation Research*, vol. 118, no. 11, pp. 1771–1785, 2016.

[54] P. Song, D. Rudan, M. Wang, X. Chang, and I. Rudan, "National and subnational estimation of the prevalence of peripheral artery disease (PAD) in China: a systematic review and meta-analysis," *Journal of Global Health*, vol. 9, no. 1, article 010601, 2019.

[55] J. C. N. Chan, V. Malik, W. Jia et al., "Diabetes in Asia," *JAMA*, vol. 301, no. 20, pp. 2129–2140, 2009.

[56] T. R. Einarson, A. Acs, C. Ludwig, and U. H. Panton, "Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017," *Cardiovascular Diabetology*, vol. 17, no. 1, p. 83, 2018.

[57] M. J. O'Donnell, S. L. Chin, S. Rangarajan et al., "Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study," *Lancet (London, England)*, vol. 388, no. 10046, pp. 761–775, 2016.

[58] L. Guo, M. Yu, J. Zhong et al., "Stroke risk among patients with type 2 diabetes mellitus in Zhejiang: a population-based prospective study in China," *International Journal of Endocrinology*, vol. 2016, 2016.

[59] P. Toth, S. Tarantini, A. Csiszar, and Z. Ungvari, "Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging," *American Journal of Physiology. Heart and Circulatory Physiology*, vol. 312, no. 1, pp. H1–H20, 2017.

[60] X. Fang, H. Liu, X. Zhang, H. Zhang, X. Qin, and X. Ji, "Metabolic syndrome, its components, and diabetes on 5-year risk of recurrent stroke among mild-to-moderate ischemic stroke survivors: a multiclinic registry study," *Journal of Stroke and Cerebrovascular Diseases : The Official Journal of National Stroke Association*, vol. 25, no. 3, pp. 626–634, 2016.

[61] E. Di Angelantonio, S. Kaptoge, D. Wormser et al., "Association of cardiometabolic multimorbidity with mortality," *JAMA*, vol. 314, no. 1, pp. 52–60, 2015.

[62] A. Icks, H. Claessen, S. Morbach, G. Glaeske, and F. Hoffmann, "Time-dependent impact of diabetes on mortality in patients with stroke: survival up to 5 years in a health insurance population cohort in Germany," *Diabetes Care*, vol. 35, no. 9, pp. 1868–1875, 2012.

[63] S. M. Haffner, S. Lehto, T. Rönnemaa, K. Pyörälä, and M. Laakso, "Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction," *The New England Journal of Medicine*, vol. 339, no. 4, pp. 229–234, 1998.

[64] T. K. Schramm, G. H. Gislason, L. Køber et al., "Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people," *Circulation*, vol. 117, no. 15, pp. 1945–1954, 2008.

[65] J. A. Beckman, M. A. Creager, and P. Libby, "Diabetes and atherosclerosis," *JAMA*, vol. 287, no. 19, pp. 2570–2581, 2002.

[66] R. H. Ritchie and E. D. Abel, "Basic mechanisms of diabetic heart disease," *Circulation Research*, vol. 126, no. 11, pp. 1501–1525, 2020.

[67] S. James, D. J. Angiolillo, J. H. Cornel et al., "Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient outcomes (PLATO) trial," *European Heart Journal*, vol. 31, no. 24, pp. 3006–3016, 2010.

[68] C. Y. Ho and C. M. Shanahan, "Medial arterial calcification," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 36, no. 8, pp. 1475–1482, 2016.

[69] M. Volmer-Thole and R. Lobmann, "Neuropathy and Diabetic Foot Syndrome," *International Journal of Molecular Sciences*, vol. 17, no. 6, p. 917, 2016.

[70] C. W. Hicks and E. Selvin, "Epidemiology of peripheral neuropathy and lower extremity disease in diabetes," *Current Diabetes Reports*, vol. 19, no. 10, p. 86, 2019.

[71] K. Kröger, C. Berg, F. Santosa, N. Malyar, and H. Reinecke, "Lower limb amputation in Germany," *Deutsches Ärzteblatt International*, vol. 114, no. 7, pp. 130–136, 2017.

[72] J. R. Kurowski, L. Nedkoff, D. E. Schoen, M. Knuiman, P. E. Norman, and T. G. Briffa, "Temporal trends in initial and recurrent lower extremity amputations in people with and without diabetes in Western Australia from 2000 to 2010," *Diabetes Research and Clinical Practice*, vol. 108, no. 2, pp. 280–287, 2015.

[73] J. H. Stewart, M. R. E. McCredie, and S. M. Williams, "Geographic, ethnic, age-related and temporal variation in the incidence of end-stage renal disease in Europe, Canada and the Asia-Pacific region, 1998-2002," *Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association-European Renal Association*, vol. 21, no. 8, pp. 2178–2183, 2006.

[74] X.-X. Zhang, J. Kong, and K. Yun, "Prevalence of diabetic nephropathy among patients with type 2 diabetes mellitus in China: a meta-analysis of observational studies," *Journal of Diabetes Research*, vol. 2020, 2020.

[75] J. Weng, Z. Zhou, L. Guo et al., "Incidence of type 1 diabetes in China, 2010-13: population based study," *BMJ (Clinical research ed.)*, vol. 360, article j5295, 2018.

[76] A. I. Adler, R. J. Stevens, S. E. Manley et al., "Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64)," *Kidney International*, vol. 63, no. 1, pp. 225–232, 2003.

[77] V. T. F. Yeung, K. F. Lee, S. H. Chan et al., "MicroAlbuminuria Prevalence Study (MAPS) in hypertensive type 2 diabetic patients in Hong Kong," *Hong Kong medical journal = Xianggang yi xue za zhi*, vol. 12, no. 3, pp. 185–190, 2006.

[78] Y.-M. Huang, D. Xu, J. Long et al., "Spectrum of chronic kidney disease in China: a national study based on hospitalized patients from 2010 to 2015," *Nephrology (Carlton, Vic.)*, vol. 24, no. 7, pp. 725–736, 2019.

[79] P. Song, J. Yu, K. Y. Chan, E. Theodoratou, and I. Rudan, "Prevalence, risk factors and burden of diabetic retinopathy in China: a systematic review and meta-analysis," *Journal of Global Health*, vol. 8, no. 1, article 010803, 2018.

[80] Y. Groeneveld, D. Tavenier, J. W. Blom, and B. C. P. Polak, "Incidence of sight-threatening diabetic retinopathy in people with type 2 diabetes mellitus and numbers needed to screen: a systematic review," *Diabetic medicine: a journal of the British Diabetic Association*, vol. 36, no. 10, pp. 1199–1208, 2019.

[81] J. Q. Li, T. Welchowski, M. Schmid et al., "Prevalence, incidence and future projection of diabetic eye disease in Europe: a systematic review and meta-analysis," *European Journal of Epidemiology*, vol. 35, no. 1, pp. 11–23, 2020.

[82] M. Nowicki, J. Kosacka, H. Serke, M. Blüher, and K. Spanel-Borowski, "Altered sciatic nerve fiber morphology and endoneural microvessels in mouse models relevant for obesity, peripheral diabetic polyneuropathy, and the metabolic syndrome," *Journal of Neuroscience Research*, vol. 90, no. 1, pp. 122–131, 2012.

[83] E. L. Feldman, B. C. Callaghan, R. Pop-Busui et al., "Diabetic neuropathy," *Diabetic neuropathy. Nature reviews. Disease primers*, vol. 5, no. 1, p. 41, 2019.

[84] S. Tesfaye, A. J. M. Boulton, P. J. Dyck et al., "Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments," *Diabetes Care*, vol. 33, no. 10, pp. 2285–2293, 2010.

[85] B. Lu, J. Hu, J. Wen et al., "Determination of peripheral neuropathy prevalence and associated factors in Chinese subjects with diabetes and pre-diabetes - ShangHai diabetic neuRopathy epidemiology and molecular genetics study (SH-DREAMS)," *PLoS One*, vol. 8, no. 4, article e61053, 2013.

[86] X. Xu, J. Hall, J. Byles, and Z. Shi, "Dietary pattern is associated with obesity in older people in China: data from China Health and Nutrition Survey (CHNS)," *Nutrients*, vol. 7, no. 9, pp. 8170–8188, 2015.

[87] L. J. Dominguez, A. Galioto, A. Ferlisi et al., "Ageing, lifestyle modifications, and cardiovascular disease in developing countries," *The Journal of Nutrition, Health & Aging*, vol. 10, no. 2, pp. 143–149, 2006.

[88] F. Imamura, L. O'Connor, Z. Ye et al., "Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction," *BMJ (Clinical research ed.)*, vol. 351, article h3576, 2015.

[89] A. Sampath Kumar, A. G. Maiya, B. A. Shastry et al., "Exercise and insulin resistance in type 2 diabetes mellitus: a systematic review and meta-analysis," *Annals of Physical and Rehabilitation Medicine*, vol. 62, no. 2, pp. 98–103, 2019.

[90] E. S. Nylen, P. Kokkinos, J. Myers, and C. Faselis, "Prognostic effect of exercise capacity on mortality in older adults with diabetes mellitus," *Journal of the American Geriatrics Society*, vol. 58, no. 10, pp. 1850–1854, 2010.

[91] S. Zhen, Y. Ma, Z. Zhao, X. Yang, and D. Wen, "Dietary pattern is associated with obesity in Chinese children and adolescents: data from China Health and Nutrition Survey (CHNS)," *Nutrition Journal*, vol. 17, no. 1, p. 68, 2018.

[92] P. Valensi and C. Meune, "Congestive heart failure caused by silent ischemia and silent myocardial infarction," *Herz*, vol. 44, no. 3, pp. 210–217, 2019.

[93] J. B. Muhlestein, D. L. Lappé, J. A. C. Lima et al., "Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial," *JAMA*, vol. 312, no. 21, pp. 2234–2243, 2014.

[94] A. Wang, G. Lv, X. Cheng et al., "Guidelines on multidisciplinary approaches for the prevention and management of diabetic foot disease (2020 edition)," *Burns & trauma*, vol. 8, article tkaa017, 2020.

[95] L.-Z. Guan, Q. Tong, and J. Xu, "Elevated serum levels of mannose-binding lectin and diabetic nephropathy in type 2 diabetes," *PLoS One*, vol. 10, no. 3, article e0119699, 2015.

[96] S.-Q. Zhao and Z. Hu, "Mannose-binding lectin and diabetic nephropathy in type 1 diabetes," *Journal of Clinical Laboratory Analysis*, vol. 30, no. 4, pp. 345–350, 2016.

[97] C. C. Low Wang, J. I. Blomster, G. Heizer et al., "Cardiovascular and limb outcomes in patients with diabetes and peripheral artery disease: the EUCLID trial," *Journal of the American College of Cardiology*, vol. 72, no. 25, pp. 3274–3284, 2018.

[98] V. Perkovic, H. L. Heerspink, J. Chalmers et al., "Intensive glucose control improves kidney outcomes in patients with type 2 diabetes," *Kidney International*, vol. 83, no. 3, pp. 517–523, 2013.

[99] I. M. Stratton, A. I. Adler, H. A. Neil et al., "Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study," *BMJ (Clinical research ed.)*, vol. 321, no. 7258, pp. 405–412, 2000.

[100] B. C. Callaghan, A. A. Little, E. L. Feldman, R. A. C. Hughes, and Cochrane Neuromuscular Group, "Enhanced glucose control for preventing and treating diabetic neuropathy," *The Cochrane Database of Systematic Reviews*, vol. 6, p. CD007543, 2012.

[101] H. Yang, D. Young, J. Gao et al., "Are blood lipids associated with microvascular complications among type 2 diabetes mellitus patients? A cross-sectional study in Shanghai, China," *Lipids in Health and Disease*, vol. 18, no. 1, p. 18, 2019.

[102] Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, "Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy," *Lancet (London, England)*, vol. 355, no. 9200, pp. 253–259, 2000.

[103] J. Hewitt, L. Castilla Guerra, M. D. C. Fernández-Moreno, and C. Sierra, "Diabetes and stroke prevention: a review," *Stroke research and treatment*, vol. 2012, Article ID 673187, 2012.

[104] M. Arnold, S. Mattle, A. Galimanis et al., "Impact of admission glucose and diabetes on recanalization and outcome after intra-arterial thrombolysis for ischaemic stroke," *International journal of stroke: official journal of the International Stroke Society*, vol. 9, no. 8, pp. 985–991, 2014.

[105] A. M. Schmidt, "Diabetes mellitus and cardiovascular disease," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 39, no. 4, pp. 558–568, 2019.

[106] K. Ramanathan, J. G. Abel, J. E. Park et al., "Surgical versus percutaneous coronary revascularization in patients with diabetes and acute coronary syndromes," *Journal of the American College of Cardiology*, vol. 70, no. 24, pp. 2995–3006, 2017.

[107] T. Ishihara, Y. Sotomi, T. Tsujimura et al., "Impact of diabetes mellitus on the early-phase arterial healing after drug-eluting stent implantation," *Cardiovascular Diabetology*, vol. 19, no. 1, p. 203, 2020.

[108] S. Raza, E. H. Blackstone, P. L. Houghtaling et al., "Influence of diabetes on long-term coronary artery bypass graft patency," *Journal of the American College of Cardiology*, vol. 70, no. 5, pp. 515–524, 2017.

[109] M. C. Courtois, M. Sapoval, C. del Giudice, R. Ducloux, T. Mirault, and E. Messas, "Distal revascularization in diabetic patients with chronic limb ischemia," *Journal des Maladies Vasculaires*, vol. 40, no. 1, pp. 24–36, 2015.

[110] E. Arvela, M. Venermo, M. Söderström, A. Albäck, and M. Lepäntalo, "Outcome of infrainguinal single-segment great saphenous vein bypass for critical limb ischemia is superior to alternative autologous vein bypass, especially in patients with high operative risk," *Annals of Vascular Surgery*, vol. 26, no. 3, pp. 396–403, 2012.

[111] S. M. Taylor, C. A. Kalbaugh, D. W. Blackhurst, D. C. Kellicut, E. M. Langan III, and J. R. Youkey, "A comparison of percutaneous transluminal angioplasty versus amputation for critical limb ischemia in patients unsuitable for open

surgery," *Journal of Vascular Surgery*, vol. 45, no. 2, pp. 304–310, 2007.

[112] D.-M. Olinic, D. A. Tataru, C. Homorodean, M. Spinu, and M. Olinic, "Antithrombotic treatment in peripheral artery disease," *VASA. Zeitschrift fur Gefasskrankheiten*, vol. 47, no. 2, pp. 99–108, 2018.

[113] G. Adams, N. Shammas, S. Mangalmurti et al., "Intravascular lithotripsy for treatment of calcified lower extremity arterial stenosis: initial analysis of the disrupt PAD III study," *Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists*, vol. 27, no. 3, pp. 473–480, 2020.

[114] H. Wu, E. S. H. Lau, A. Yang et al., "Trends in diabetes-related complications in Hong Kong, 2001-2016: a retrospective cohort study," *Cardiovascular Diabetology*, vol. 19, no. 1, p. 60, 2020.

[115] S.-C. Chung, J. Sundström, C. P. Gale et al., "Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom: population based cohort study using nationwide clinical registries," *BMJ (Clinical research ed.)*, vol. 351, article h3913, 2015.

[116] L. Zhang, X. He, Y. Shen et al., "Effectiveness of smartphone app-based interactive management on glycemic control in Chinese patients with poorly controlled diabetes: randomized controlled trial," *Journal of Medical Internet Research*, vol. 21, no. 12, article e15401, 2019.

[117] G. A. Fleming, J. R. Petrie, R. M. Bergenstal, R. W. Holl, A. L. Peters, and L. Heinemann, "Diabetes digital app technology: benefits, challenges, and recommendations. A consensus report by the European Association for the Study of diabetes (EASD) and the American Diabetes Association (ADA) diabetes technology working group," *Diabetes Care*, vol. 43, no. 1, pp. 250–260, 2020.

Hindawi
Journal of Diabetes Research
Volume 2022, Article ID 6758297, 10 pages
https://doi.org/10.1155/2022/6758297

Research Article

Diabetes Increases Risk of Cardiovascular Events in Patients Receiving Permanent Pacemaker: A Propensity Score-Matched Cohort Study

Huang-Chung Chen, Wen-Hao Liu, Chien-Hao Tseng, Yung-Lung Chen, Wei-Chieh Lee, Yen-Nan Fang, Shaur-Zheng Chong, and Mien-Cheng Chen

Division of Cardiology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, College of Medicine, Chang Gung University, Taiwan

Correspondence should be addressed to Mien-Cheng Chen; chenmien@ms76.hinet.net

Received 6 January 2022; Revised 27 February 2022; Accepted 5 March 2022; Published 28 March 2022

Academic Editor: Krzysztof Zmudka

Background. Type 2 diabetes was associated with a higher risk for permanent pacemaker (PPM) treatment. The difference in cardiovascular outcomes between patients with and without diabetes receiving PPM treatment remains unexplored. *Method.* Between January 2003 and December 2017, 1742 patients receiving naïve PPM treatment comprised this retrospective cohort study and were categorized into two groups by the diagnosis of diabetes: group with diabetes ($n = 632$, 36.3%) and group without diabetes ($n = 1110$, 63.7%). The primary outcome was cardiovascular events including heart failure (HF) hospitalization and acute myocardial infarction (AMI). The secondary outcomes of this study included pacemaker infection, pacing-induced cardiomyopathy, cerebrovascular accident, cardiovascular mortality, and all-cause mortality. Propensity score matching (PSM) was applied to reduce selection bias between the study groups. *Result.* During a mean follow-up period of 7.8 ± 4.8 years, 264 patients had a cardiovascular event. Before PSM, the incidence of cardiovascular events was higher in patients with diabetes compared to patients without diabetes (19.8% vs. 12.5%, $P < 0.001$), and the incidences of pacing-induced cardiomyopathy, cardiovascular mortality, and all-cause mortality were all higher in patients with diabetes compared to patients without diabetes. After PSM, the incidence of cardiovascular events was higher in patients with diabetes compared to patients without diabetes (18.8% vs. 12.3%, $P = 0.015$). The incidence of HF hospitalization was higher in patients with diabetes compared to patients without diabetes (15.3% vs. 10.2%, $P = 0.037$), whereas the incidence of AMI did not differ between the two groups. Moreover, after PSM, patients with diabetes had higher cumulative incidences of pacing-induced cardiomyopathy and all-cause mortality compared to patients without diabetes. *Conclusions.* The prevalence of diabetes was over one-third of naïve PPM recipients of this cohort, and diabetes increased the risk of cardiovascular events in PPM recipients, especially for HF hospitalization.

1. Introduction

Diabetes mellitus is a serious chronic disease with an imperative influence on the health of a human being in the world. Owing to the aging population, economic development, and change of lifestyle, the growth in global and regional prevalences of type 2 diabetes markedly increased [1–4]. The number of patients with type 2 diabetes had doubled during the past two decades, and half of people with diabetes are not even aware that they have diabetes [1, 4]. Diabetes is a well-known risk factor for cardiovascular events, such as acute myocardial infarction (AMI) and heart failure (HF) [5, 6]. Previous studies demonstrated that lethal tachyarrhythmia occurs commonly in patients with diabetes, possibly related to myocardial ischemia and sympathoadrenal activation in response to hypoglycemia [7, 8]. On the other hand, an association between bradyarrhythmia and diabetes has also been reported, which is possibly caused by microangiopathy and

increased cholinergic sensitivity [9–11]. From a national diabetes registry study, Rautio et al. reported that type 2 diabetes was associated with a 1.6-fold higher risk for permanent pacemaker (PPM) treatment after adjustments for age, sex, and other factors [12]. However, the difference in cardiovascular outcomes between patients with and without type 2 diabetes receiving PPM treatment remains unexplored. Moreover, type 2 diabetes as an independent risk factor for cardiovascular events in pacemaker recipients remains unexplored. Accordingly, we conducted this retrospective cohort study to investigate and compare the clinical outcomes between patients with and without type 2 diabetes receiving PPM treatment after propensity score matching (PSM). Moreover, this study is also aimed at identifying whether type 2 diabetes increases risk of cardiovascular events in PPM recipients.

2. Methods

2.1. Study Cohort. This retrospective cohort study enrolled 2706 consecutive patients receiving cardiac implantable electronic devices implantation in our hospital between January 2003 and December 2017. A total of 964 patients, including 191 patients with implantable intracardiac defibrillators, 78 patients with cardiac resynchronization therapy, and 695 patients with replacement of generator, were excluded (Figure 1). His-Purkinje conduction system pacing was also excluded in this study because pacing leads for His-Purkinje conduction system pacing were not available in our institute between January 2003 and December 2017. Finally, 1742 patients receiving single ventricular or dual chamber PPMs comprised this retrospective cohort study population and were categorized into two groups by the presence or absence of diagnosis of type 2 diabetes at the time of PPM implantation: group with diabetes ($n = 632$, 36.3%) and group without diabetes ($n = 1110$, 63.7%) (Figure 1). The standard protocol for PPM implantation in our center had been described in our previous study [13], mainly right ventricular lead placed at the right ventricular outflow tract or high septum.

2.2. Definitions. Based on recommendations from the American Diabetes Association [14], diabetes was defined as prescription for oral antidiabetic drugs or insulin, or HbA1c ≥ 6.5% (48 mmol/mol), or fasting plasma glucose level ≥ 126 mg/dL (7.0 mmol/L), or a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis during hospitalization for PPM implantation. According to the guidelines of Kidney Disease: Improving Global Outcomes [15], microalbuminuria was defined as at least two positive results obtained within 1 year and was defined as an albumin-to-creatinine ratio of 30-300 mg/g (3-30 mg/mmol); macroalbuminuria was defined as an albumin-to-creatinine ratio ≥300 mg/g (>30 mg/mmol). Estimated glomerular filtration rate (eGFR) was estimated from the creatinine value and calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [16]. Chronic kidney disease (CKD) was defined as eGFR lower than 60 mL/min/1.73 m^2 without renal replacement therapy and end-stage renal disease as the need for peritoneal dialysis, hemodialysis, or renal transplantation. Hyperlipidemia was defined as total cholesterol ≥ 240 mg/dL, low-density lipoprotein ≥ 150 mg/dL, or triglyceride ≥ 200 mg/dL, or on lipid-lowering medications [17]. Valvular heart disease was defined as moderate to severe regurgitation or stenosis of aortic, mitral, or tricuspid valves. Cardiovascular surgery included coronary artery bypass graft and valvular surgery. Chronic lung disease was defined as a history of asthma, chronic obstructive pulmonary disease, or pulmonary fibrosis.

2.3. Clinical Outcomes. The primary outcome of this study was cardiovascular events of patients after PPM implantation. Cardiovascular events included hospitalization related to HF event of New York Heart Association functional class of III-IV, or AMI. The secondary outcomes of this study included pacemaker infection, pacing-induced cardiomyopathy, cerebrovascular accident, cardiovascular mortality, and all-cause mortality. Pacemaker infection was divided into major and minor infections according to clinical presentation and management. Major infection was defined as any presentation of (1) erosive wound, (2) bloodstream infection, (3) pacemaker-related endocarditis, or (4) need for surgical removal. Minor infection was defined as (1) the local inflammatory signs including erythema, warmth, fluctuance, or tenderness at the pocket sites, (2) presentation of any discharge, or (3) wound dehiscence [18]. Pacing-induced cardiomyopathy was defined as a ≥10% decrease of the baseline left ventricular ejection fraction (LVEF) with a resultant LVEF < 50%. Cerebrovascular accident was defined as an episode of transient ischemic attack, ischemic stroke, intracranial hemorrhage, or any incident finding by images, including brain computed tomography or magnetic resonance imaging after PPM implantation. Cardiovascular mortality was defined as death from AMI, HF, refractory ventricular arrhythmias, or cardiac arrest. After PPM implantation, patients were followed up monthly for the first three months and then every three to six months until clinical outcomes of interest, death, loss to follow up, or the latest date in the dataset (31 December, 2020), whichever came first.

2.4. Study Covariates. Baseline variables considered in the analyses included patient's age, sex, body mass index, and comorbidities associated with clinical outcomes including hypertension, hyperlipidemia, coronary artery disease, HF, atrial fibrillation, valvular heart disease, CKD, history of cardiovascular surgery, cancer, and chronic lung disease. The prescription for medication, such as beta-blocker, antihypertensive drugs, diuretic agents, and lipid-lowering agents, laboratory data including hemoglobin and serum creatinine, the indication and lead number of PPM, and baseline and pacing QRS duration were also obtained.

2.5. Statistical Analysis. Continuous variables are expressed as a mean ± standard deviation or percentages. The clinical characteristics of the study groups were compared using the independent *t*-test for continuous variables and Chi-

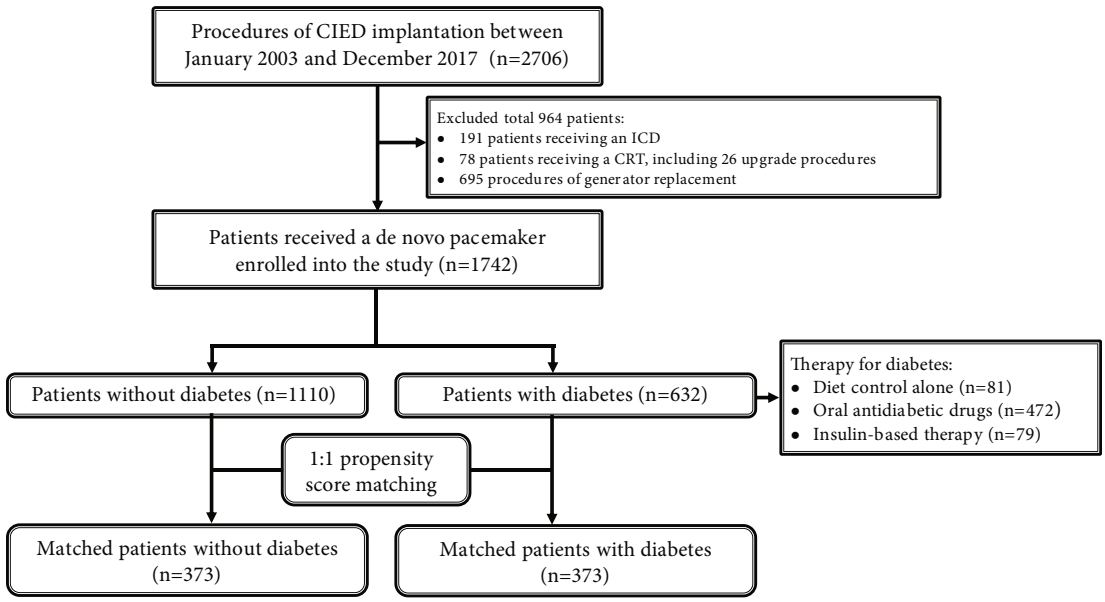


Figure 1: Flow chart of enrollment of patients receiving cardiac implantable electronic devices. CIED: cardiac implantable electronic devices; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy.

square test or Fisher's exact test for categorical variables. PSM was applied to make the covariates balanced between the study groups. The propensity score was calculated using multivariable logistic regression where the study group was regressed on all of the covariates listed in Table 1, except eGFR, HbA1c, low-density lipoprotein, high-density lipoprotein, triglyceride, albuminuria, and preprocedural echocardiographic data. Using NCSS 10 Statistical Software (LLC, Kaysville, Utah, USA), the greedy method was used for matching at a 1 : 1 ratio between the study groups with a caliper width 0.2-fold of the standard deviation of the logit of the propensity score. The quality of matching was checked using the absolute value of standardized difference between the groups, where a value <0.1 was considered negligible difference [19]. The incidences of all clinical outcomes during long-term follow-up were expressed with Kaplan-Meier survival curves and compared by log-rank test. The significance of each variable in predicting all clinical outcomes was tested using the Cox proportional hazards model, analyzed with forward option. A two-sided P value < 0.05 was considered statistically significant. SPSS for Windows (version 22.0; SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis.

3. Results

3.1. Baseline Characteristics of the Study Patients with and without Type 2 Diabetes. Table 1 lists the clinical characteristics of the study patients before and after PSM. Before PSM, the mean age of the patient population was 73 ± 11 years and 48.6% of the study patients were male. There were 632 (36.3%) patients with diabetes, which were under diet control alone (12.8%), oral antidiabetic drugs (74.7%), or insulin-based therapy (12.5%), and 1110 (63.7%) patients without diabetes (Figure 1). The patients with diabetes had more patients with overweight and higher prevalence of hypertension, hyperlipidemia, coronary artery disease, CKD, and end-stage renal disease (all $P < 0.001$) compared to the patients without diabetes. Patients with diabetes also had a higher prevalence of history of HF ($P = 0.033$), atrial fibrillation ($P = 0.007$), and cerebrovascular accident ($P = 0.028$) compared to patients without diabetes. Patients with diabetes had more prescription for beta-blocker ($P = 0.001$), angiotensin-converting enzyme inhibitors/angiotensin receptor blocker (ACEi/ARB), diuretic agents, and statin (all $P < 0.001$). Patients with diabetes had higher serum creatinine, HbA1c, and triglyceride and a higher prevalence of albuminuria including microalbuminuria and macroalbuminuria (all $P < 0.001$) compared to patients without diabetes. Patients with diabetes had lower levels of hemoglobin, eGFR, low-density lipoprotein, and high-density lipoprotein (all $P < 0.001$) compared to patients without diabetes. Patients with diabetes had a higher prevalence of atrioventricular block ($P = 0.001$), larger number of PPM leads ($P = 0.025$), wider baseline and pacing QRS durations ($P = 0.037$ and $P = 0.019$, respectively), and higher percentage of right ventricular pacing ($P < 0.001$) compared to patients without diabetes. Patients with diabetes had larger preprocedural left atrial size ($P = 0.010$) and LV end-diastolic volume ($P = 0.049$) and lower preprocedural LVEF ($P = 0.042$) compared to patients without diabetes (Table 1).

In the study cohort after 1 : 1 PSM, 373 pairs with and without diabetes were analyzed. The baseline characteristics were balanced in the matched groups (Table 1). After PSM, the matched patients with diabetes still had lower low-density lipoprotein ($P = 0.001$) and high-density lipoprotein ($P = 0.005$) and higher triglyceride ($P = 0.049$) levels as well as higher prevalence of albuminuria ($P < 0.001$) compared to the matched patients without diabetes (Table 1).

3.2. Clinical Outcomes of the Study Patients with and without Type 2 Diabetes before and after PSM. During a mean

Table 1: Baseline characteristics of the study patients before and after propensity score matching.

	Before matching				After matching			
	Diabetes (n = 632; 36.3%)	Nondiabetes (n = 1110; 63.7%)	P value	SMD	Diabetes (n = 373)	Nondiabetes (n = 373)	P value	SMD
Baseline characteristics								
Age, (years)	73 ± 9	73 ± 12	0.080	0.080	74 ± 9	75 ± 11	0.232	0.088
Male	300 (47.5)	547 (49.3)	0.467	0.030	185 (49.6)	190 (50.9)	0.714	0.027
Body mass index, (kg/m^2)	26 ± 4	24 ± 4	<0.001	N/A	25 ± 4	25 ± 4	0.046	N/A
Overweight (>30 kg/m^2)	59 (9.3)	44 (4.0)	<0.001	0.187	22 (5.9)	26 (7.0)	0.551	0.044
Underweight (<20 kg/m^2)	21 (3.3)	116 (10.5)	<0.001	0.248	17 (4.6)	21 (5.6)	0.505	0.049
Hypertension	524 (82.9)	716 (64.5)	<0.001	0.433	296 (79.4)	295 (79.1)	0.928	0.007
Hyperlipidemia	319 (50.5)	293 (26.4)	<0.001	0.567	160 (42.9)	163 (43.7)	0.825	0.016
Coronary artery disease	187 (29.6)	162 (14.6)	<0.001	0.368	79 (21.2)	74 (19.8)	0.650	0.033
Heart failure history	130 (20.6)	183 (16.5)	0.033	0.092	63 (16.9)	63 (16.9)	1.000	<0.001
Valvular heart disease†	27 (4.3)	68 (6.1)	0.101	0.081	19 (5.1)	21 (5.6)	0.745	0.024
Atrial fibrillation	219 (34.7)	457 (41.2)	0.007	0.188	143 (38.3)	147 (39.4)	0.764	0.022
Cerebrovascular accident	142 (22.5)	201 (18.1)	0.028	0.077	75 (20.1)	75 (20.1)	1.000	<0.001
Chronic kidney disease‡	291 (46.0)	396 (35.7)	<0.001	0.210	170 (45.6)	169 (45.3)	0.941	0.005
End-stage renal disease§	68 (10.8)	46 (4.1)	<0.001	0.254	20 (5.4)	20 (5.4)	1.000	<0.001
Chronic lung disease‖	27 (4.3)	54 (4.9)	0.572	0.073	14 (3.8)	16 (4.3)	0.709	0.027
History of cardiovascular surgery	31 (4.9)	55 (5.0)	0.963	0.014	17 (4.6)	16 (4.3)	0.859	0.013
History of cancer	74 (11.7)	121 (10.9)	0.607	0.055	45 (12.1)	51 (13.7)	0.512	0.048
Prescription for drugs								
Beta-blocker	121 (19.1)	146 (13.2)	0.001	0.177	64 (17.2)	51 (13.7)	0.187	0.097
ACEi/ARB	370 (58.5)	506 (45.6)	<0.001	0.297	212 (56.8)	203 (54.4)	0.507	0.049
Diuretic agents	212 (33.5)	257 (23.2)	<0.001	0.265	113 (30.3)	114 (30.6)	0.937	0.006
Statin	193 (30.5)	152 (13.7)	<0.001	0.439	89 (23.9)	95 (25.5)	0.610	0.037
Diabetic therapy								
Diet control alone	81 (12.8)				59 (15.8)			
Oral antidiabetic drugs	472 (74.7)				282 (75.6)			
Insulin-based therapy	79 (12.5)				32 (8.6)			
Laboratory data								
Hemoglobin, (g/dL)	12.0 ± 1.9	12.8 ± 1.9	<0.001	0.409	12.3 ± 1.9	12.2 ± 1.9	0.754	0.023
Serum creatinine, (mg/dL)	2.0 ± 2.1	1.4 ± 1.7	<0.001	0.301	1.7 ± 1.8	1.6 ± 2.0	0.732	0.025
eGFR, (mL/min/1.73m^2)	54 ± 30	67 ± 29	<0.001	N/A	58 ± 28	61 ± 29	0.171	N/A
HbA1c								
mmol/mol	54 ± 10	39 ± 3	<0.001	N/A	52 ± 8	39 ± 3	<0.001	N/A
%	7.1 ± 1.3	5.7 ± 0.4	<0.001	N/A	6.9 ± 1.1	5.7 ± 0.4	<0.001	N/A

Table 1: Continued.

	Before matching				After matching			
	Diabetes (n = 632; 36.3%)	Nondiabetes (n = 1110; 63.7%)	P value	SMD	Diabetes (n = 373)	Nondiabetes (n = 373)	P value	SMD
LDL, (mg/dL)	90 ± 34	101 ± 34	<0.001	N/A	89 ± 33	101 ± 39	0.001	N/A
HDL, (mg/dL)	47 ± 13	53 ± 16	<0.001	N/A	48 ± 13	52 ± 15	0.005	N/A
Triglyceride, (mg/dL)	128 ± 87	103 ± 55	<0.001	N/A	124 ± 99	109 ± 59	0.049	N/A
Albuminuria, (mg/g)	141 (22.3)	70 (6.3)	<0.001	N/A	89 (23.9)	36 (9.7)	<0.001	N/A
Microalbuminuria	91 (14.4)	53 (4.8)	<0.001	N/A	58 (15.5)	25 (6.7)	<0.001	N/A
Macroalbuminuria	50 (7.9)	17 (1.5)	<0.001	N/A	31 (8.3)	11 (2.9)	0.001	N/A
Electrocardiographic and pacemaker data								
Patients with atrioventricular block	278 (44.0)	397 (35.8)	0.001	0.282	154 (41.4)	156 (41.8)	0.882	0.011
Number of pacemaker lead	1.9 ± 3.8	1.8 ± 3.8	0.025	0.107	1.9 ± 0.3	1.9 ± 0.3	0.661	0.034
Baseline QRS duration (ms)	103 ± 25	101 ± 24	0.037	0.127	103 ± 24	103 ± 25	0.928	0.007
Pacing QRS duration (ms)	167 ± 19	164 ± 19	0.019	0.154	165 ± 17	164 ± 18	0.180	0.098
Percentage of right ventricular pacing (%)	64 ± 42 (range: 0-100)	52 ± 44 (range: 0-100)	<0.001	N/A	62 ± 42 (range: 0-100)	54 ± 42 (range: 0-100)	0.075	N/A
Percentage with right ventricular pacing >40% (%)	146 (23.1)	267 (24.1)	0.677	N/A	95 (25.5)	89 (23.9)	0.610	N/A
Pre-procedural echocardiographic data								
LA size, (mm)	39 ± 7	38 ± 8	0.010	N/A	39 ± 7	39 ± 8	0.895	N/A
LVEDV, (ml)	114 ± 35	110 ± 38	0.049	N/A	114 ± 33	113 ± 39	0.676	N/A
LVESV, (ml)	39 ± 23	37 ± 38	0.065	N/A	38 ± 21	38 ± 24	0.898	N/A
LVEF, (%)	67 ± 12	68 ± 11	0.042	N/A	68 ± 11	67 ± 12	0.876	N/A

*Data are presented as mean ± SD or number (%) of patients. †Defined as moderate to severe regurgitation or stenosis of aortic, mitral, or tricuspid valves. ‡Defined as eGFR lower than 60 mL/min/1.73 m^2 without renal replacement therapy. §Defined as the need for peritoneal dialysis, hemodialysis, or renal transplantation. ||Defined as the history of asthma, or chronic obstructive pulmonary disease, or pulmonary fibrosis. ACEi/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; LA: left atrium; LDL: low-density lipoprotein; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; N/A: not applicable; SMD: standardized mean difference.

Table 2: Clinical outcomes of the patients with and without diabetes and univariate Cox regression analysis for hazard ratio of diabetes vs. nondiabetes for all outcomes during a nearly 8-year follow-up period.

	Before matching				After matching			
	Diabetes ($n = 632$)	Nondiabetes ($n = 1110$)	HR (95% CI)	P value	Diabetes ($n = 373$)	Nondiabetes ($n = 373$)	HR (95% CI)	P value
Primary outcome								
Cardiovascular events	125 (19.8)	139 (12.5)	2.06 (1.61-2.62)	<0.001	70 (18.8)	46 (12.3)	1.82 (1.25-2.63)	0.002
HF hospitalization	94 (14.9)	112 (10.1)	1.91 (1.45-2.52)	<0.001	57 (15.3)	38 (10.2)	1.78 (1.18-2.68)	0.006
AMI	31 (4.9)	27 (2.4)	2.47 (1.47-4.15)	0.001	13 (3.5)	8 (2.1)	1.87 (0.77-4.51)	0.165
Secondary outcomes								
Pacemaker infection	16 (2.5)	28 (2.5)	1.00 (0.54-1.87)	0.991	14 (3.8)	8 (2.1)	1.78 (0.74-4.29)	0.200
Major infection	3 (0.5)	4 (0.4)	1.32 (0.29-5.91)	0.718	2 (0.5)	1 (0.3)	2.01 (0.18-22.21)	0.571
Minor infection	13 (2.1)	24 (2.2)	0.95 (0.48-1.88)	0.884	12 (3.2)	7 (1.9)	1.74 (0.68-4.47)	0.251
PICM	105 (16.6)	108 (9.7)	2.24 (1.71-2.93)	<0.001	64 (17.2)	46 (12.3)	1.62 (1.11-2.36)	0.013
Cerebrovascular accident	83 (13.1)	141 (12.7)	1.32 (1.00-1.73)	0.047	56 (15.0)	49 (13.1)	1.33 (0.91-1.95)	0.146
Cardiovascular mortality	56 (8.9)	68 (6.1)	1.81 (1.27-2.58)	0.001	25 (6.7)	21 (5.6)	1.38 (0.77-2.46)	0.279
All-cause mortality	186 (29.4)	237 (21.4)	1.75 (1.44-2.12)	<0.001	95 (25.5)	77 (20.6)	1.41 (1.05-1.92)	0.023

*Data are presented as number (%) of patients. AMI: acute myocardial infarction; CI: confidence interval; HF: heart failure; HR: hazard ratio; PICM: pacing-induced cardiomyopathy.

follow-up period of 7.8 ± 4.8 years, before PSM, the incidence of cardiovascular events was higher in patients with diabetes compared to patients without diabetes (19.8% vs. 12.5%; hazard ratio (HR) = 2.06; 95% confidence interval (CI), 1.61-2.62; $P < 0.001$) (Table 2), and the incidences of pacing-induced cardiomyopathy (16.6% vs. 9.7%; HR = 2.24; 95% CI, 1.71-2.93; $P < 0.001$), cerebrovascular accident (13.1% vs. 12.7%; HR = 1.32; 95% CI, 1.00-1.73; $P = 0.047$), cardiovascular mortality (8.9% vs. 6.1%; HR = 1.81; 95% CI, 1.27-2.58; $P = 0.001$), and all-cause mortality (29.4% vs. 21.4%; HR = 1.75; 95% CI, 1.44-2.12; $P < 0.001$) were also higher in patients with diabetes compared to patients without diabetes (Table 2). The incidences of pacemaker infection including major and minor infections did not differ between the two groups (Table 2). After PSM, the incidence of cardiovascular events was still higher in patients with diabetes compared to patients without diabetes (18.8% vs. 12.3%; HR = 1.82; 95% CI, 1.25-2.63; $P = 0.002$) (Table 2). Patients with diabetes had a higher incidence of HF hospitalization compared to patients without diabetes (15.3% vs. 10.2%; HR = 1.78; 95% CI, 1.18-2.68; $P = 0.006$), whereas the incidence of AMI did not differ between the two groups (Table 2). After PSM, patients with diabetes had a higher incidence of pacing-induced cardiomyopathy (17.2% vs. 12.3%; HR = 1.62; 95% CI, 1.11-2.36; $P = 0.013$) and all-cause mortality (25.5% vs. 20.6%; HR = 1.41; 95% CI, 1.05-1.92; $P = 0.023$) compared to patients without diabetes (Table 2). However, after PSM, the incidences of pacemaker infection, cerebrovascular accident, and cardiovascular mortality did not differ between the two groups.

The Kaplan–Meier curve analysis for cardiovascular events showed that patients with diabetes had a higher cumulative incidence of cardiovascular events compared to patients without diabetes before and after PSM (log-rank test, $P < 0.001$ and $P = 0.001$, respectively) (Figures 2(a) and 2(d)). Moreover, patients with diabetes had a higher cumulative incidence of HF hospitalization compared to patients without diabetes before and after PSM (log-rank test, $P < 0.001$ and $P = 0.005$, respectively) (Figures 2(b) and 2(e)). However, the cumulative incidence of AMI did not differ between the two groups before and after PSM (Figures 2(c) and 2(f)). The Kaplan–Meier curve analysis for pacing-induced cardiomyopathy showed that patients with diabetes had a higher cumulative incidence of pacing-induced cardiomyopathy compared to patients without diabetes before and after PSM (log-rank test, $P < 0.001$ and $P = 0.012$, respectively) (Figures 3(a) and 3(d)). Furthermore, patients with diabetes had a higher cumulative incidence of all-cause mortality compared to the patients without diabetes before and after PSM (log-rank test, $P < 0.001$ and $P = 0.022$, respectively) (Figures 3(c) and 3(f)). However, the cumulative incidence of cardiovascular mortality did not differ between the two groups after PSM (Figure 3(e)).

4. Discussion

In this cohort study, the prevalence of diabetes was 36.3%, over one-third of naïve PPM recipients. During a mean follow-up of 7.8 ± 4.8 years, after PSM, the incidences of cardiovascular events and HF hospitalization were significantly higher in patients with diabetes compared to patients without diabetes. Moreover, the cumulative incidences of cardiovascular events and HF hospitalization were significantly higher in the matched group with diabetes compared to the matched group without diabetes. Furthermore, patients with diabetes had a higher cumulative incidence of pacing-induced cardiomyopathy and all-cause mortality compared to patients without diabetes before and after PSM.

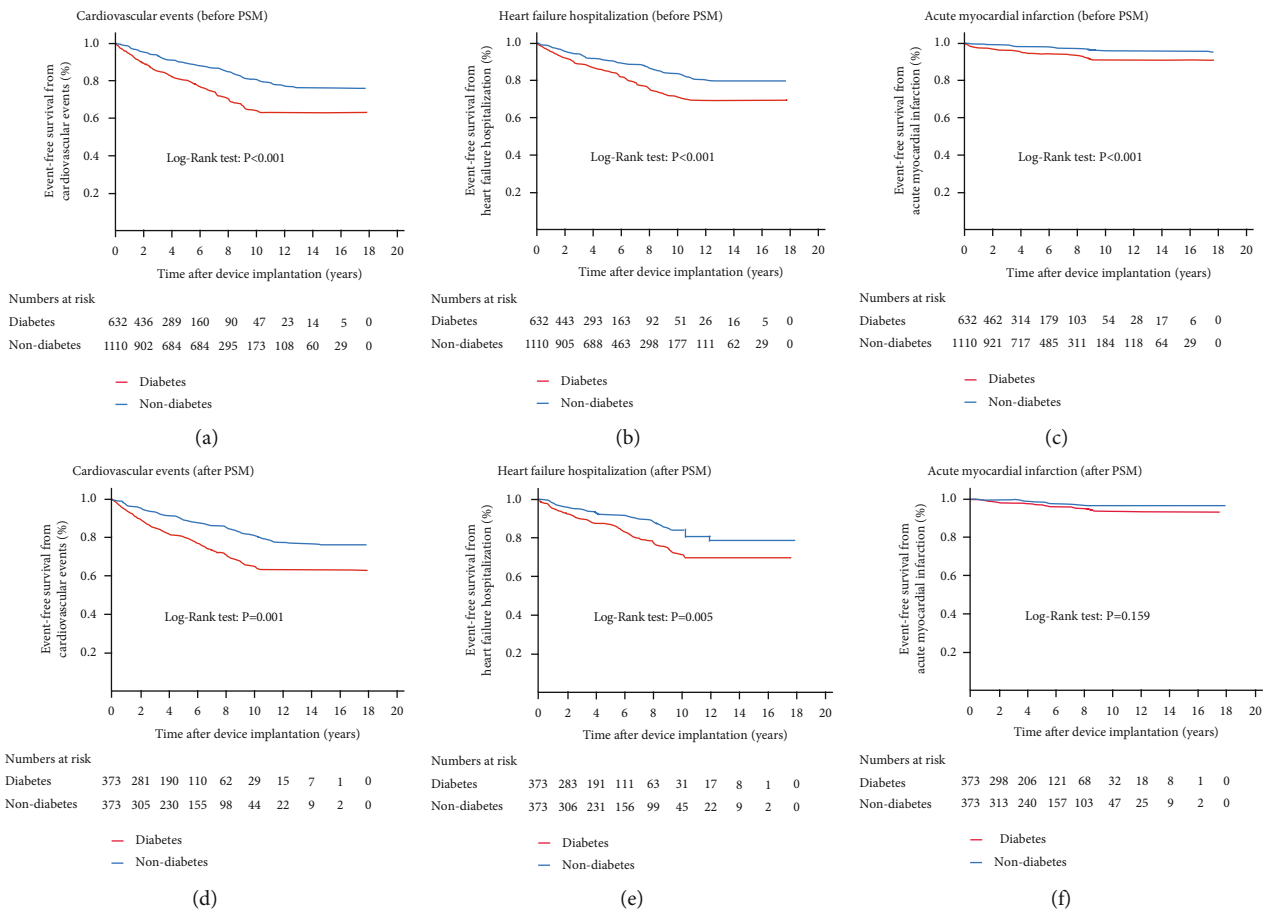


Figure 2: The Kaplan-Meier event-free survival curves of cardiovascular events (primary outcome) (a, d), heart failure hospitalization (b, e), and acute myocardial infarction (c, f) between the groups with and without diabetes before and after propensity score matching. PSM: propensity score matching.

4.1. The Prevalence of Diabetes in Patients Receiving Pacemakers. The global prevalence of diabetes is rising from 8% in 1980 to 9.3% in 2019 and is estimated to be 10.9% by 2045, which may be attributable to population growth and ageing [1, 2]. In the Taiwanese population, the annual prevalence of diabetes increased significantly from 5.8% in 2000 to 8.3% in 2007, especially in the subgroup of men, age ≥ 80 years, and individuals residing in aging society areas [3]. In the elderly aged ≥65 years, around 15%-20% of people live with diabetes [1, 20]. In this study, PPM recipients were aged and the prevalence of diabetes was 36.3%, which was higher than general population [1–3, 20] and was compatible with previous data of PPM recipients [21, 22]. Moreover, similar to other reports [1–3, 20], the trend in the prevalence of diabetes in this study also increased from 28.8% (between 2003 and 2007) and 36.0% (between 2008 and 2012) to 41.4% (between 2013 and 2017).

Prior study reported that diabetes was possibly associated with sinus nodal dysfunction and cardiac conduction abnormalities [9–11, 23]. Movahed et al. reported that the incidence of complete atrioventricular block in patients with diabetes was 1.1%, which was 3-fold increased risk compared to patients without diabetes [11]. Patients with diabetes of this study had a higher prevalence of atrioventricular block compared to patients without diabetes (44.0% vs. 35.8%, $P = 0.001$) (Table 1), similar to other reports [10–12]. From a national diabetes registry study, Rautio et al. reported that diabetes increased 1.6-fold risk for implantation of PPM after adjustments for age, sex, and other factors [12]. Therefore, type 2 diabetes is a risk factor for PPM implantation and vigilant follow-up for bradyarrhythmia in patients with diabetes is necessary.

4.2. Heart Failure Hospitalization in Patients with Diabetes after Pacemaker Implantation. The prevalence of diabetes in HF patients is around 20%, and diabetes increased 1.74-fold risk and 1.95-fold risk of HF in men and women, respectively [6, 24]. In the Reduction of Atherothrombosis for Continued Health (REACH) Registry, diabetes was also associated with a 33% greater risk of HF hospitalization [25]. The reasons for increasing risk of HF in patients with diabetes included combined comorbidities, such as hypertension, acceleration of the development of coronary atherosclerosis, and diabetic cardiomyopathy, which was related to microangiopathy, metabolic factors, or myocardial fibrosis [24]. Moreover, a study using the National Readmission Database showed that the most common cause for readmission in PPM recipients was HF hospitalization [26]. Similar

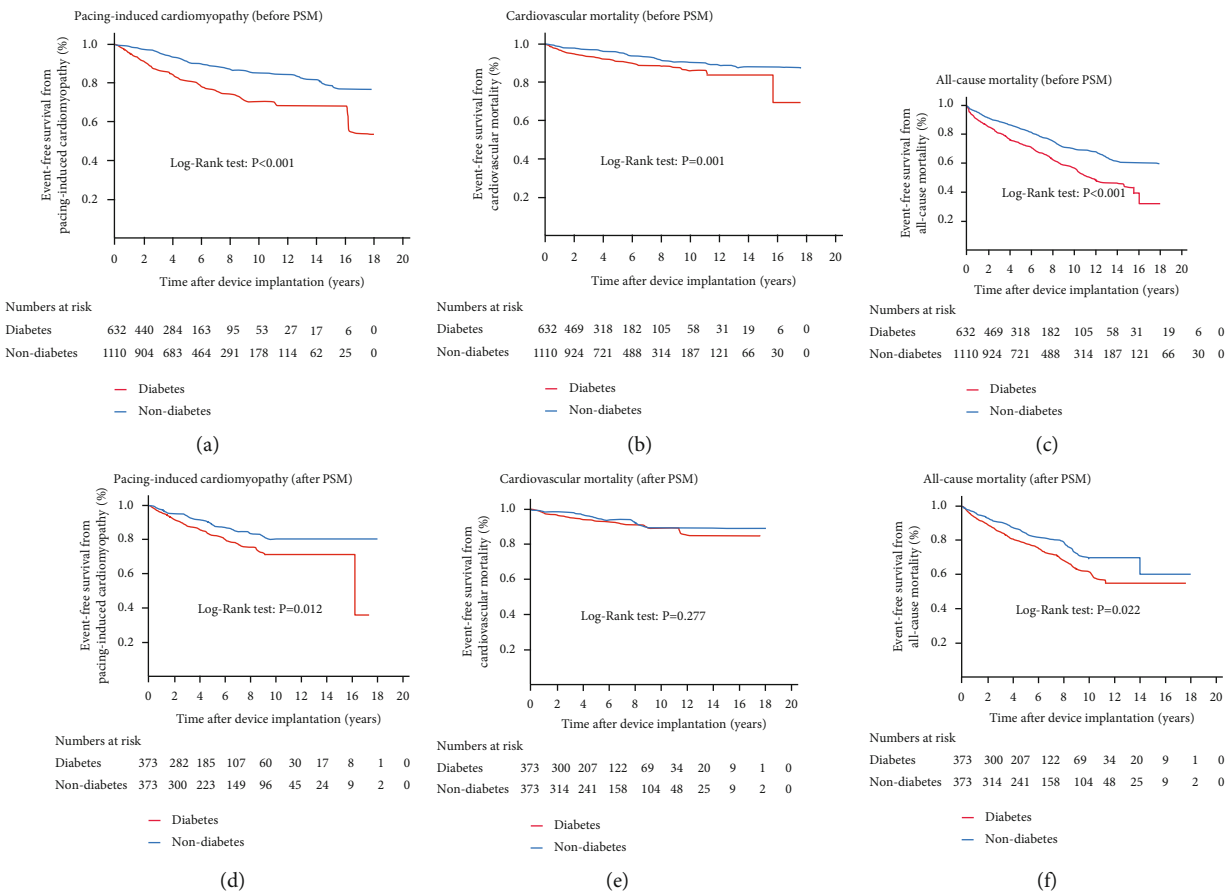


Figure 3: The Kaplan-Meier event-free survival curves of pacing-induced cardiomyopathy (a, d), cardiovascular mortality (b, e), and all-cause mortality (c, f) between the groups with and without diabetes before and after propensity score matching. PSM: propensity score matching.

to general population, in this study of pacemaker recipients, we found that patients with diabetes had a higher risk for HF hospitalization compared to patients without diabetes (Table 2). Diabetic cardiomyopathy is characterized by diastolic relaxation abnormalities in its early stage and later systolic dysfunction [27]. The pathophysiological mechanisms of diabetic cardiomyopathy include systemic metabolic disorders, inappropriate activation of the renin–angiotensin–aldosterone system, subcellular component abnormalities, oxidative stress, inflammation and dysfunctional immune modulation, and finally, interstitial fibrosis of cardiac tissue, which contributed to substantial cardiac stiffness with diastolic dysfunction and later, systolic dysfunction [27]. Furthermore, diabetes is an important phenotype for HF with preserved LVEF and is also an independent predictor for HF hospitalization, despite under treatments of ACEi/ARB [28]. Interestingly, the study population in this study had preserved LVEF and the administration of ACEi/ARB was higher in patients with diabetes compared to patients without diabetes before PSM (Table 1). These findings deserve further investigations regarding angiotensin receptor-neprilysin inhibitor or sodium-glucose cotransporter 2 inhibitor in patients with diabetes with preserved LVEF for PPM implantation [29, 30].

Many studies have shown that right ventricular pacing is associated with HF hospitalization [31, 32]. Our prior study showed that right ventricular pacing QRS duration ≥ 163 milliseconds increased 3.5-fold risk of HF admission, and diabetes increased 2.7-fold risk of HF hospitalization [32]. Right ventricular pacing > 50% has been reported to be associated with an increased risk of HF hospitalization [31]. In this study, after PSM, the mean percentage of right ventricular pacing did not differ between patients with diabetes and patients without diabetes (Table 1). Moreover, the distribution of patients with right ventricular pacing > 40% was similar between patient with and without diabetes before and after PSM (Table 1). Of note, patients with diabetes had a higher cumulative incidence of pacing-induced cardiomyopathy compared to patients without diabetes before and after PSM, consequently, more HF hospitalization in patients with diabetes, and these findings were consistent with our prior study [32]. Recently, conduction system pacing, such as His-bundle pacing and left bundle branch pacing, has been reported to reduce HF hospitalization compared to right ventricular pacing [33, 34]. Our study was the first to show that diabetes was an independent predictor for cardiovascular events, including HF hospitalization, in patients after right ventricular PPM implantation,

potentially related to more pacing-induced cardiomyopathy. Our findings provided the hypothesis for future studies of conduction system pacing in patients with diabetes who required PPM implantation.

4.3. Limitation. In this study, some potential limitations existed. First, although this was a retrospective single-center study, the sample size was large. Still, the potential bias inherent to nonrandomized investigations cannot be excluded. However, we performed PSM to minimize the bias between patients with and without diabetes. Second, the compliance period and dosage of prescription for beta-blocker, ACEi/ARB, diuretic agents, and statin during the follow-up period were not available in this study. Third, the duration of diagnosed diabetes before PPM implant was unknown. Finally, the preprocedural echocardiographic parameters of diastolic function by tissue Doppler or speckle-tracking imaging were not performed.

5. Conclusion

The prevalence of diabetes was over one-third of naïve PPM recipients of this cohort, and diabetes increased the risk of cardiovascular events in PPM recipients, especially for HF hospitalization.

Data Availability

The retrospective data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

The study protocol was approved by the Institutional Review Board of Chang Gung Medical Foundation (permit number: 202100907B0).

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Authors' Contributions

HCC contributed to the analysis and interpretation of data and wrote the manuscript. WHL and CHT contributed to discussion and reviewed and edited the manuscript. YLC, WCL, YNF, and SZC contributed to collection of data. MCC contributed to study design and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Acknowledgments

We appreciate the Biostatistics Center, Kaohsiung Chang Gung Memorial Hospital, for assistance with the statistical analysis.

References

[1] P. Saeedi, I. Petersohn, P. Salpea et al., "Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas," *Diabetes Research and Clinical Practice*, vol. 157, 2019.

[2] G. Danaei, M. M. Finucane, Y. Lu et al., "National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2∗7 million participants," *The Lancet*, vol. 378, no. 9785, pp. 31–40, 2011.

[3] C. C. Lin, C. I. Li, C. Y. Hsiao et al., "Time trend analysis of the prevalence and incidence of diagnosed type 2 diabetes among adults in Taiwan from 2000 to 2007: a population-based study," *BMC Public Health*, vol. 13, p. 318, 2013.

[4] P. Z. Zimmet, D. J. Magliano, W. H. Herman, and J. E. Shaw, "Diabetes: a 21st century challenge," *The Lancet Diabetes and Endocrinology*, vol. 2, no. 1, pp. 56–64, 2014.

[5] S. M. Haffner, S. Lehto, T. Rönnemaa, K. Pyörälä, and M. Laakso, "Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction," *The New England Journal of Medicine*, vol. 339, no. 4, pp. 229–234, 1998.

[6] T. Ohkuma, Y. Komorita, S. A. E. Peters, and M. Woodward, "Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals," *Diabetologia*, vol. 62, no. 9, pp. 1550–1560, 2019.

[7] K. Weidner, M. Behnes, T. Schupp et al., "Type 2 diabetes is independently associated with all-cause mortality secondary to ventricular tachyarrhythmias," *Cardiovascular Diabetology*, vol. 17, no. 1, p. 125, 2018.

[8] B. M. Frier, "Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications," *Nature Reviews. Endocrinology*, vol. 10, no. 12, pp. 711–722, 2014.

[9] T. Wasada, K. Katsumori, S. Hasumi et al., "Association of sick sinus syndrome with hyperinsulinemia and insulin resistance in patients with non-insulin-dependent diabetes mellitus: report of four cases," *Internal Medicine*, vol. 34, no. 12, pp. 1174–1177, 1995.

[10] R. L. Blandford and A. C. Burden, "Abnormalities of cardiac conduction in diabetics," *British Medical Journal*, vol. 289, no. 6459, p. 1659, 1984.

[11] M. R. Movahed, M. Hashemzadeh, and M. M. Jamal, "Increased prevalence of third-degree atrioventricular block in patients with type II diabetes mellitus," *Chest*, vol. 128, no. 4, pp. 2611–2614, 2005.

[12] E. Rautio, F. Gadler, S. Gudbjörnsdottir et al., "Patients with type 2 diabetes have an increased demand for pacemaker treatment: a comparison with age- and sex-matched control subjects from the general population," *Diabetes Care*, vol. 43, no. 11, pp. 2853–2858, 2020.

[13] H. C. Chen, Y. L. Chen, B. F. Guo et al., "Thrombocytopenia, dual antiplatelet therapy, and heparin bridging strategy increase pocket hematoma complications in patients undergoing cardiac rhythm device implantation," *The Canadian Journal of Cardiology*, vol. 29, no. 9, pp. 1110–1117, 2013.

[14] American Diabetes Association, "2. Classification and diagnosis of diabetes: Standards of medical care in Diabetes-2019," *Diabetes Care*, vol. 42, Supplement 1, pp. S13–S28, 2019.

[15] I. H. de Boer, M. L. Caramori, J. C. N. Chan et al., "KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease," *Kidney International*, vol. 98, no. 4, pp. S1–S115, 2020.

[16] A. S. Levey, L. A. Stevens, C. H. Schmid et al., "A new equation to estimate glomerular filtration rate," *Annals of Internal Medicine*, vol. 150, no. 9, pp. 604–612, 2009.

[17] Y. H. Li, K. C. Ueng, J. S. Jeng et al., "2017 Taiwan lipid guidelines for high risk patients," *Journal of the Formosan Medical Association*, vol. 116, pp. 217–248, 2017.

[18] H. C. Chen, M. C. Chen, Y. L. Chen, T. H. Tsai, K. L. Pan, and Y. S. Lin, "Bundled preparation of skin antisepsis decreases the risk of cardiac implantable electronic device-related infection," *Europace*, vol. 18, no. 6, pp. 858–867, 2016.

[19] P. C. Austin, "Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples," *Statistics in Medicine*, vol. 28, no. 25, pp. 3083–3107, 2009.

[20] A. Sinclair, P. Saeedi, A. Kaundal, S. Karuranga, B. Malanda, and R. Williams, "Diabetes and global ageing among 65-99-year-old adults: Findings from the International Diabetes Federation Diabetes Atlas, 9th edition," *Diabetes Research and Clinical Practice*, vol. 162, 2020.

[21] R. Podlaha and A. Falk, "The prevalence of diabetes mellitus and other risk factors of atherosclerosis in bradycardia requiring pacemaker treatment," *Hormone and Metabolic Research Supplement*, vol. 26, pp. 84–87, 1992.

[22] J. T. Lear, I. G. Lawrence, and A. C. Burden, "Prevalence of diabetes in elderly patients requiring permanent cardiac pacemaker insertion," *Acta Diabetologica*, vol. 33, no. 2, pp. 169-170, 1996.

[23] M. R. Movahed, "Diabetes as a risk factor for cardiac conduction defects: a review," *Diabetes, Obesity & Metabolism*, vol. 9, pp. 276–281, 2006.

[24] C. Bauters, N. Lamblin, E. P. Mc Fadden, E. Van Belle, A. Millaire, and P. de Groote, "Influence of diabetes mellitus on heart failure risk and outcome," *Cardiovascular Diabetology*, vol. 2, p. 1, 2003.

[25] M. A. Cavender, P. G. Steg, S. C. Smith Jr. et al., "Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and Death," *Circulation*, vol. 132, no. 10, pp. 923–931, 2015.

[26] D. K. Pasupula, A. Rajaratnam, R. Rattan et al., "Trends in hospital admissions for and readmissions after cardiac implantable electronic device procedures in the United States: an analysis from 2010 to 2014 using the National Readmission Database," *Mayo Clinic Proceedings*, vol. 94, no. 4, pp. 588–598, 2019.

[27] G. Jia, A. Whaley-Connell, and J. R. Sowers, "Diabetic cardiomyopathy: a hyperglycaemia- and insulin-resistance-induced heart disease," *Diabetologia*, vol. 61, no. 1, pp. 21–28, 2018.

[28] S. Lejeune, C. Roy, A. Slimani et al., "Diabetic phenotype and prognosis of patients with heart failure and preserved ejection fraction in a real life cohort," *Cardiovascular Diabetology*, vol. 20, no. 1, pp. 1–12, 2021.

[29] S. D. Solomon, J. J. V. McMurray, I. S. Anand et al., "Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction," *The New England Journal of Medicine*, vol. 381, no. 17, pp. 1609–1620, 2019.

[30] S. D. Anker, J. Butler, G. Filippatos et al., "Empagliflozin in heart failure with a preserved ejection fraction," *The New England Journal of Medicine*, vol. 385, pp. 1451–1461, 2021.

[31] M. D. Smit, P. F. Van Dessel, W. Nieuwland et al., "Right ventricular pacing and the risk of heart failure in implantable cardioverter-defibrillator patients," *Heart Rhythm*, vol. 3, no. 12, pp. 1397–1403, 2006.

[32] W. C. Lee, H. Y. Fang, H. C. Chen et al., "Post-pacemaker implant QRS duration and heart failure admission in patients with sick sinus syndrome and complete atrioventricular block," *ESC Heart Failure*, vol. 6, no. 4, pp. 686–693, 2019.

[33] P. Vijayaraman, A. Naperkowski, F. A. Subzposh et al., "Permanent His-bundle pacing: long-term lead performance and clinical outcomes," *Heart Rhythm*, vol. 15, no. 5, pp. 696–702, 2018.

[34] P. S. Sharma, N. R. Patel, V. Ravi et al., "Clinical outcomes of left bundle branch area pacing compared to right ventricular pacing: results from the Geisinger-Rush Conduction System Pacing Registry," *Heart Rhythm*, vol. 19, no. 1, pp. 3–11, 2022.

Hindawi
Journal of Diabetes Research
Volume 2022, Article ID 8183487, 10 pages
https://doi.org/10.1155/2022/8183487

Research Article

Comparison of Risk Assessment Strategies for Patients with Diabetes Mellitus and Stable Chest Pain: A Coronary Computed Tomography Angiography Study

Jia Zhao,[1,2] Shuo Wang,[3] Pengyu Zhao,[4] Yong Huo,[5] Chunjie Li,[1] and Jia Zhou[1]

[1]*Department of Cardiology, Tianjin Chest Hospital, Tianjin, China*
[2]*Graduate School, Tianjin Medical University, Tianjin, China*
[3]*Graduate School, Tianjin University of Traditional Chinese Medicine, Tianjin, China*
[4]*School of Electrical and Information Engineering, Tianjin University, Tianjin, China*
[5]*Department of Cardiology, Peking University First Hospital, Beijing, China*

Correspondence should be addressed to Chunjie Li; ykwn@sina.com and Jia Zhou; zhoujiawenzhang@126.com

Received 5 October 2021; Revised 14 December 2021; Accepted 7 January 2022; Published 25 January 2022

Academic Editor: Pawel Kleczynski

Background. To compare two risk assessment strategies to identify individuals likely to benefit from further imaging testing in patients with diabetes mellitus (DM) and stable chest pain (SCP) suspected of obstructive coronary artery disease (CAD). *Methods*. 602 DM patients referred to coronary computed tomography angiography (CCTA) for SCP were included. They were divided into high- and low-risk groups according to the 2016 National Institute of Health and Care Excellence guideline-determined strategy (NICE strategy) which focused on symptom evaluation and 2019 European Society of Cardiology guideline-determined strategy (ESC strategy) which was based on pretest probability (PTP) sequentially determined by the ESC-PTP estimator and risk factor-weighted clinical likelihood (RF-CL) model, respectively. The associations of clinical outcomes with risk groups and net reclassification improvement (NRI) were evaluated. *Results*. The NICE and ESC strategy classified 44% and 39% patients into the low-risk group, respectively. Compared to the NICE strategy, the ESC strategy indicated stronger associations between risk groups and events (hazard ratios: 4.24 versus 1.91), intensive clinical management, and a positive NRI (27.71%, $p < 0.0001$). The application of the RF-CL model ameliorated the underestimation of risk in patients with borderline ESC-PTP, which principally account for the improvement of the ESC strategy. *Conclusion*. Compared to the NICE strategy, the ESC strategy seemed to be associated with greater efficiency in identifying high risk individuals in patients with DM and SCP.

1. Introduction

In patients with diabetes mellitus (DM), coronary artery disease (CAD) is a major cause of mortality [1]. Stable chest pain (SCP) is the most common clinical manifestation in patients with obstructive CAD. In an analysis for the largest contemporary cohort of SCP, the PROMISE trial, patients with DM were more likely to have a positive cardiovascular imaging testing (CIT) result and major adverse cardiovascular event (MACE) [2]. Consequently, a risk assessment strategy to efficiently identify high-risk individuals deriving maximum benefit from further CIT is initial and essential in the clinical management for DM patients presenting with SCP suggestive of obstructive CAD [2–4].

To improve this identification, the 2016 U.K. National Institute of Health and Care Excellence (NICE) guideline recommended a symptom-based risk assessment strategy for SCP [5]. However, this strategy has been controversial since its release [6–8] and numerous studies have indicated that atypical symptoms were more likely to be a manifestation in patients with DM [2, 3, 9]. On the other hand, the 2019 European Society of Cardiology (ESC) guideline advocated an updated pretest probability (PTP) estimator based on age, sex, and symptom and recommended CIT for

patients with high ESC-PTP [10]. For patients with borderline ESC-PTP, the addition of other risk factors can improve the estimation of clinical likelihood of obstructive CAD [11].

The 2016 NICE guideline-determined risk assessment strategy (NICE strategy) [12, 13] and ESC-PTP estimator [14–16] have been externally validated in general SCP patients. But to date, no comparative analysis has been conducted to systematically evaluate the NICE strategy and 2019 ESC guideline-determined risk assessment strategy (ESC strategy) in patients with both DM and SCP, for whom the appropriate referral for intensive investigation was fundamental but difficult [2, 3, 17]. Thus, we aimed to compare the two newest risk assessment strategies to optimize decision-making of downstream clinical management in a coronary computed tomography angiography- (CCTA-) based cohort comprised of patients with DM and SCP.

2. Methods

2.1. Study Population. As described previously, 5289 patients referred to CCTA for SCP indicative of obstructive CAD were recruited from December 2015 to December 2017 in Tianjin Chest Hospital [18–21]. In the present analysis, 602 patients with a diagnosis of DM were included and followed up until December 2019. Patients were considered suffering from DM if one of the following was met: treatment with insulin or hypoglycemic medications, fasting blood glucose ≥ 7.0 mmol/L, a 2 h plasma glucose level on their oral glucose tolerance test ≥ 11.1 mmol/L, or a glycated hemoglobin value ≥ 6.5%. This observational study was conducted after obtaining the informed consent from the participating patients and upon the approval by the ethics committee of Tianjin Chest Hospital.

2.2. Baseline Data. Baseline data such as age, sex, hypertension, hyperlipidemia, smoking, abnormal electrocardiograph, creatinine, and symptom were collected and defined as described previously [18–21]. SCP symptom was categorized as nonanginal chest pain, atypical angina, or typical angina [22]. For each patient, creatinine was routinely measured unless the measurement has happened within 2 months before CCTA. The estimated glomerular filtration rate was calculated based on the CKD-EPI formula [23].

2.3. Risk Assessment Strategies. A patient in the high-risk group based on each strategy should take CIT. Details of risk groups in the NICE and ESC strategy were as follows [5, 10]:

NICE strategy: patients with nonanginal SCP and normal ECG were at low risk. The high-risk group included SCP patients who were diagnosed with typical and atypical angina or nonanginal pectoris with abnormal ECG [5].

ESC strategy: PTP of obstructive CAD was determined according to the ESC-PTP estimator based on age, sex, and symptom [10]. Patients with ESC-PTP < 5% were divided into the low-risk group, and patients with ESC-PTP > 15% were divided into the high-risk group. For other patients, we used the risk factor-weighted clinical likelihood (RF-CL) model for further assessment [24]. The RF-CL model incorporating clinical variables plus age, sex, and symptom showed the most robust performance. According to the data from the original study of the RF-CL model, low RF-CL (<15%) was associated with less obstructive CAD (<5%) and risk of clinical events (<2% annual risk) [24]. Thus, patients with ESC-PTP between 5% and 15% and RF-CL < 15% were at low risk, and patients with ESC-PTP between 5% and 15% and RF-CL > 15% were at high risk.

2.4. CCTA. All scans were performed according to the established guideline [25] and institutional protocols [18–21]. In image evaluation, each coronary segment with a >2 mm diameter was analyzed for the presence of coronary diameter stenosis. According to the Coronary Artery Disease-Reporting and Data System [26], the maximal degree of coronary diameter stenosis was defined as 0%, 1-49%, and 50%. Obstructive CAD was defined as present if a patient had at least one lesion with ≥50% diameter stenosis or any unassessable segments at CCTA. The patient with obstructive CAD was defined as positive.

2.5. Follow-Up and Clinical Events. After CCTA, all patients were followed at 6, 12, 24, 36, and 48 months by phone call or physician visit. MACE, defined as cardiac death and myocardial infarction, was the primary endpoint. Cardiac death was defined as any death caused by cardiac disease or for which no other cause could be found. Myocardial infarction was defined as described in the Fourth Universal Definition of Myocardial Infarction [27]. The changes of downstream clinical management, which included medication prescriptions (such as antiplatelet agents, anti-ischemic drugs, and lipid-lowering agents), referrals to CIT (noninvasive and invasive imaging testing), and coronary revascularization (CR) within 60 days after CCTA, were identified on an electronic medical system. Increase of medication (IM), invasive coronary angiography (ICA), and CR were regarded as secondary endpoints. All endpoints were adjudicated via review of follow-up information and medical records by an independent clinical event committee who were blinded to other data.

2.6. Statistical Analysis. Student's *t*-test or Mann-Whitney *U* test was used to evaluate the differences in continuous variables appropriately. The χ^2 test or Fisher exact test was used to evaluate the differences in categorical variables appropriately. All statistical analyses were performed using MedCalc (version 15.2.2; MedCalc Software, Mariakerke, Belgium) and R (version 3.2.4; R Foundation for Statistical Computing, Vienna, Austria). The discrimination and calibration of the ESC-PTP estimator were assessed by the area under receiver operating characteristic curve (AUC) and Hosmer–Lemeshow goodness-of-fit statistic (H-L χ^2) according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement [28]. Net reclassification improvement (NRI) was assessed in a reclassification table and used to determine how a risk assessment strategy reclassified patients into various risk groups compared with another [29]. The cumulative MACE-free survivals were estimated using Kaplan–Meier curves and were compared by the log-rank test. We

used Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Two-tailed $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline Characteristics. The study cohort consisted of 602 DM patients, of whom 45.02% (271/602) were found to have obstructive CAD on CCTA which are listed in Table 1. Most baseline characteristics were significantly associated with the presence of obstructive CAD. According to the NICE strategy, of the 602 patients, 43.68% (263/602) were assigned to the low-risk group. There were 87 patients with a RF-CL < 15% among 208 patients with an ESC-PTP of 5-15%. Together with the 150 patients with an ESC-PTP below 5%, the ESC strategy totally classified 39.37% (237/602) into the low-risk group.

Table 2 shows the distribution of clinical characteristics by risk groups based on different strategies. Except hypertension and hyperlipidemia, differences of the other baseline characteristics were statistically significant between two risk groups based on the NICE strategy. There were significant differences in most characteristics except abnormal ECG in terms of the ESC strategy. Compared with low-risk patients, high-risk patients had more obstructive CAD (NICE strategy: 61% versus 25%, $p < 0.0001$; ESC strategy: 71% versus 5%, $p < 0.0001$) and MACE (NICE strategy: 9% versus 5%, $p = 0.0422$; ESC strategy: 10% versus 3%, $p = 0.0001$).

3.2. Follow-Up. Patients were followed up for a median of 36 (interquartile range: 30 to 43) months, and 37 patients experienced MACE (8 cardiac deaths and 29 nonfatal MI). Figure 1 illustrates the Kaplan–Meier estimates of patients surviving free from MACE. The high-risk group according to both NICE and ESC strategies had a significantly higher risk of MACE, respectively (p for the log-rank test: 0.0445 for the NICE strategy and 0.0003 for the ESC strategy), but the association of ESC strategy-determined risk groups (high versus low) with MACE was stronger than that of the NICE strategy (HR for NICE strategy: 1.91, 95% CI 1.01-3.63, $p = 0.0485$; HR for ESC strategy: 4.24, 95% CI 1.80-9.97, $p = 0.0010$).

3.3. Subsequent Clinical Management. The associations between risk groups and secondary endpoints according to the NICE and ESC strategy are manifested in Figure 2. 175 patients had ICA based on CCTA, 138 patients had obstructive CAD on ICA, and 65 patients underwent CR. Compared with low-risk patients, high-risk patients had more IM (NICE strategy: 48% (164/339) versus 29% (77/263), odds ratio (OR): 2.26, 95% CI: 1.61-3.18, $p < 0.0001$; ESC strategy: 53% (195/365) versus 19% (46/237), OR: 4.76, 95% CI: 3.25-6.98, $p < 0.0001$), ICA (NICE strategy: 37% (125/339) versus 19% (49/263), OR: 2.55, 95% CI: 1.74-3.73, $p < 0.0001$; ESC strategy: 40% (145/365) versus 12% (29/237), OR: 4.73, 95% CI: 3.04-7.35, $p < 0.0001$), and CR (NICE strategy: 13% (44/339) versus 8% (20/263), OR: 2.03, 95% CI: 1.14-3.60, $p = 0.0156$; ESC strategy: 16% (59/365) versus 2% (5/237), OR: 8.89, 95% CI: 3.51-22.50, $p < 0.0001$).

3.4. Validation of the ESC-PTP Estimator. The receiver operating characteristic curves of the ESC-PTP estimator are illustrated in Figure 3. The discrimination of the ESC-PTP estimator was acceptable, with an AUC of 0.783 (95% CI 0.747 to 0.819, $p < 0.0001$). The calibration plot for the ESC-PTP estimator is presented in Figure 4. Graphically, the ESC-PTP estimator underestimated the probability of obstructive CAD in patients with an ESC-PTP between 5% and 15% and overestimated the probability of obstructive CAD in patients with an ESC-PTP > 15%, resulting in a poor calibration (H-L $\chi^2 = 92.47$, $p < 0.0001$).

3.5. Comparison of the ESC Strategy and NICE Strategy by NRI. Table 3 is the reclassification table comparing the ESC strategy to the NICE strategy. Compared to the NICE strategy, among the 331 negative patients, 35 patients were correctly reclassified from high- to low-risk groups by the ESC strategy, but 8 negative patients were incorrectly reclassified from low- to high-risk groups by the ESC strategy. Among the 271 positive patients, the ESC strategy correctly reclassified 59 patients from low- to high-risk groups, but 6 patients were incorrectly reclassified from high- to low-risk groups. Therefore, the NRI of the ESC strategy compared with the NICE strategy was 8.15% for negative patients, 19.66% for positive patients, and 27.71% for all patients. Table 4 is the reclassification table comparing the RF-CL model to the NICE strategy in patients with ESC-PTP between 5% and 15%. Compared to the NICE strategy, the RF-CL model correctly reclassified 36 positive patients into the high-risk group, in large measure accounting for the NRI of 32.29% in positive and the NRI of 42.11% in all. As shown in Table 5, the improvement was attenuated when the analysis was applied to patients with ESC-PTP below 5% and above 15%, either comparing the RF-CL model to the NICE strategy (NRI = 24.33%, $p < 0.0001$) or comparing the ESC strategy to the NICE strategy (NRI = 19.88%, $p < 0.0001$), resulting from the similar classification of the ESC strategy and RF-CL model (NRI = −4.45%, $p = 0.0598$).

4. Discussion

In this CCTA-based cohort comprised of patients with DM and SCP, based on two newest risk assessment strategies, low-risk groups were associated with fewer obstructive CAD, MACE, and clinical interventions than high-risk groups did. Compared to the NICE strategy which focused on symptom evaluation, the ESC strategy which sequentially incorporated the ESC-PTP estimator with the RF-CL model had more potential to optimize decision-making of downstream referral for CIT in patients with DM and SCP.

It has been well established that DM confers a two-fold increased risk of MACE in patients presenting with SCP potentially related to CAD [2]. Thus, the referral of CIT to screening for obstructive CAD guided by the risk assessment strategy is vital in the clinical management of patients with DM and SCP, but the most efficient strategy for these

Table 1: Baseline characteristics by the presence of obstructive CAD on CCTA.

Characteristic	Total $N = 602$	Obstructive CAD Yes ($N = 271$)	Obstructive CAD No ($N = 331$)	p
Age (years, mean ± SD)	62.26 ± 11.61	65.83 ± 12.79	59.34 ± 11.96	<0.0001
Male	331 (55)	176 (65)	155 (47)	<0.0001
Hypertension	409 (68)	198 (73)	211 (64)	0.0188
Hyperlipidemia	313 (52)	160 (59)	153 (46)	0.0023
Smoking	284 (47)	143 (53)	141 (43)	0.0162
Abnormal ECG	259 (43)	132 (49)	127 (38)	0.0136
eGFR (mL/min/1.73 m^2, mean ± SD)	71.59 ± 9.47	70.34 ± 10.49	72.61 ± 12.07	0.0152
Symptom				0.0182
Nonanginal chest pain	284 (47)	115 (42)	169 (51)	
Atypical angina	239 (40)	110 (41)	129 (39)	
Typical angina	79 (13)	46 (17)	33 (10)	

SD: standard deviation; CAD: coronary artery disease; ECG: electrocardiogram; CCTA: coronary computed tomographic angiography; eGFR: estimated glomerular filtration rate. Values are presented as n (%) unless stated otherwise.

Table 2: Characteristics by risk groups based on the NICE and ESC strategy.

	Total $n = 602$	NICE strategy Low $n = 263$	NICE strategy High $n = 339$	p	ESC strategy Low $n = 237$	ESC strategy High $n = 365$	p
Age (years, mean ± SD)	62.26 ± 11.61	59.99 ± 12.53	64.02 ± 12.10	<0.0001	57.44 ± 12.44	65.39 ± 12.27	<0.0001
Female	331 (55)	128 (49)	203 (60)	0.0078	101 (43)	230 (63)	<0.0001
Hypertension	409 (68)	172 (65)	237 (70)	0.2763	143 (60)	266 (73)	0.0017
Hyperlipidemia	313 (52)	130 (49)	183 (54)	0.3045	109 (46)	204 (56)	0.0219
Smoking	284 (47)	111 (42)	173 (51)	0.0385	91 (38)	193 (53)	0.0007
Abnormal ECG	259 (43)	0 (0)	259 (76)	<0.0001	95 (40)	164 (45)	0.2760
Symptom				<0.0001			0.0001
Nonanginal chest pain	284 (47)	263 (100)	21 (6)		91 (38)	193 (53)	
Atypical angina	239 (40)	0 (0)	239 (71)		100 (42)	139 (38)	
Typical angina	79 (13)	0 (0)	79 (23)		46 (20)	33 (9)	
Obstructive CAD[b]	271 (45)	65 (25)	206 (61)	<0.0001	12 (5)	259 (71)	<0.0001
MACE	45 (7)	13 (5)	32 (9)	0.0422	6 (3)	39 (10)	0.0001
Cardiac death	11 (2)	2 (1)	9 (3)	0.1244	0 (0)	11 (3)	0.0044
Nonfatal MI	34 (5)	11 (4)	23 (6)	0.2325	6 (3)	28 (7)	0.0067

SD: standard deviation; CAD: coronary artery disease; NICE strategy: 2016 National Institute of Health and Care Excellence guideline-determined risk assessment strategy; ESC strategy: 2019 European Society of Cardiology guideline-determined risk assessment strategy; ECG: electrocardiogram; MI: myocardial infarction; MACE: major adverse cardiovascular events. Values are presented as n (%) unless stated otherwise.

patients has been debated until now [2, 3]. In stark contrast to the "screen all" strategy which was not supported by contemporary evidence [17, 30], the NICE strategy recommended a simple evaluation based on symptom [5] and improved diagnostic certainty and clinical outcomes compared to traditional PTP calculator-based strategies in two external validation studies conducted in general SCP patients [12, 13]. However, compared to the ESC strategy, the NICE strategy was demonstrated to be less efficient in the risk assessment for patients with DM and SCP.

Because of autonomic neuropathy affecting the pain perceptual threshold, the association between ischemia and SCP may be diminished, which could lead to an atypical presentation in patients with DM [9, 31, 32]. As a result, current evidence implied that the suboptimal performance of the NICE strategy may, to a large extent, be attributed to the insufficient power of symptom evaluation alone in patients with DM and SCP. In the DM subgroup of the PROMISE cohort, neither typical nor atypical chest pain was an independent predictor of positive CIT [2]. Meanwhile, an analysis conducted in 8662 patients referred for new-onset SCP suggested that among patients diagnosed with noncardiac chest pain, those with DM remained at two-fold increased risk of MACE, compared with non-DM patients [3]. In conformity with these findings, when comparing the NICE strategy to the ESC strategy in the present study, the NRI

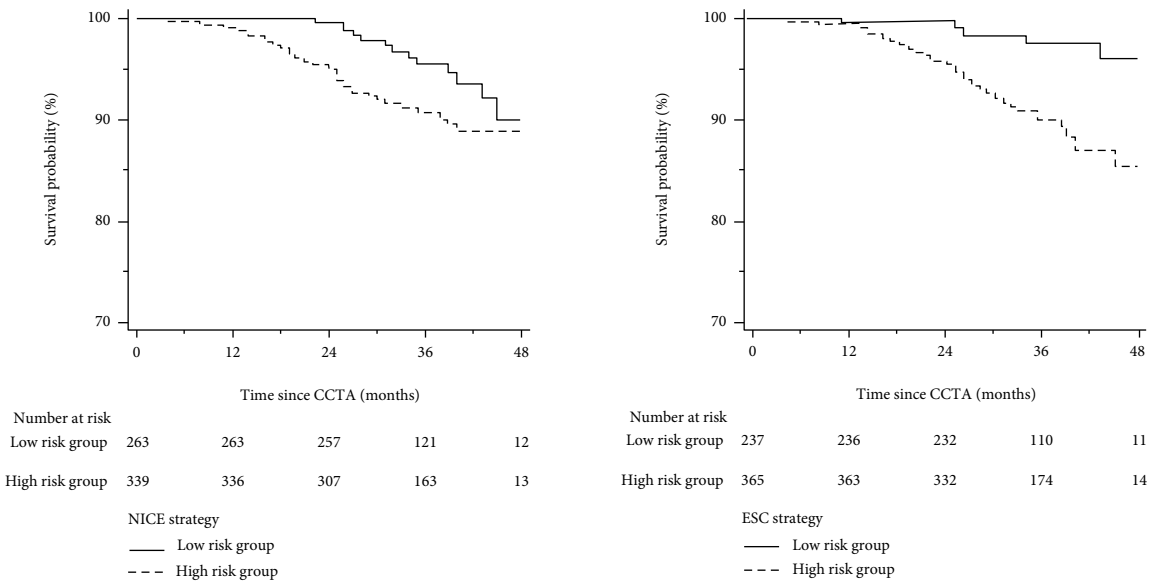


Figure 1: Cumulative survival probability from MACE in low- and high-risk groups determined by the NICE and ESC strategy. Abbreviations as in Table 3.

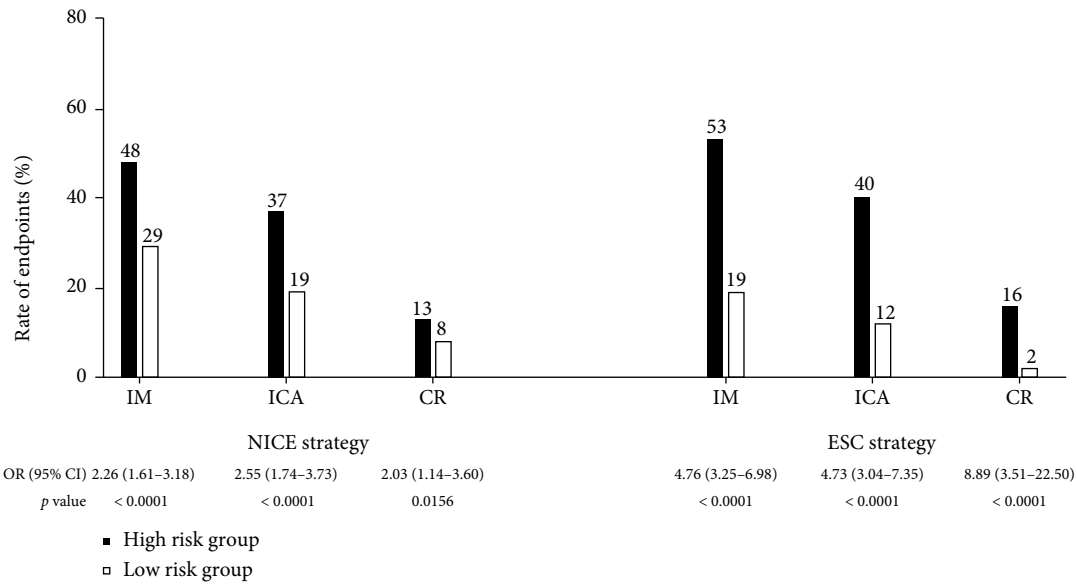


Figure 2: Rates for secondary endpoints in low- and high-risk groups determined by the NICE and ESC strategy. ICA: invasive coronary angiography; IM: increase of medication; CR: coronary revascularization; other abbreviations as in Table 3.

was negative and the association between study endpoints and risk groups was attenuated.

Both the ESC-PTP estimator and RF-CL model were developed in the most contemporary SCP cohorts and indicative of the best performance to predict obstructive CAD and MACE in general SCP patients [14–16, 24], which were compliant with the modest AUC for the ESC-PTP estimator and positive NRI comparing the RF-CL model to the NICE strategy in the present study. In addition, the RF-CL model has also taken the interaction effect between symptom and DM into account [24]. As a result, the ESC strategy based on the sequential amalgamation of the ESC-PTP estimator and RF-CL model demonstrated superiority in terms of the diagnosis for obstructive CAD, prediction of MACE, and use of downstream diagnostic and therapeutic interventions in patients with DM and SCP.

As illustrated in Figure 3, the ESC-PTP estimator overestimated the probability of obstructive CAD in patients with ESC-PTP > 15%. The overestimation may not change the further clinical management, because all patients with ESC -PTP > 15% should be referred to CIT according to the ESC strategy [11]. On the contrary, the underestimation for probability of obstructive CAD in patients with ESC-PTP between 5% and 15% may result in a significant number of missing referrals for CIT. To provide a more in-depth and comprehensive insight into the risk assessment

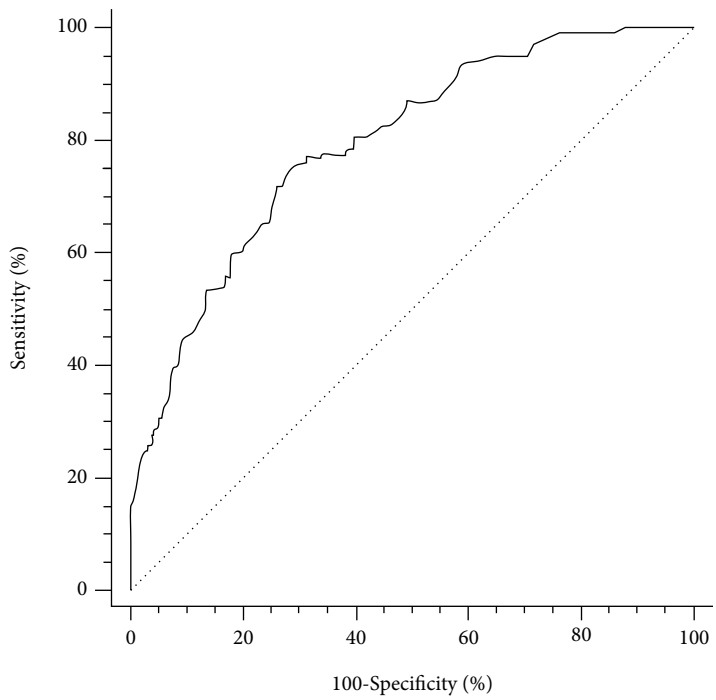


Figure 3: ROC curves for the ESC-PTP estimator to predict obstructive CAD. ROC: receiver operating characteristic; other abbreviations as in Table 4.

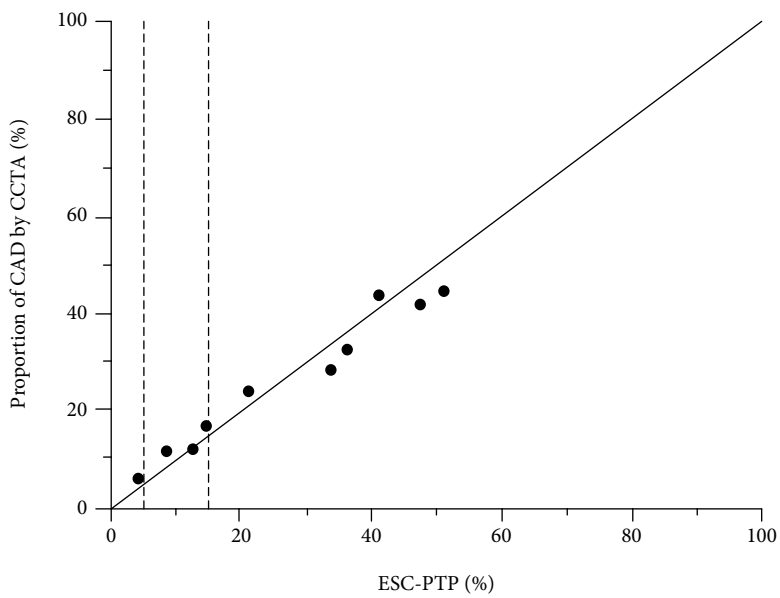


Figure 4: Comparison of ESC-PTP and proportion of obstructive CAD on CCTA by deciles of ESC-PTP. The area between two dotted lines represents ESC-PTP between 5% and 15%. CCTA: coronary computed tomographic angiography. Other abbreviations as in Figure 3.

for patients with borderline ESC-PTP, we also conducted the comparison between the RF-CL model and NICE strategy in patients with ESC-PTP between 5% and 15% (Table 4) and among the RF-CL model, ESC strategy, and NICE strategy in ESC-PTP below 5% and above 15% (Table 5), respectively. Taking all these into consideration, when comparing the ESC strategy to the NICE strategy, the application of the RF-CL model obviously ameliorated the underestimation of risk in 208 patients with borderline ESC-PTP and the total reclassification of 59 positive patients should be principally (61.02%, 36/59) attributed to this application.

More importantly, the RF-CL model incorporated symptom assessment plus risk factors which were easily accessible in daily clinical practice. Thus, one additional collection of information for risk factors in every $602/208 \approx 3$ DM patients and one avoidance of missing referrals for CIT

Table 3: Reclassification table comparing the ESC strategy to the NICE strategy.

	Risk groups by ESC strategy		Total	Reclassification		NRI	p
	Low	High		Up	Down		
Risk groups by NICE strategy							
Negative patients				2.42%	10.57%	27.71%	<0.0001
Low	190	8	198				
High	35	98	133				
Total	225	106	331				
Positive patients				21.77%	2.21%		
Low	6	59	65				
High	6	200	206				
Total	12	259	271				

CAD: coronary artery disease; NICE strategy: 2016 National Institute of Health and Care Excellence guideline-determined risk assessment strategy; ESC strategy: 2019 European Society of Cardiology guideline-determined risk assessment strategy.

Table 4: Reclassification table comparing the RF-CL model to the NICE strategy in patients with borderline ESC-PTP.

	Risk groups by RF-CL model		Total	Reclassification		NRI	p
	Low	High		Up	Down		
Risk groups by NICE strategy							
Negative patients				2.68%	12.50%	42.11%	<0.0001
Low	65	3	68				
High	14	30	44				
Total	79	33	112				
Positive patients				37.50%	5.21%		
Low	3	36	39				
High	5	52	57				
Total	8	88	96				

RF-CL: risk factor-weighted clinical likelihood; ESC-PTP: 2019 European Society of Cardiology guideline-determined pretest probability; other abbreviations as in Table 3.

corresponding to $208/(36\text{-}5) \approx 7$ additional collection of information for risk factors made the ESC strategy more efficient. As mentioned above, the optimal risk assessment strategy to guide the screening of CAD in patients with DM and SCP has great clinical importance. In this context, instead of the NICE strategy which mainly focused on symptom evaluation, the ESC strategy which sequentially incorporated different PTP models might provide more feasible identification of DM patients who may derive maximal benefit from further CIT.

4.1. Limitations. Although this is the first study to evaluate proposed risk assessment strategies for patients with DM and SCP, several issues merit consideration. First, this study was an observational cohort. Clinical management of patients with DM and SCP before and after CCTA relied on a local physician. More details about medical therapy and CR during follow-up were not available. Thus, whether the ESC strategy will lead to more appropriate decision-making of downstream referral and better clinical outcomes for patients with DM and SCP needs to be addressed in further studies, such as randomized controlled trials. Second, using data from the PROMISE cohort, Fordyce et al. developed a new tool to identify patients deriving minimal value from CIT [33]. Although the PROMISE minimal risk tool [34] has been externally validated, no recent clinical guideline recommends it as the risk assessment tool for patients with SCP. Third, this analysis focused on the presence of obstructive CAD documented by CCTA. Previous studies have demonstrated that CCTA had a high negative predictive value compared with ICA [35, 36]. So CCTA could offer robust reassurance for both strategies to exclude obstructive CAD. Moreover, we defined unassessable segments as positive ones based on current guideline recommendations in which further testing should be referred for nonconclusive CCTA. Fourth, a coronary artery calcium score [20, 37] and high-sensitivity cardiac troponin [38, 39] have shown the potential to improve risk assessment for patients with DM and SCP. However, additional imaging or blood testing is needed for the two attractive biomarkers, and their cost-effectiveness warrants further evaluation. Fifth, as the majority of patients had missing data about other ECG changes such as Q wave, we only analyzed ST-T changes. This could reduce the size of the high-risk group in the NICE strategy,

Table 5: Reclassification table comparing the RF-CL model, NICE strategy, and ESC strategy in patients with ESC-PTP below 5% and above 15%.

	Low	High	Total	Reclassification* Up	Reclassification* Down	NRI†	*p*
	Risk groups by ESC strategy						
Risk groups by NICE strategy							
Negative patients				2.28%	9.59%	19.88%	<0.0001
Low	125	5	130				
High	21	68	89				
Total	146	73	219				
Positive patients				13.14%	0.57%		
Low	3	23	26				
High	1	148	149				
Total	4	171	175				
	Risk groups by RF-CL model						
Risk groups by NICE strategy							
Negative patients				2.28%	14.61%	24.33%	<0.0001
Low	125	5	130				
High	32	57	89				
Total	157	62	219				
Positive patients				12.57%	0.57%		
Low	4	22	26				
High	1	148	149				
Total	5	170	175				
	Risk groups by ESC strategy						
Risk groups by RF-CL model							
Negative patients				6.85%	1.83%	-4.45%	0.0598
Low	142	15	157				
High	4	58	62				
Total	146	73	219				
Positive patients				1.71%	1.14%		
Low	2	3	5				
High	2	168	170				
Total	4	171	175				

Abbreviations as in Table 3.

especially in DM patients for whom the silent ischemia is common [9, 31, 32]. Finally, more researches about the performance of different strategies in different subgroups of age and sex were needed in the future.

5. Conclusions

Compared to the symptom-focused strategy, the ESC strategy based on PTP estimation seemed to be associated with greater efficiency in identifying high-risk individuals who may derive maximum benefit from further CIT in patients with DM and SCP. This superiority should be dominantly ascribed to the application of the RF-CL model in borderline patients. For more accurate and convenient risk assessment in patients with DM and SCP suggestive of obstructive CAD, further investigations with comprehensive and rigorous design are needed.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

No conflicting relationship exists for any author.

Authors' Contributions

Jia Zhao, Shuo Wang, and Pengyu Zhao contributed equally to this work.

Acknowledgments

This study was supported by the Tianjin Key Research Program of Traditional Chinese Medicine (2022001), National Key Research and Development Program of China (2016YFC1301100 and 2016YFC1300300), and Research Program of Tianjin Chest Hospital (2018XKC10).

References

[1] W. Ling, Y. Huang, Y. M. Huang, R. R. Fan, Y. Sui, and H. L. Zhao, "Global trend of diabetes mortality attributed to vascular complications, 2000-2016," *Cardiovascular Diabetology*, vol. 19, no. 1, p. 182, 2020.

[2] A. Sharma, N. K. Sekaran, A. Coles et al., "Impact of diabetes mellitus on the evaluation of stable chest pain patients: insights from the PROMISE (prospective multicenter imaging study for evaluation of chest pain) trial," *Journal of the American Heart Association*, vol. 6, no. 11, 2017.

[3] C. Junghans, N. Sekhri, M. J. Zaman, H. Hemingway, G. S. Feder, and A. Timmis, "Atypical chest pain in diabetic patients with suspected stable angina: impact on diagnosis and coronary outcomes," *European Heart Journal–Quality of Care and Clinical Outcomes*, vol. 1, no. 1, pp. 37–43, 2015.

[4] J. Narula, Y. Chandrashekhar, A. Ahmadi et al., "SCCT 2021 expert consensus document on coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography," *Journal of Cardiovascular Computed Tomography*, vol. 15, no. 3, pp. 192–217, 2021.

[5] A. Timmis and C. A. Roobottom, "National Institute for Health and Care Excellence updates the stable chest pain guideline with radical changes to the diagnostic paradigm," *Heart*, vol. 103, no. 13, pp. 982–986, 2017.

[6] P. C. Cremer and S. E. Nissen, "The National Institute for Health and Care Excellence update for stable chest pain: poorly reasoned and risky for patients," *Heart*, vol. 103, no. 13, pp. 972–974, 2017.

[7] J. E. Udelson and U. Hoffmann, "The United Kingdom's National Institute for Health and Care Excellence guideline on chest pain of recent onset: a United States perspective," *Journal of Nuclear Cardiology*, vol. 24, no. 5, pp. 1535–1539, 2017.

[8] H. S. Hecht, L. Shaw, Y. S. Chandrashekhar, J. J. Bax, and J. Narula, "Should NICE guidelines be universally accepted for the evaluation of stable coronary disease? A debate," *European heart journal*, vol. 40, no. 18, pp. 1440–1453, 2019.

[9] P. G. Jørgensen, M. T. Jensen, R. Mogelvang et al., "Abnormal echocardiography in patients with type 2 diabetes and relation to symptoms and clinical characteristics," *Diabetes & Vascular Disease Research*, vol. 13, no. 5, pp. 321–330, 2016.

[10] J. Knuuti, W. Wijns, A. Saraste et al., "2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes," *European Heart Journal*, vol. 41, no. 3, pp. 407–477, 2020.

[11] A. Saraste, E. Barbato, D. Capodanno et al., "Imaging in ESC clinical guidelines: chronic coronary syndromes," *European Heart Journal Cardiovascular Imaging*, vol. 20, no. 11, pp. 1187–1197, 2019.

[12] P. D. Adamson, D. E. Newby, C. L. Hill, A. Coles, P. S. Douglas, and C. B. Fordyce, "Comparison of international guidelines for assessment of suspected stable angina: insights from the PROMISE and SCOT-HEART," *JACC. Cardiovascular Imaging*, vol. 11, no. 9, pp. 1301–1310, 2018.

[13] P. D. Adamson, A. Hunter, M. C. Williams et al., "Diagnostic and prognostic benefits of computed tomography coronary angiography using the 2016 National Institute for Health and Care Excellence guidance within a randomised trial," *Heart*, vol. 104, no. 3, pp. 207–214, 2018.

[14] R. Bing, T. Singh, M. R. Dweck et al., "Validation of European Society of Cardiology pre-test probabilities for obstructive coronary artery disease in suspected stable angina," *European Heart Journal-Quality of Care and Clinical Outcomes*, vol. 6, no. 4, pp. 293–300, 2020.

[15] L. D. Rasmussen, L. Nissen, J. Westra et al., "Validation and update of the minimal risk tool in patients suspected of chronic coronary syndrome," *The International Journal of Cardiovascular Imaging*, vol. 37, no. 2, pp. 699–706, 2021.

[16] S. Winther, S. E. Schmidt, L. D. Rasmussen et al., "Validation of the European Society of Cardiology pre-test probability model for obstructive coronary artery disease," *European Heart Journal*, vol. 42, no. 14, pp. 1401–1411, 2021.

[17] J. B. Muhlestein, D. L. Lappé, J. A. Lima et al., "Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial," *Journal of the American Medical Association*, vol. 312, no. 21, pp. 2234–2243, 2014.

[18] Y. Zhang, Y. Liu, H. Zhang, and J. Zhou, "Impact of sex-specific differences in calculating the pretest probability of obstructive coronary artery disease in symptomatic patients: a coronary computed tomographic angiography study," *Coronary Artery Disease*, vol. 30, no. 2, pp. 124–130, 2019.

[19] J. Zhou, Y. Chen, Y. Zhang et al., "Epicardial fat volume improves the prediction of obstructive coronary artery disease above traditional risk factors and coronary calcium score," *Circulation. Cardiovascular Imaging*, vol. 12, no. 1, p. e008002, 2019.

[20] J. Zhou, Y. Liu, L. Huang et al., "Validation and comparison of four models to calculate pretest probability of obstructive coronary artery disease in a Chinese population: a coronary computed tomographic angiography study," *Journal of Cardiovascular Computed Tomography*, vol. 11, no. 4, pp. 317–323, 2017.

[21] J. Zhou, J. Zhao, Z. Li et al., "Coronary calcification improves the estimation for clinical likelihood of obstructive coronary artery disease and avoids unnecessary testing in patients with borderline pretest probability," *European Journal of Preventive Cardiology*, 2021.

[22] G. A. Diamond and J. S. Forrester, "Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease," *New England Journal of Medicine*, vol. 300, no. 24, pp. 1350–1358, 1979.

[23] A. S. Levey, L. A. Stevens, C. H. Schmid et al., "A new equation to estimate glomerular filtration rate," *Annals of Internal Medicine*, vol. 150, no. 9, pp. 604–612, 2009.

[24] S. Winther, S. E. Schmidt, T. Mayrhofer et al., "Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease," *Journal of the American College of Cardiology*, vol. 76, no. 21, pp. 2421–2432, 2020.

[25] J. Leipsic, S. Abbara, S. Achenbach et al., "SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee," *Journal of Cardiovascular Computed Tomography*, vol. 8, no. 5, pp. 342–358, 2014.

[26] R. C. Cury, S. Abbara, S. Achenbach et al., "CAD-RADS^{TM} Coronary Artery Disease - Reporting and Data System. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging (NASCI). Endorsed by the American College of Cardiology," *Journal of Cardiovascular Computed Tomography*, vol. 10, no. 4, pp. 269–281, 2016.

[27] K. Thygesen, J. S. Alpert, A. S. Jaffe et al., "Fourth universal definition of myocardial infarction (2018)," *Journal of the American College of Cardiology*, vol. 72, no. 18, pp. 2231–2264, 2018.

[28] G. S. Collins, J. B. Reitsma, D. G. Altman, K. G. Moons, and Group T, "Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD)," *The TRIPOD Group. Circulation*, vol. 131, no. 2, pp. 211–219, 2015.

[29] A. C. Alba, T. Agoritsas, M. Walsh et al., "Discrimination and calibration of clinical prediction models," *Journal of the American Medical Association*, vol. 318, no. 14, pp. 1377–1384, 2017.

[30] F. Turrini, S. Scarlini, C. Mannucci et al., "Does coronary atherosclerosis deserve to be diagnosed early in diabetic patients? The DADDY-D trial. Screening diabetic patients for unknown coronary disease," *European Journal of Internal Medicine*, vol. 26, no. 6, pp. 407–413, 2015.

[31] J. S. Yun, Y. M. Park, S. A. Cha, Y. B. Ahn, and S. H. Ko, "Progression of cardiovascular autonomic neuropathy and cardiovascular disease in type 2 diabetes," *Cardiovascular diabetology*, vol. 17, no. 1, p. 109, 2018.

[32] V. Spallone, "Update on the impact, diagnosis and management of cardiovascular autonomic neuropathy in diabetes: what is defined, what is new, and what is unmet," *Diabetes and Metabolism Journal*, vol. 43, no. 1, pp. 3–30, 2019.

[33] C. B. Fordyce, P. S. Douglas, R. S. Roberts et al., "Identification of patients with stable chest pain deriving minimal value from noninvasive testing: the PROMISE minimal-risk tool, a secondary analysis of a randomized clinical trial," *JAMA Cardiology*, vol. 2, no. 4, pp. 400–408, 2017.

[34] P. D. Adamson, C. B. Fordyce, D. A. McAllister, J. E. Udelson, P. S. Douglas, and D. E. Newby, "Identification of patients with stable chest pain deriving minimal value from coronary computed tomography angiography: an external validation of the PROMISE minimal-risk tool," *International Journal of Cardiology*, vol. 252, pp. 31–34, 2018.

[35] R. Haase, P. Schlattmann, P. Gueret et al., "Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable chest pain depending on clinical probability and in clinically important subgroups: meta-analysis of individual patient data," *BMJ*, vol. 365, p. l1945, 2019.

[36] J. Knuuti, H. Ballo, L. E. Juarez-Orozco et al., "The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability," *European Heart Journal*, vol. 39, no. 35, pp. 3322–3330, 2018.

[37] T. S. Genders, E. W. Steyerberg, M. G. Hunink et al., "Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts," *BMJ*, vol. 344, p. e3485, 2012.

[38] J. L. Januzzi Jr., S. Suchindran, U. Hoffmann et al., "Single-molecule hsTnI and short-term risk in stable patients with chest pain," *Journal of the American College of Cardiology*, vol. 73, no. 3, pp. 251–260, 2019.

[39] B. M. Everett, M. M. Brooks, H. E. Vlachos, B. R. Chaitman, R. L. Frye, and D. L. Bhatt, "Troponin and cardiac events in stable ischemic heart disease and diabetes," *The New England Journal of Medicine*, vol. 373, no. 7, pp. 610–620, 2015.

Hindawi
Journal of Diabetes Research
Volume 2021, Article ID 8636050, 9 pages
https://doi.org/10.1155/2021/8636050

Research Article

Biodegradable Polymer DES (Ultimaster) vs. Magnesium Bioresorbable Scaffold (BRS Magmaris) in Diabetic Population with NSTE-ACS: A One-Year Clinical Outcome of Two Sirolimus-Eluting Stents

Piotr Rola,[1,2] **Adrian Włodarczak**,[1] **Mateusz Barycki**,[2] **Marek Szudrowicz**,[1] **Magdalena Łanocha**,[3] **Jan Jakub Kulczycki**,[1] **Karol Turkiewicz**,[1] **Katarzyna Woźnica**,[4] **Maciej Lesiak**,[5] **and Adrian Doroszko**[6]

[1]*Department of Cardiology, The Copper Health Centre (MCZ), 59-300 Lubin, Poland*
[2]*Department of Cardiology, Provincial Specialized Hospital in Legnica, 59-220 Legnica, Poland*
[3]*Adalbert's Hospital, 61-144 Poznan, Poland*
[4]*Faculty of Mathematics and Information Science, Warsaw University of Technology, 00-662 Warsaw, Poland*
[5]*1st Department of Cardiology, Poznan University of Medical Sciences, 61-491 Poznan, Poland*
[6]*Department of Internal Medicine, Hypertension and Clinical Oncology, Wroclaw Medical University, 50-556 Wroclaw, Poland*

Correspondence should be addressed to Piotr Rola; piotr.rola@gmail.com

Received 9 September 2021; Revised 17 October 2021; Accepted 5 November 2021; Published 23 November 2021

Academic Editor: Akira Sugawara

Background. Cardiovascular disease (CVD) with significant involvement of coronary artery disease (CAD) remains a major cause of death and disability among the diabetic population. Although percutaneous coronary intervention (PCI) continues to evolve, type 2 diabetes mellitus (T2DM) is a well-established marker of poor clinical prognosis after PCI, which is mainly attributed to the rapid progression of atherosclerosis requiring recurrent revascularizations. Hence, the use of bioresorbable materials could provide some solution to this problem. *Material and Methods.* The study was divided into two arms. For the first one, we qualified 169 patients with NSTE-ACS treated with PCI who received the drug-eluting stent (DES) coated with a biodegradable polymer Ultimaster (Terumo, Tokyo, Japan). The second arm was composed of 193 patients with ACS who underwent PCI with a magnesium bioresorbable scaffold Magmaris (Biotronik, Berlin, Germany). Both arms were divided into two subsequent groups: the T2DM (59 and 72) and the non-DM (110 and 121, respectively). The primary outcomes were cardiovascular death, myocardial infarction, and in-stent thrombosis. The main secondary outcomes included target lesion failure (TLF) and were recorded at a 1-year-follow-up. *Results.* There were no significant differences between the diabetic and nondiabetic populations in the primary endpoints or main secondary endpoints (TLF, scaffold restenosis, death from any reason, and other cardiovascular events) either in the Ultimaster or Magmaris group. At a 1-year follow-up, the primary endpoint in the DM t.2 population was recorded in 2.7% Ultimaster vs. 5.1% Magmaris, respectively. *Conclusion.* Both, Ultimaster and Magmaris revealed relative safety and efficiency at a one-year follow-up in the diabetic population in ACS settings. The observed rates of TLF were low, which combined with a lack of in-stent thrombosis suggests that both investigated devices might be an interesting therapeutic option for diabetics with ACS. Nevertheless, further large randomized clinical trials are needed to confirm fully our results.

1. Introduction

Among patients with acute coronary syndrome, diabetes mellitus in particular is a marker of poor clinical prognosis. Diabetics tend to have rapid progression of atherosclerosis, leading to an increased rate of multivessel disease, which commonly requires recurrent revascularization. According to the current European Society of Cardiology (ESC) guidelines on myocardial revascularization [1], coronary artery bypass grafting (CABG) is preferred over percutaneous coronary intervention in diabetic patients. This recommendation is strictly related to a higher rate of short- and long-term adverse cardiovascular outcomes demonstrated after PCI. However, due to the aging and numerous comorbidities, PCI often remains the only available revascularization option. Many factors are postulated to play a role in the pathophysiological background of unfavorable results. Chronic vascular inflammation, endothelial dysfunction with increased oxidative stress, and increased platelet activation are cardiovascular responses to hyperglycemia [2]. In addition, these chronic inflammatory responses are often exacerbated by the drug-eluting stent [3] which can lead to delayed endothelialization of stent and subsequently impaired vascular healing process. To overcome these limitations, the bioresorbable materials have been widely used to develop new generations of scaffolds. These devices focus on suppressing the persistent inflammatory stimulus of the vascular wall by the stent surface.

Recently, the new generation of sirolimus-eluting bioresorbable polymer DES Ultimaster (Terumo, Tokyo, Japan) has demonstrated a favorable 1-year safety and efficacy profile with concomitant rapid vascular wall healing and a high degree of strut coverage [4]. A thin, biodegradable gradient coating is a novel feature of the scaffold design. Thus, the bioresorbable DES technology refers not only to the polymer but also the entire stent platform. Bioresorbable vascular scaffolds (BRS) constitute a novel vessel-supporting technology that enables the vessel restoration without permanent presence of foreign material in the vessel wall. The initial enthusiasm for the first generation of BRS Absorb (Abbott, Chicago, United States) subsided following publication of the long-term results [5]. However, the second generation of magnesium BRS Magmaris (Biotronik, Berlin, Germany) has recently entered the market and has shown promising short-term outcomes [6].

The aim of this study is to investigate the performance of sirolimus-releasing bioresorbable polymer stents (Ultimaster) compared to bioresorbable magnesium scaffold (Magmaris) and to evaluate the theoretical advantages of this new technology in high-risk population patients with diabetes mellitus in the setting of ACS.

2. Materials and Methods

Patients with acute coronary syndrome–NSTE-ACS (with exclusion of the STEMI cases) and clinical indication for percutaneous coronary intervention (PCI) were enrolled in this retrospective, observational, study. This study consisted of two major arms (Figure 1). The first arm included 193 patients who received a bioresorbable magnesium scaffold—Magmaris. The second arm was composed of 169 patients who were implanted with a scaffold covered with a biodegradable polymer—Ultimaster. The decision to implant Magmaris BRS was based on operator dissertation in accordance with the inclusion and exclusion criteria (Figure 1), which were closely followed the manufacturer's recommendations [7]. Patients in the second arm were selected among all ACS-Ultimaster cases (541) from our cardiac departments between January 2015 and March 2020. The criteria for inclusion in the registry were the same as for the Magmaris group. In addition, scaffolds in the Ultimaster group—in parallel to the Magmaris group—had to meet the additional size-related criteria (diameter 3.0 mm or 3.5 mm).

2.1. Devices. Magmaris is a novel metallic (magnesium) sirolimus-eluting scaffold coated with a biodegradable polymer (BIOlute) poly-L-lactide (PLLA). Currently, available scaffold sizes are 3.0 and 3.5 mm in diameter and 15, 20, and 25 mm in lengths. Ultimaster is a cobalt-chromium sirolimus-eluting stent covert abluminal with a biodegradable poly-(D, L-lactide-co-caprolactone) copolymer (PDLLA-PCL).

2.2. Coronary Stenting Procedure. All patients receive a periprocedural medication regimen according to the routine practice in accordance with current revascularization guidelines [8]. Initially, mandatory aggressive (balloon-artery ratio 1 : 1 size according to angiographic assessment) and successful (without significant more than 20% of diameter-residual stenosis) lesion preparation was performed. In the next step, after successful stent delivery and implantation, obligatory high-pressure (at least 15 atm.) postdilation was performed with a NC balloon, which has a size at least equal to the size of the scaffold.

2.3. Endpoints and Definitions. The primary outcome included death from cardiac causes, myocardial infarction, and stent thrombosis. The main secondary outcome was a target-lesion failure (TLF) composed of cardiac death, target vessel myocardial infarction (TV-MI), or target lesion revascularization (TLR). Also, other secondary outcomes (scaffold restenosis, death from any reason, and all revascularization procedures as well as myocardial infarction [9]) were recorded.

Diabetes (type 1 or type 2) was defined as a previously diagnosed DM treated with pharmacologic or nonpharmacologic, and a new-onset DM was defined according to the American Diabetes Association [10].

2.4. Statistical Analysis. The analyses were performed using the R language [11]. Continuous variables were characterized with their mean and standard deviation, while frequencies were used for categorical variables. Patients were compared between groups using the nonparametric two-sample Mann–Whitney's test for continuous variables and Fisher's exact test for categorical variables. Bonferroni correction was applied to adjust for multiple comparisons, p values ≤ 0.05 were accepted as a threshold for statistical significance.

3. Results

The Magmaris group consisted of 72 diabetics and 121 nondiabetic cases. In the diabetic group, the majority of patients received oral antidiabetic treatment rather than

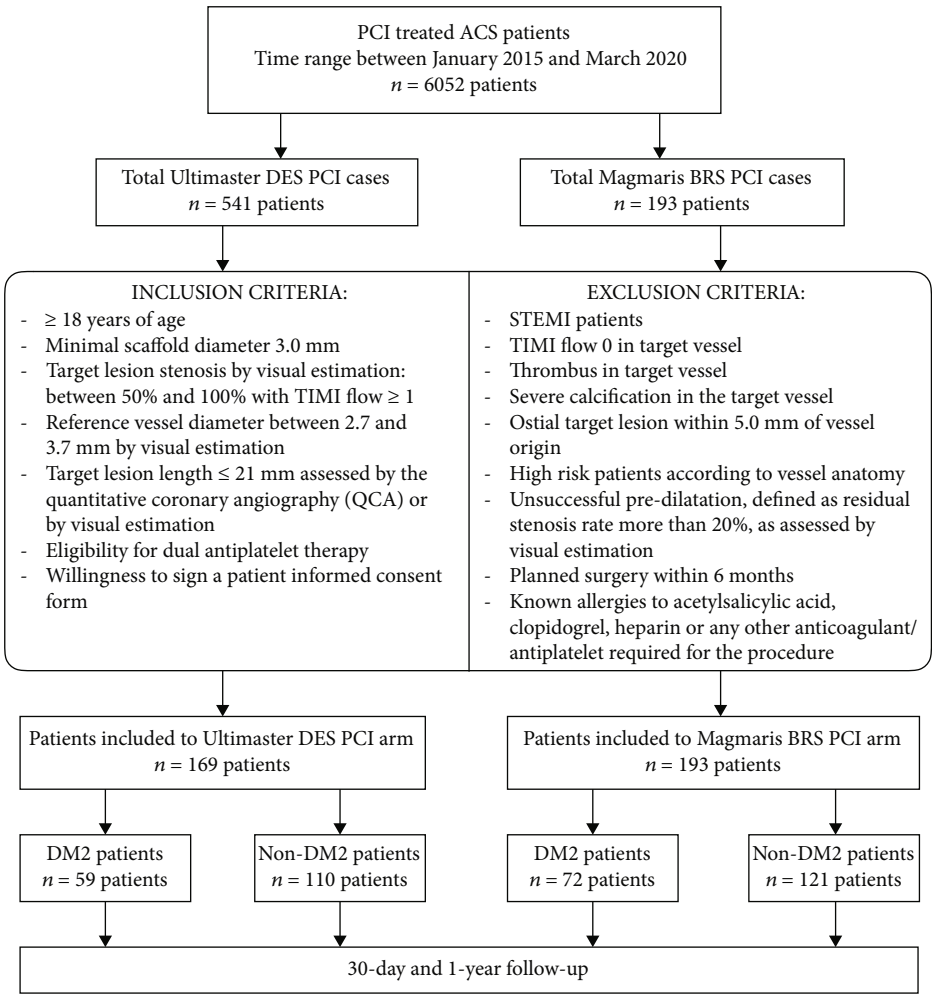


Figure 1: Study inclusion and exclusion criteria.

insulin (58 (80.5%) vs. 14 (19.5%)). The diabetic group had a significantly higher prevalence of hypertension (95.8% vs. 84.2%, respectively, $p = 0.018$) and a past history of PCI (50% vs. 34.7%, respectively, $p = 0.048$) as well as was characterized by a significantly lower left ventricular ejection fraction (57.7% vs. 59.4%, respectively, $p = 0.050$) In contrast, a nondiabetic Magmaris group had more severe initial lipid disorders—total cholesterol (4.8 ± 1.3 vs. 4.3 ± 1.3 mM, respectively, $p = 0.008$) and LDL (2.8 ± 1.2 vs. 2.1 ± 0.9 mM, respectively, $p < 0.001$).

To the Ultimaster arm, we recruited a total of 59 diabetic subjects and 110 patients to the control group. Among the diabetic participants, the minority was treated with insulin (23.7%). There were no statistically significant differences in comorbidities between the diabetic and nondiabetic Ultimaster populations. The nondiabetics had higher serum level of total cholesterol (5.2 ± 1.4 vs. 4.5 ± 1.3 mM, respectively, $p = 0.002$) and LDL (2.5 ± 1.2 vs. 3.2 ± 2.1 mM, respectively, $p < 0.002$). Table 1 summarizes the baseline clinical characteristics of the two arms.

The characteristics of the PCI procedures performed in both study arms were heterogeneous. The only statistically significant differences were found in the Ultimaster arm and related to the radiation dose used during the PCI procedure, which was higher in the diabetic group (1396.56 ± 802.95 vs. 1162.52 ± 728.34, respectively, $p = 0.029$). All procedural characteristics are shown in Table 2.

All clinical outcomes data are summarized in Tables 3 and 4. There were no statistically significant differences in clinical outcomes between the diabetic and control populations in either study arms (Magmaris and Ultimaster). We did not find any significant differences between the two diabetic study populations (Magmaris vs. Ultimaster). The only exception was a higher number of all types—revascularization at 30-day follow-up in the diabetic Ultimaster group, compared to the diabetic Magmaris group (5 vs. 0, respectively, $p = 0.016$). Noteworthy, the rates of the primary outcome were higher in the diabetic population in the Ultimaster group (3.4% vs. 0%, respectively, $p = 0.121$) at short follow-up (30 days). A similar trend was observed at long-term follow-up (1 year) for principal secondary outcome in the Magmaris arm (4.1% vs. 0%, respectively, $p = 0.051$).

4. Discussion

Despite worldwide public health interventions taken to stop the global growth of diabetes prevalence, it is inexorably increasing. A disproportionate burden of the increase in type

Table 1: Baseline clinical characteristics of both study arms.

	Magmaris group			Ultimaster group		
	Diabetes ($N = 72$)	Nondiabetes ($N = 121$)	p value	Diabetes ($N = 59$)	Non diabetes ($N = 110$)	p value
Age (years)	65.3 ± 7.9	63.2 ± 9.5	$p = 0.127$	66.1 ± 9.1	64.8 ± 9.5	$p = 0.363$
NSTEMI	58 (80.5%)	92 (76.0%)	$p = 0.592$	32 (54.2%)	56 (50.1%)	$p = 0.628$
Unstable angina	14 (19.5%)	16 (13.2%)	$p = 0.305$	27 (45.8%)	54(49.9%)	$p = 0.628$
Oral anti-diabetic treatment	58 (80.5%)	NA	—	45 (76.3%)	NA	—
Insulin	14 (19.5%)	NA	—	14 (23.7%)	NA	—
Hypertension	69 (95.8%)	102 (84.2%)	$p = 0.018$	58 (98.3%)	100 (90.1%)	$p = 0.099$
Hyperlipidemia	58 (80.5%)	94 (77.0%)	$p = 0.718$	47 (79.6%)	83 (75.5%)	$p = 0.682$
Atrial fibrillation	2 (2.7%)	7 (5.7%)	$p = 0.488$	11 (18.6%)	13 (11.8%)	$p = 0.099$
Post PCI status	36 (50%)	42 (34.7%)	$p = 0.048$	27 (46.5%)	34 (30.9%)	$p = 0.061$
Primary diagnosis of MI	28 (38.8%)	31 (25.6%)	$p = 0.075$	26 (44.1%)	34 (30.9%)	$p = 0.063$
LVEF	57.7% ± 10.7	59.4% ± 16.0	$p = 0.050$	54.1% ± 13.4	57.9% ± 27.2	$p = 0.271$
Total cholesterol (mmol/L)	4.3 ± 1.3	4.8 ± 1.3	$p = 0.008$	4.5 ± 1.3	5.2 ± 1.4	$p = 0.002$
LDL (mmol/L)	2.1 ± 0.9	2.8 ± 1.2	$p < 0.001$	2.5 ± 1.2	3.2 ± 2.1	$p = 0.002$
Triglycerides (mmol/L)	1.9 ± 1.1	1.8 ± 2.1	$p = 0.213$	1.6 ± 0.8	1.6 ± 0.8	$p = 0.889$
Creatine (μmol/L)	82.3 ± 21.5	85.1 ± 22.5	$p = 0.431$	85.5 ± 22.4	81.6 ± 21.6	$p = 0.378$

Abbreviations: NSTEMI: no ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; MI: myocardial Infarction; LVEF: left ventricle ejection fraction.

2 diabetes affects the middle-to-high-income countries, particularly Western Europe and the Pacific Ocean island nations [12]. Cardiovascular disease (CVD) including coronary artery disease (CAD) as a major contributor, remains a leading cause of death and disability among the diabetic population. Although percutaneous coronary intervention (PCI) continues to evolve, the data from randomized trials demonstrate the superiority of coronary artery bypass grafting (CABG) over percutaneous coronary intervention in the diabetic population [13]. The reasons for this are multifactorial and not fully understood. Some data link this to a chronic local inflammatory response in response to the presence of a foreign body in the vessel wall, leading to neointimal hyperplasia and increased platelet activation and adhesion [14]. Therefore, the use of bioresorbable material design to limit immune-adverse reactions is believed to be a new revolution in the field of coronary interventions. In current practice, two development paths for bioresorbable materials have been proposed.

The first, also referred to as third-generation DES, involves abluminal coating of a thin metallic backbone with a bioresorbable polymer that degrades uniformly to release the antimitotic drug sirolimus. An example of this technology is the Ultimaster.

The second concept pursues complete biosorption of the scaffold. In this scenario, BRS provides short-term performance equivalent to existing drug-eluting stents (DES); however, it avoids permanent caging of the vessel. After the widespread use of first-generation Absorb (Abbott) was discontinued, the second generation of BRS (Magmaris) with a metallic backbone (magnesium) sirolimus-eluting BRS containing an active bioabsorbable coating BIOlute poly-L-lactide (PLLA) entered the market and is currently available for commercial use.

Data on the performance of the Ultimaster in the all-comers population are encouraging and demonstrated low late lumen loss, resulting in low rates of in-stent thrombosis, restenosis, and TLR [15–17]. Clinical outcomes in the long-term follow-up were comparable to those obtained with the Xience scaffolds [18]. The long-term safety of Ultimaster was confirmed by the low rate of late in-stent thrombosis. These favorable antithrombotic properties of the scaffold have been demonstrated in the *in vitro* models [19] and are associated with an accelerated tissue coverage and scaffold apposition [3, 20] leading to improved vessel healing. Noteworthy, the presence of the "class effect" for all bioresorbable polymer stents is very likely [21].

It is well known that diabetes mellitus and ongoing ACS are independent risk factors for poor clinical outcomes after PCI. Although there is a lack of convincing data for Ultimaster, few studies conducted so far seem to confirm this paradigm [22, 23] mainly due to an increased rate of TLF. However, the data from our studies do not confirm this observation. There were no statistical differences between the diabetic and control groups in primary clinical outcomes and TLF. Moreover, the rate of TLF in diabetics was significantly lower than in the study of Beneduce et al. [23] (3.3% vs. 8%). A similar trend is observed when we consider substudies in the ACS group [24]. This could be due to the fact that only patients implanted according to the accordance "4P technique"(patient selection, proper sizing, predilatation, and post-dilatation strategy) were analyzed. It has been shown that the negative effects of diabetes on patients treated with BRS-ABSORB implantation can be minimized [25, 26].

On the other hand, our favorable results may be related to the detailed lesion selection that we adopted from inclusion

Table 2: Procedural characteristics of both study arms.

Procedural characteristic	Magmaris group DM ($N = 72$)	Magmaris group Non-DM ($N = 121$)	p value	Ultimaster group DM ($N = 59$)	Ultimaster group Non-DM ($N = 110$)	p value
Treated vessel: LAD	31 (43%)	49 (40.5%)	$p > 0.999$	21 (35.5%)	44 (40%)	$p > 0.999$
LCX	18 (25%)	31 (25.6%)	$p > 0.999$	19 (32.2%)	28 (25.4%)	$p > 0.999$
RCA	22 (30.6%)	39 (32.2%)	$p > 0.999$	18 (30.5%)	38 (34.5%)	$p > 0.999$
IM	1 (1.4%)	2 (1.7%)	$p > 0.999$	1 (1.6%)	0	$p = 0.675$
Predilatation balloon:						
(i) Mean diameter (mm)	3.20 ± 0.24	3.24 ± 0.27	$p = 0.273$	3.08 ± 0.31	3.13 ± 0.28	$p = 0.304$
(ii) Mean pressure (atm)	17.75 ± 0.75	17.57 ± 0.91	$p = 0.209$	15.93 ± 0.61	15.82 ± 0.66	$p = 0.251$
Average scaffold number	1.03 ± 0.17	1.07 ± 0.26	$p = 0.179$	1.18 ± 0.39	1.21 ± 0.43	$p = 0.224$
Average scaffold diameter:	3.26 ± 0.25	3.29 ± 0.25	$p = 0.568$	3.22 ± 0.29	3.25 ± 0.31	$p = 0.345$
Average scaffold length (mm)	21.11 ± 3.27	20.62 ± 3.26	$p = 0.308$	22.34 ± 6.87	23.38 ± 7.48	$p = 0.129$
Postdilatation balloon:						
(i) Mean diameter (mm)	3.51 ± 0.31	3.55 ± 0.29	$p = 0.495$	3.32 ± 0.35	3.35 ± 0.35	$p = 0.535$
Mean pressure (atm)	17.69 ± 0.80	17.72 ± 0.83	$p = 0.924$	16.61 ± 0.93	16.76 ± 1.08	$p = 0.335$
(i) 0.0 mm greater than scaffold	12 (16.6%)	19 (15.7%)	$p = 0.843$	42 (71.1%)	78 (70.9%)	$p = 0.861$
(ii) 0.25 mm greater than scaffold	47 (65.2%)	83 (68.6%)	$p = 0.638$	11 (18.6%)	24 (21.8%)	$p = 0.547$
(iii) 0.5 mm greater than scaffold	13 (18.2%)	19(15.7%)	$p = 0.692$	6 (10.1%)	8 (7.2%)	$p = 0.396$
Contrast volume (mL)	153.22 ± 76.76	150.21 ± 57.64	$p = 0.337$	152.49 ± 75.13	146.41 ± 64.91	$p = 0.625$
Radiation dose (mGy)	1120.18 ± 843.89	1014.70 ± 591.75	$p = 0.934$	1396.56 ± 802.95	1162.52 ± 728.34	$p = 0.029$
OCT-guided PCI	13 (18%)	28 (23.1%)	$p = 0.469$	9 (15.2%)	19 (17.2%)	$p > 0.999$
Perforation of vessel	0 (0%)	0	—	0	0	—
Side branch occlusion	0 (0%)	2 (1.6%)	$p = 0.530$	1 (1.6%)	0	$p = 0.675$
Drugs: ASA	72 (100%)	121 (100%)	—	59 (100%)	109 (99.1%)	$p > 0.999$ –
Clopidogrel	26 (36.1%)	50 (41.3%)	$p = 0.543$	52 (88.1%)	97 (88.1%)	$p > 0.999$
Ticagrelor	46 (63.9%)	71 (58.7%)	$p = 0.543$	7 (11.8%)	13 (11.8%)	$p > 0.999$
Statin	71 (98.6%)	119 (98.3%)	$p > 0.999$	58 (98.3%)	110 (100%)	$p > 0.999$
ACEI/ARB	61 (84.7%)	100 (82.6%)	$p > 0.999$	55 (93.2%)	99 (90%)	$p = 0.678$
B-blocker	64 (88.8%)	106 (87.6%)	$p > 0.999$	55 (93.2%)	97 (88.1%)	$p = 0.422$

Abbreviations: OCT: optical coherence tomography; PCI: percutaneous coronary intervention; ASA: acetylsalicylic acid; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers.

criteria of the Magmaris Registry. We avoided high-risk patients with heavy calcification, the STEMI patients with present thrombus, or low-size of the treated vessel. However, the latter factor has been proven to have no effect on clinical outcome after Ultimaster implantation [22, 23]. Therefore, concerning the results of the LEADERS trial [27], it seems to be no "class effect" of DES with abluminal biodegradable coating.

Data regarding the performance of Magmaris in the diabetic population are strictly limited [28], yet encouraging. In the contrast, the data on implantation of Magmaris in ACS conditions are more comprehensive and reliable. Several observational registries confirmed favorable short-term and long-term outcomes [6, 29] Furthermore, recently published data from the largest all-comers Magmaris registry [30] which included 2054 subjects showed that the one-year TLF rate was 4.3% with only one subacute in-stent thrombosis event. The results obtained are far more favorable than the first generation of BRS and comparable to the newest DES. There is only one study comparing Magmaris to third generation of DES (Orsiro) [31]. The study population consisted mainly of the patient with stable CAD. The authors observed Magmaris and Orsiro unadjusted TLF rates at levels 6.0 and 6.4% with no significant difference between the groups.

To the best of our knowledge, this is the first in human study designed to compare the efficacy and safety of fully bioresorbable magnesium scaffold (Magmaris) with a third generation of metallic DES with bioresorbable polymer, in DM t.2 population in ACS settings. We found no differences between the two scaffolds in the diabetic subpopulation. As

Table 3: Clinical outcomes in both study arms.

Clinical outcomes	Magmaris group			Ultimaster group		
	DM ($N = 72$)	Non-DM ($N = 121$)	p value	DM ($N = 59$)	Non-DM ($N = 110$)	p value
30-day follow-up						
Primary outcome: cardiac death, myocardial infarction, and stent thrombosis	0 (0%)	0 (0%)	—	2 (3.4%)	0 (0%)	$p = 0.121$
Principal secondary outcome: target lesion failure (cardiac death, target vessel myocardial infract, and target lesion revascularization)	0 (0%)	0 (0%)	—	0 (0%)	0 (0%)	—
Death						
(i) Cardiac	0 (0%)	0 (0%)	—	0 (0%)	0 (0%)	—
(ii) Any	0 (0%)	0 (0%)	—	0 (0%)	0 (0%)	—
Myocardial infarction:						
(i) Target vessel	0 (0%)	0 (0%)	—	0 (0%)	0 (0%)	—
(ii) Any	0 (0%)	0 (0%)	—	2 (3.4%)	0 (0%)	$p = 0.121$
Scaffold:						
(i) Thrombosis	0 (0%)	0 (0%)	—	0 (0%)	0 (0%)	—
(ii) Restenosis	0 (0%)	0 (0%)	—	0	0	—
Revascularization:						
(i) Target lesion	0 (0%)	0 (0%)	—	0 (0%)	0 (0%)	—
(ii) Target vessel	0 (0%)	0 (0%)	—	0 (0%)	0 (0%)	—
(iii) Any	0 (0%)	0 (0%)	—	5 (8.5%)	4 (3.6%)	$p = 0.279$
1-year follow-up						
Primary outcome: cardiac death, myocardial infarction, and stent thrombosis	2 (2.7%)	1 (0.8%)	$p = 0.557$	3 (5.1%)	6 (5.45%)	$p > 0.999$
Principal secondary outcome: target lesion failure (cardiac death, target vessel myocardial infract, and target lesion revascularization)	3 (4.1%)	0 (0%)	$p = 0.051$	2 (3.3%)	4 (3.6%)	$p > 0.999$
Death						
(i) Cardiac	0(0%)	0 (0%)	—	0 (0%)	0 (0%)	—
(ii) Any	2 (2.7%)	1 (2.33%)	$p = 0.138$	0 (0%)	0 (0%)	—
Myocardial infarction:						
(i) Target vessel	2 (2.7%)	0	$p = 0.557$	1 (1.6%)	4 (3.6%)	$p = 0.612$
(ii) Any	2 (2.7%)	1 (2.33%)	$p = 0.138$	2 (3.4%)	2 (1.8%)	$p = 0.659$
Scaffold:						
(i) Thrombosis	0 (0%)	0	—	0 (0%)	0 (0%)	—
(ii) restenosis	2 (2.7%)	0	$p = 0.138$	1 (1.7%)	1 (0.9%)	$p > 0.999$
Revascularization:						
(i) Target lesion	2 (2.7%)	0 (0%)	$p = 0.138$	1 (1.7%)	2 (1.8%)	$p > 0.999$
(ii) Target vessel	3 (2.7%)	0 (0%)	$p = 0.051$	2 (3.4%)	5 (4.5%)	$p > 0.999$
(iii) Any	10 (13.8%)	8 (6.6%)	$p = 0.124$	10 (16.9%)	14 (12.7%)	$p = 0.492$

reported in our study, the 1-year TLF in DM subpopulation for both devices (4.1% vs. 3.3%) is comparable [30] and even better [23, 31] than in the previously mentioned studies. Diabetes, especially when treated with insulin, is a well-established risk factor of scaffold thrombosis, particularly in the first generation of BRS (Absorb) [32]. Our data contradict such an association. We did not observe the in-stent thrombosis in any of the tested devices. Noteworthy, both used scaffolds released the same antimitotic drug (sirolimus), and therefore, the results are not differentiated by this factor.

4.1. Limitations. This was a nonrandomized study with retrospective data collected in the relatively short observation

Table 4: Differences in clinical outcomes between the Magmaris and Ultimaster diabetic groups.

Clinical outcomes	Magmaris DM ($N = 72$)	Ultimster DM ($N = 59$)	p value
30-day follow-up			
Primary outcome: cardiac death, myocardial infarction, and stent thrombosis	0 (0%)	2 (3.4%)	$p = 0.201$
Principal secondary outcome: target lesion failure (cardiac death, target vessel myocardial infract, and target lesion revascularization)	0 (0%)	0 (0%)	—
Death			
(i) Cardiac	0 (0%)	0 (0%)	—
(ii) Any	0 (0%)	0 (0%)	—
Myocardial infarction:			
(i) Target vessel	0 (0%)	0 (0%)	—
(ii) Any	0 (0%)	2 (3.4%)	$p = 0.201$
Scaffold: (i) Thrombosis	0 (0%)	0 (0%)	—
(ii) restenosis	0 (0%)	0	—
Revascularization:			
(i) Target lesion	0 (0%)	0 (0%)	—
(ii) Target vessel	0 (0%)	0 (0%)	—
(ii) Any	0 (0%)	5 (8.5%)	$p = 0.016$
1-year follow-up			
Primary outcome: cardiac death, myocardial infarction, and stent thrombosis	2 (2.7%)	3 (5.1%)	$p = 0.657$
Principal secondary outcome: target lesion failure (cardiac death, target vessel myocardial infract, and target lesion revascularization)	3 (4.1%)	2 (3.3%)	$p > 0.999$
Death			
(i) Cardiac	0(0%)	0 (0%)	—
(ii) Any	2 (2.7%)	0 (0%)	$p = 0.501$
Myocardial infarction:			
(i) Target vessel	2 (2.7%)	1 (1.7%)	$p > 0.999$
(ii) Any	2 (2.7%)	2 (3.4%)	$p > 0.999$
Scaffold:			
(i) Thrombosis	0 (0%)	0 (0%)	$p > 0.999$
(ii) Restenosis	2 (2.7%)	1 (1.7%)	$p > 0.999$
Revascularization:			
(i) Target lesion	2 (2.7%)	1 (1.7%)	$p > 0.999$
(ii) Target vessel	3 (2.7%)	2 (3.4%)	$p > 0.999$
(iii) Any	10 (13.8%)	10 (16.9%)	$p = 0.635$

period (1-year follow-up). The study population was not very large and underpowered for reliable assessment of events, especially in the diabetic subpopulation. Also, the rate of intravascular guidance PCI was comparatively low.

5. Conclusions

In our study both biodegradable polymer DES (Ultimaster) and Magnesium bioresorbable scaffold (Magmaris) revealed relative safety and efficiency features at a one-year follow-up in the diabetic population in ACS settings. The observed rates of TLF were low, which combined with a lack of in-stent thrombosis suggests that both investigated devices might be an interesting therapeutic option for diabetics with ACS. Nevertheless, further large randomized clinical trials are needed in order to confirm fully our results.

Data Availability

Data not included in manuscript available on request from corresponding author due to local law and privacy restrictions.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

[1] F. Neumann, M. Sousa-Uva, A. Ahlsson et al., "2018 ESC/EACTS guidelines on myocardial revascularization," *European Heart Journal*, vol. 40, no. 2, pp. 87–165, 2019.

[2] A. Doroszko, A. Radziwon-Balicka, and R. Skomro, "Novel approaches for diagnosing and management of cardiovascular disorders mediated by oxidative stress," *Oxidative Medicine and Cellular Longevity*, vol. 2020, Article ID 7096727, 2020.

[3] A. Chisari, A. Pistritto, R. Piccolo, A. la Manna, and G. Danzi, "The ultimaster biodegradable-polymer sirolimus-eluting stent: an updated review of clinical evidence," *International Journal of Molecular Sciences*, vol. 17, no. 9, p. 1490, 2016.

[4] B. Chevalier, P. C. Smits, D. Carrié et al., "Serial assessment of strut coverage of biodegradable polymer drug-eluting stent at 1, 2, and 3 months after stent implantation by optical frequency domain Imaging," *Circulation: Cardiovascular Interventions*, vol. 10, no. 12, article e004801, 2017.

[5] P. W. Serruys, B. Chevalier, Y. Sotomi et al., "Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus- eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial," *The Lancet.*, vol. 388, no. 10059, pp. 2479–2491, 2016.

[6] A. Wlodarczak, M. Lanocha, A. Jastrzebski et al., "Early outcome of magnesium bioresorbable scaffold implantation in acute coronary syndrome-the initial report from the Magmaris-ACS registry," *Catheterization and Cardiovascular Interventions*, vol. 93, no. 5, pp. E287–E292, 2019.

[7] J. Fajadet, M. Haude, M. Joner et al., "Magmaris preliminary recommendation upon commercial launch: a consensus from the expert panel on 14 April 2016," *EuroIntervention*, vol. 12, no. 7, pp. 828–833, 2016.

[8] M. Roffi, C. Patrono, J. P. Collet et al., "2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation," *European Heart Journal*, vol. 37, no. 3, pp. 267–315, 2016.

[9] K. Thygesen, et al.J. S. Alpert, A. S. Jaffe et al., "Fourth universal definition of myocardial infarction (2018)," *Journal of the American College of Cardiology*, vol. 72, no. 18, pp. 2231–2264, 2018.

[10] American Diabetes Association, "Classification and diagnosis of diabetes: standards of medical care in diabetes—2021," *Diabetes Care*, vol. 44, Supplement 1, pp. S15–S33, 2021.

[11] R Core Team, *A language and environment for statistical computing: R Foundation for Statistical Computing*, R Core Team, Vienna, Austria, 2020, https://www.R-project.org.

[12] M. A. Khan, M. J. Hashim, J. K. King, R. D. Govender, H. Mustafa, and J. al Kaabi, "Epidemiology of type 2 diabetes–global burden of disease and forecasted trends," *Journal of epidemiology and global health.*, vol. 10, no. 1, pp. 107–111, 2020.

[13] K. Ramanathan, J. G. Abel, J. E. Park et al., "Surgical versus percutaneous coronary revascularization in patients with diabetes and acute coronary syndromes," *Journal of the American College of Cardiology*, vol. 70, no. 24, pp. 2995–3006, 2017.

[14] A. Sakamoto, H. Jinnouchi, S. Torii, R. Virmani, and A. Finn, "Understanding the impact of stent and scaffold material and strut design on coronary artery thrombosis from the basic and clinical points of view," *Bioengineering*, vol. 5, no. 3, p. 71, 2018.

[15] E. Barbato, S. Salinger-Martinovic, D. Sagic et al., "A first-in-man clinical evaluation of Ultimaster, a new drug-eluting coronary stent system: CENTURY study," *EuroIntervention*, vol. 11, no. 5, pp. 541–548, 2015.

[16] C. Godino, A. Beneduce, G. Ferrante et al., "One-year clinical outcome of biodegradable polymer sirolimus-eluting stent in all-comers population. Insight from the ULISSE registry (ULtimaster Italian multicenter all comerS Stent rEgistry)," *International journal of cardiology.*, vol. 260, pp. 36–41, 2018.

[17] S. Vlieger, G. B. Danzi, F. Kauer et al., "One-year performance of thin-strut cobalt chromium sirolimus-eluting stent versus thicker strut stainless steel biolimus-eluting coronary stent: a propensity-matched analysis of two international all-comers registries," *Coronary Artery Disease.*, vol. 32, no. 5, pp. 391–396, 2021.

[18] W. Wijns, M. Valdes-Chavarri, G. Richardt et al., "Long-term clinical outcomes after bioresorbable and permanent polymer drug-eluting stent implantation: final five-year results of the CENTURY II randomised clinical trial," *EuroIntervention*, vol. 14, no. 3, pp. e343–e351, 2018.

[19] C. Verhaegen, S. Kautbally, D. C. Zapareto et al., "Early thrombogenicity of coronary stents: comparison of bioresorbable polymer sirolimus-eluting and bare metal stents in an aortic rat model," *American journal of cardiovascular disease.*, vol. 10, no. 2, pp. 72–83, 2020.

[20] T. Itoh, H. Otake, T. Kimura et al., "A serial optical frequency-domain imaging study of early and late vascular responses to bioresorbable-polymer sirolimus-eluting stents for the treatment of acute myocardial infarction and stable coronary artery disease patients: results of the MECHANISM-ULTIMASTER study," *Cardiovascular Intervention and Therapeutics.*, pp. 1-2, 2021.

[21] G. G. Stefanini, R. A. Byrne, P. W. Serruys et al., "Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials," *European Heart Journal*, vol. 33, no. 10, pp. 1214–1222, 2012.

[22] Y. Tadano, J. I. Kotani, Y. Kashima et al., "Predictors of clinical outcomes after coronary implantation of bioresorbable polymer sirolimus-eluting Ultimaster stents in all-comers: a report of 1, 727 cases," *Catheterization and Cardiovascular Interventions.*, vol. 94, no. 1, pp. 91–97, 2019.

[23] A. Beneduce, G. Ferrante, A. Ielasi et al., "One-year clinical outcome of biodegradable polymer sirolimus-eluting stent in diabetic patients: insight from the ULISSE registry (ULtimaster Italian multicenter all comerS stent rEgistry)," *Catheterization and Cardiovascular Interventions.*, vol. 96, no. 2, pp. 255–265, 2020.

[24] V. A. Jiménez, A. Iñiguez, J. A. Baz et al., "A randomized comparison of novel bioresorbable polymer sirolimus-eluting stent and durable polymer everolimus-eluting stent in patients with acute coronary syndromes: the CENTURY II high risk ACS substudy," *Cardiovascular Revascularization Medicine*, vol. 17, no. 6, pp. 355–361, 2016.

[25] R. Anadol, K. Schnitzler, L. Lorenz et al., "Three-years outcomes of diabetic patients treated with coronary bioresorbable scaffolds," *BMC Cardiovascular Disorders*, vol. 18, no. 1, pp. 92–110, 2018.

[26] T. M. Hommels, R. S. Hermanides, S. Rasoul et al., "Everolimus-eluting bioresorbable scaffolds for treatment of coronary

artery disease in patients with diabetes mellitus: the midterm follow-up of the prospective ABSORB DM Benelux study," *Cardiovascular Diabetology*, vol. 18, no. 1, p. 25, 2019.

[27] J. J. Wykrzykowska, P. W. Serruys, Y. Onuma et al., "Impact of vessel size on angiographic and clinical outcomes of revascularization with biolimus-eluting stent with biodegradable polymer and sirolimus-eluting stent with durable polymer: the LEADERS Trial Substudy," *JACC. Cardiovascular Interventions*, vol. 2, no. 9, pp. 861–870, 2009.

[28] A. Włodarczak, M. Łanocha, M. Szudrowicz et al., "The 1-year safety and efficacy outcomes of Magmaris, novel magnesium bioresorbable vascular scaffolds in diabetes mellitus patients with acute coronary syndrome," *Journal of Clinical Medicine*, vol. 10, no. 14, p. 3166, 2021.

[29] A. Włodarczak, M. Łanocha, M. Lesiak et al., "Long-term clinical follow-up of the resorbable magnesium scaffolds in acute coronary syndrome patients," *Polish Heart Journal.*, vol. 79, no. 7-8, pp. 827–832, 2021.

[30] S. Verheye, A. Wlodarczak, P. Montorsi et al., "Twelve-month outcomes of 400 patients treated with a resorbable metal scaffold: insights from the BIOSOLVE-IV registry," *EuroIntervention*, vol. 15, no. 15, pp. e1383–e1386, 2020.

[31] A. Hideo-Kajita, H. M. Garcia-Garcia, P. Kolm et al., "Comparison of clinical outcomes between Magmaris and Orsiro drug eluting stent at 12 months: pooled patient level analysis from BIOSOLVE II-III and BIOFLOW II trials," *International journal of cardiology.*, vol. 300, pp. 60–65, 2020.

[32] D. J. Kereiakes, S. G. Ellis, T. Kimura et al., "Efficacy and safety of the absorb everolimus-eluting bioresorbable scaffold for treatment of patients with diabetes mellitus: results of the Absorb Diabetic Substudy," *JACC. Cardiovascular Interventions*, vol. 10, no. 1, pp. 42–49, 2017.

Hindawi
Journal of Diabetes Research
Volume 2021, Article ID 6606830, 9 pages
https://doi.org/10.1155/2021/6606830

Review Article

Association of KCNQ1rs2237892C⟶T Gene with Type 2 Diabetes Mellitus: A Meta-Analysis

Wen-Jia Han,[1] Jian-Yi Deng,[2] Hua Jin,[3] Li-Ping Yin,[4] Jin-Xia Yang,[5] and Jiang-Jie Sun[5]

[1]*School of Dentistry, Anhui Medical University, Hefei, Anhui 230032, China*
[2]*Clinical Medical College, Anhui Medical University, Hefei, Anhui 230032, China*
[3]*Inner Mongolia University For Nationalities, Affiliated Hospital, Nationalities, 028000, China*
[4]*Medical Examination Center, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China*
[5]*Health Management College, Anhui Medical University, Hefei, Anhui 230032, China*

Correspondence should be addressed to Jin-Xia Yang; yangjinxiamu@163.com and Jiang-Jie Sun; sunjiangjie@ahmu.edu.cn

Received 17 September 2021; Revised 21 October 2021; Accepted 25 October 2021; Published 22 November 2021

Academic Editor: Pawel Kleczynski

Background. Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases in adults, causing high morbidity and mortality worldwide. In recent years, the prevalence of T2DM has been increasing significantly, and genome-wide association studies (GWAS) have shown that KCNQ1 significantly increases the risk of T2DM. *Objective*. To find large-scale evidence on whether the KCNQ1rs2237892C⟶T gene polymorphism is associated with T2DM susceptibility. *Methods*. A comprehensive review of the Chinese and English literature on the association of T2DM with KCNQ1rs2237892 is published by PubMed and Baidu Academic. The included literature was part or all of the studied loci which were evaluated for association with T2DM. Forest plots were made of the included literature to analyze the association of KCNQ1 with polymorphisms of the studied loci, and funnel plots and Egger's test were used to evaluate the publication bias of the selected included literature. *Results*. Ten case-control studies including a total of 7027 cases and 8208 controls met our inclusion criteria. Allele (C allele frequency distribution) (OR: 1.19; 95% CI: 0.87,1.62; $P < 0.00001$), recessive (OR: 0.73; 95% CI: 0.45,1.18; $P < 0.00001$) genetic model under the full population was observed between KCNQ1rs2237892C⟶T gene polymorphism and T2DM without a significant relationship. In a stratified analysis by race, a meaningful association was found in non-Asian populations under the allelic genetic model, but no association was found in Asian populations. *Conclusion*. This meta-analysis showed no significant association between the rs2237892 polymorphism of the KCNQ1 gene and the risk of T2DM.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a genetically heterogeneous metabolic disorder characterized by chronic hyperglycemia due to impaired insulin secretion and sensitivity influenced by genetic and environmental factors. Patients with T2DM are often associated with macrovascular disease, diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy [1]. The Global Diabetes Map (9th edition) published by IDF-2019 shows that an estimated 463 million people aged 20-79 years currently have diabetes worldwide, the vast majority with type 2 diabetes, with 578 million and 700 million expected in 2030 and 2045 [2]. People around the world suffer from type 2 diabetes and its complications. Currently, the etiology of T2DM is unknown, and two independent genome-wide association studies suggest that KCNQ1 is a novel gene susceptible to T2DM [3, 4]. KCNQ1 is commonly expressed in epithelial cells, and KCNQ1 expression was also observed in insulin-secreting INS-1 cells. The selective inhibitor chromanol 293B inhibited KCNQ1 potassium channel activity and significantly increased insulin secretion [5]; Yazdi et al. demonstrated a significant association between KCNQ1 and T2DM [6], but, research showed there was no significant association between KCNQ1 and T2DM [7]; Liu et al. and Yu et al. performed meta-analysis of multiple loci in the KCNQ1 gene, and the results again demonstrated the association between

KCNQ1 and T2DM [8, 9], but these two papers introduced data from meta-analyses, respectively, and their strength of proof may be weakened.

Therefore, we performed this meta-analysis to further demonstrate whether genetic factors play a crucial role in the pathogenesis of T2DM.

2. Materials and Methods

2.1. Literature Search. The advanced search of the literature search library was conducted by using "T2DM, KCNQ1, rs2237892" as the search term in China National Knowledge Infrastructure (CNKI) and Baidu Academic with the following search formula: subject (T2DM) and keyword (KCNQ1) and keyword (rs2237892). English literature was obtained for case-control studies and cohort studies on the association of KCNQ1 gene polymorphism with T2DM. The last search was conducted on June 12, 2021. Inclusion criteria were (i) meeting the diagnostic criteria for diabetes mellitus published by the World Health Organization in 1990 or ADA in 2010; (ii) the study type was a case-control study; (iii) there were year of publication; there were clear regulations on sample content; the study results were informative enough for analyzing whether the differences in genotypes and alleles between the case and control groups were statistically significant; (iv) the control groups all met the H-W genetic equilibrium pattern; (v) sources of information on control and case groups were provided; and (vi) patients were randomly selected, with no special restrictions on age, sex, or family history. The exclusion criteria were (i) lack of sufficient control group; (ii) exclusion of literature review; (iii) exclusion of studies with gestational diabetes as an endpoint; and (iv) insufficient sample size.

2.2. Data Extraction. Two investigators independently performed literature reading and information extraction from the eligible literature based on exclusion and inclusion criteria. When ambiguities were encountered, agreement was eventually reached in whether to extract data from the papers by conferring with the third investigator. For each paper, the following paper information was collected: (i) author's name; (ii) year of publication; (iii) country; (iv) number of included cases and controls; (v) allele and genotype data; and (vi) mean age of included cases and controls. The literature screening process is shown in Figure 1.

2.3. Statistical Analysis. Statistical analysis was completed using RevMan 5 software, and the OR values and their corresponding 95% CIs were used as criteria for data statistics to compare rs2237892 allele distributions. Allelic (KCNQ1rs2237892C⟶C allele frequency distribution of T gene polymorphism), recessive (TT vs. CC+CT) genetic models were used, and the significance level was set at $P < 0.05$. If there was heterogeneity between individual studies ($I^2 > 50\%$), a random effects model was used to calculate combined effect estimates; otherwise, a fixed effects model was used, and the Z test was used to determine combined OR significance. Potential publication bias was estimated using funnel plots. The degree of asymmetry was statistically assessed using the Egger unweighted regression asymmetry test using STATA 11.0 software.

3. Results

3.1. Literature Search. We obtained studies on association between diabetes and gene locus polymorphism from Baidu Academic and China Knowledge Network, and some literature had duplicate publications, such as, double submission in Chinese and English, multiple submissions in one manuscript, and overlapping databases. After reading the titles and abstracts of the papers for the first screening, and reading the full text for the second screening, 10 papers were finally included. The required data were recorded by reading the full text to form a dataset for meta-analysis. The number of T2DM patients in the group included in the meta-analysis was 7027, and the number of controls was 8208, with 8 datasets for studies originating from Asia and 2 datasets for studies originating from non-Asia. Information on the first author and year of publication, sample size, mean age of control and case groups, genotype data, and matching criteria for each study are shown in Table 1.

3.2. Meta-Analysis. In assessing the effect of the KCNQ1 rs2237892 locus polymorphism on the occurrence of T2DM susceptibility, a total of 10 studies were included in the meta-analysis after a literature data search. The association between T2DM risk and rs2237892 locus polymorphism was assessed using recessive model and allelic model, respectively. Most of the populations were from Asia, so stratified analysis was performed for Asian and non-Asian populations, and the results are shown in Figures 2–5.

We found significant heterogeneity in the total population and Asian subgroups, and non-Asian populations reflected significant homogeneity (see Table 2), so a random effects model was chosen. No significant relationship between allele (OR: 1.19; 95% CI:0.87, 1.62; $P = 0.28$) and recessive (OR: 0.73; 95% CI: 0.45, 1.18; $P = 0.25$) genetic model was observed between KCNQ1rs2237892C⟶T gene polymorphism and T2DM in the total population. In subgroup analysis stratified by race, individuals carrying the C allele in the Asian subgroup were not associated with T2DM incidence observed under the allelic (OR: 1.17; 95% CI: 0.80, 1.69; $P = 0.42$) genetic model, and recessive (OR: 0.73; 95% CI: 0.42-1.25; $P = 0.25$) genetic model individuals with CT+TT genotype in the Asian subgroup were not significantly predisposed to increased risk of T2DM. The recessive (OR: 0.69; 95% CI: 0.37, 1.30; $P = 0.25$) genetic model observed no association between CT+TT genotype and T2DM incidence in non-Asian subgroups. However, a significantly increased risk of T2DM patients carrying the C allele was observed in the non-Asian subgroup under the allelic (OR: 1.25; 95% CI: 1.08, 1.45; $P = 0.003$) genetic model.

4. Discussion

In Asian populations, two independent GWASs have identified KCNQ1 as a susceptibility gene for T2DM, but various studies have shown conflicting results.

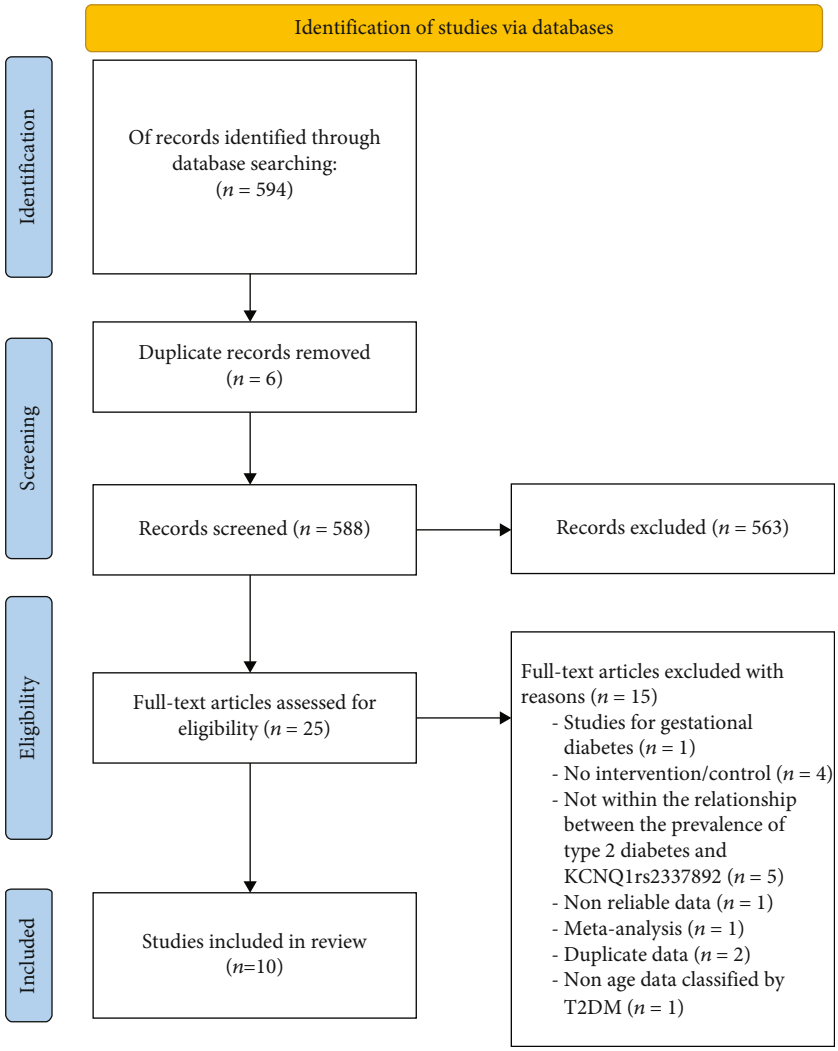


Figure 1: Literature screening process.

The KCNQ1 gene, a member of the voltage-dependent potassium channel family, is located on chromosome 11 at 11p15.5 and expressed primarily in the heart and less frequently in the pancreas, placenta, lung, liver, kidney, brain, and adipose tissue. Mutations in KCNQ1 cause K+ channel dysfunction, which leads to cardiac long QT syndrome, familial atrial fibrillation, etc. In addition, its mutation has been found to be associated with hearing loss. T2DM development and progression are characterized by insulin resistance and islet β-cell dysfunction as the main pathophysiological features, and islet β-cell dysfunction is the determinant of DM development. Mutations in any specific protein gene involved in glucose recognition, insulin processing, or secretion can lead to islet β-cell dysfunction. Based on previous studies, it is hypothesized that regulation of potassium channels increases KCNQ1 protein expression on pancreatic β-cells, which reduces insulin secretion and raises blood glucose levels. However, the contribution of KCNQ1 to the pathogenesis of type 2 diabetes is currently unclear [10].

In this paper, we performed allelic model and recessive gene model meta-analysis of the 10 included studies on the KCNQ1rs2237892 locus and T2DM. Meta-analysis revealed no significant differences in the frequencies of the three genotypes (CC, CT, and TT) and two alleles (C and T) of KCNQ1 rs2237892SNP in the case and control groups. The finding is inconsistent with previous studies in which Japanese researcher first found a statistically significant association between the KCNQ1 rs2237892 locus and T2DM onset in an Asian population in a whole gene chain scan study [4] and did not conclude a correlation between KCNQ1 rs2237892 locus and T2DM susceptibility in our study. It has been demonstrated in several independent studies that for Asian populations, variants in the KCNQ1 rs2237892 locus confer susceptibility to T2DM. rs2237892, rs2237895, and rs2237897 were in a block of linkage disequilibrium, as confirmed by Liu et al. using a conditional independent effects test. rs2237892 and rs2237895 on type 2 diabetes can be attributed to rs2237897 [11]. A study confirmed that the C allele increased the risk of type 2 diabetes in a Chinese Han population, replicating the association of KCNQ1 rs2237892 with T2DM susceptibility, and their study also indicated that genotype CC tended to be associated with an increased risk of hypertension and macrovascular

Table 1: Characteristics of KCNQ1 gene rs2237892 polymorphism and T2DM gene association study.

Author (year)	Ethnicity	No. of case/control	Age of case/control	Matching criteria	Control			T2DM		
					CC	CT	TT	CC	CT	TT
Y. Liu (2009)	China	1,880/1,996	63.9 ± 9.5/58.1 ± 9.4	Ethnicity	853	919	224	902	813	165
Latonya F Been (2011)	US-India	139/557	48.0 ± 13.5/48.0 ± 13.5	Ethnicity	523	32	2	133	6	0
Wanlin Zhang (2015)	China	530/452	60.95 ± 12.62/58.83 ± 11.40	Ethnicity	194	192	66	274	217	39
Xueyan Zhou (2016)	China	305/200	48.93 ± 11.89/50.07 ± 6.42	Ethnicity	72	102	26	148	136	21
L. J. Cui (2016)	China	100/100	51.21 ± 11.60/49.85 ± 12.41	Ethnicity	53	35	12	39	46	15
Nattachet Plengvidhya (2018)	Thailand	500/500	53.0 ± 8.4/57.2 ± 12.2	Ethnicity, sex	254	205	41	285	192	23
Kazem Vatankhah Yazdi (2020)	Iran	162/106	65 ± 7.5/65.5 ± 7.3	Ethnicity	85	15	6	152	9	1
Yong-Ho Lee (2008)	Korea	865/496	58.2 ± 11.1/55.0 ± 9.4	Ethnicity	182	239	75	389	377	99
Jirong Long (2012)	African American	1,551/2,725	59.7 ± 8.7/57.7 ± 9.0	Ethnicity, sex	2158	534	33	1284	254	13
Wassim Y. Almawi (2013)	Lebanon	995/1076	58.6 ± 13.4/57.3 ± 10.4	Ethnicity	800	225	51	500	371	124

Study or subgroup	T2DM Events	T2DM Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% CI
Jirong Long 2012	2822	3102	4850	5450	11.2%	1.25 (1.07, 1.45)
Kazem Vatankhah Yazdi 2020	313	324	185	212	7.0%	4.15 (2.01, 8.57)
L.J. Cui 2016	124	200	141	200	9.5%	0.68 (0.45, 1.04)
Latonya F Been 2011	272	278	1078	1114	6.0%	1.51 (0.63, 3.63)
Nattachet Plengvidhya 2018	762	1000	713	1000	11.0%	1.29 (1.06, 1.57)
Wanlin Zhang 2015	765	1060	580	904	11.0%	1.45 (1.20, 1.75)
Wassim Y. Almawi 2013	1371	1990	1825	2152	11.2%	0.40 (0.34, 0.46)
Xueyan Zhou 2016	432	610	246	400	10.6%	1.52 (1.16, 1.98)
Y. Liu 2009	2617	3760	2625	3992	11.4%	1.19 (1.08, 1.31)
Yong-Ho Lee 2008	1155	1730	603	992	11.1%	1.30 (1.10, 1.52)
Total (95% CI)		14054		16416	100.0%	1.19 (0.87, 1.62)
Total events	10633		12846			

Heterogeneity: Tau^2 = 0.22; Chi^2 = 217.87, df = 9 (P < 0.00001); I^2 = 96%
Test for overall effect: Z = 1.09 (P = 0.28)

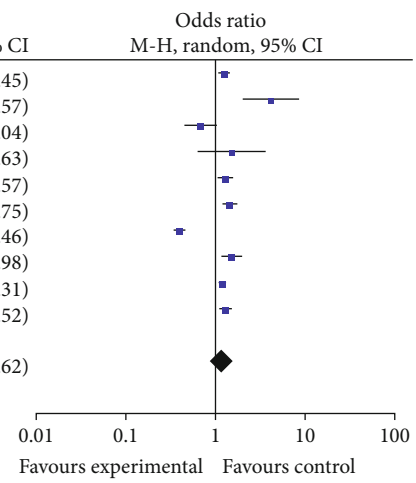


Figure 2: Forest plot of meta-analysis of the association between KCNQ12237892 locus and T2DM under the allele model.

Study or subgroup	T2DM Events	T2DM Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% Cl
1.3.1 Non-Asian						
Jirong Long 2012	2822	3102	4850	5450	11.2%	1.25 (1.07, 1.45)
Latonya F Been 2011	272	278	1078	1114	6.0%	1.51 (0.63, 3.63)
Subtotal (95% Cl)		3380		6564	17.2%	1.25 (1.08, 1.45)
Total events	3094		5928			

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.18, df = 1 (P = 0.67); I^2 = 0%
Test for overall effect: Z = 3.01 (P = 0.003)

Study or subgroup	T2DM Events	T2DM Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% Cl
1.3.2 Asian						
Kazem Vatankhah Yazdi 2020	313	324	185	212	7.0%	4.15 (2.01, 8.57)
L.J. Cui 2016	124	200	141	200	9.5%	0.68 (0.45, 1.04)
Nattachet Plengvidhya 2018	762	1000	713	1000	11.0%	1.29 (1.06, 1.57)
Wanlin Zhang 2015	765	1060	580	904	11.0%	1.45 (1.20, 1.75)
Wassim Y. Almawi 2013	1371	1990	1825	2152	11.2%	0.40 (0.34, 0.46)
Xueyan Zhou 2016	432	610	246	400	10.6%	1.52 (1.16, 1.98)
Y. Liu 2009	2617	3760	2625	3992	11.4%	1.19 (1.08, 1.31)
Yong-Ho Lee 2008	1155	1730	603	992	11.1%	1.30 (1.10, 1.52)
Subtotal (95% Cl)		10674		9852	82.8%	1.17 (0.80, 1.69)
Total events	7539		6918			

Heterogeneity: Tau^2 = 0.27; Chi^2 = 212.68, df = 7 (P<0.00001); I^2 = 97%
Test for overall effect: Z = 0.81 (P = 0.42)

Total (95% Cl)		14054		16416	100.0%	1.19 (0.87, 1.62)
Total events	10633		12846			

Heterogeneity: Tau^2 = 0.22; Chi^2 = 217.87, df = 9 (P < 0.00001); I^2 = 96%
Test for overall effect: Z = 1.09 (P = 0.28)

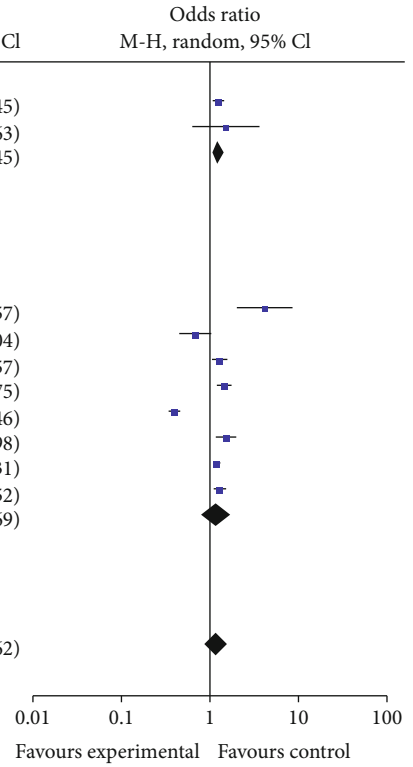


Figure 3: Forest plot of meta-analysis of the association between KCNQ12237892 locus and T2DM under the allele model (stratified analysis).

complications in patients with T2DM [1], and Zhou et al. presented new data suggesting that KCNQ1 polymorphisms affect T2DM risk by regulating the IRS-2/PI(3)K/Akt signaling pathway [12]. Nattachet et al. found a significant correlation between rs2237892SNP and T2D under additive and recessive models [13]. It was proved that rs2237892SNP is associated with T2DM in Korean population and in Lebanese population [14, 15], but Cui et al. suggested that Chinese Kazakhs rs2237892SNP may not be associated with T2DM [7], which is consistent with our findings. The frequency of KCNQ1 rs2237892SNP in Asians noted by Liu et al. is lower than that in Europeans (92-96%), and the gene KCNQ1 rs2237892SNP was not significantly associated with T2D in the original European genome-wide association study. While the high percentage of non-Asian population and low percentage of Asians in our study may be one of the reasons for the lack of significant association between KCNQ1 rs2237892SNP and T2DM, the second possible reason is that

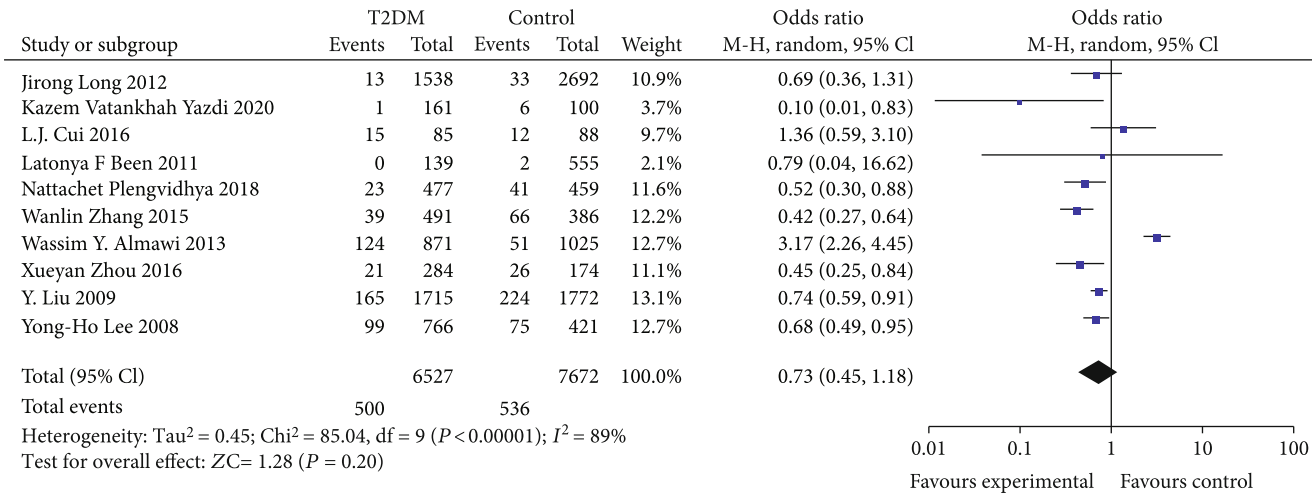


Figure 4: Forest plot of meta-analysis of the association between KCNQ12237892 locus and T2DM under the recessive model.

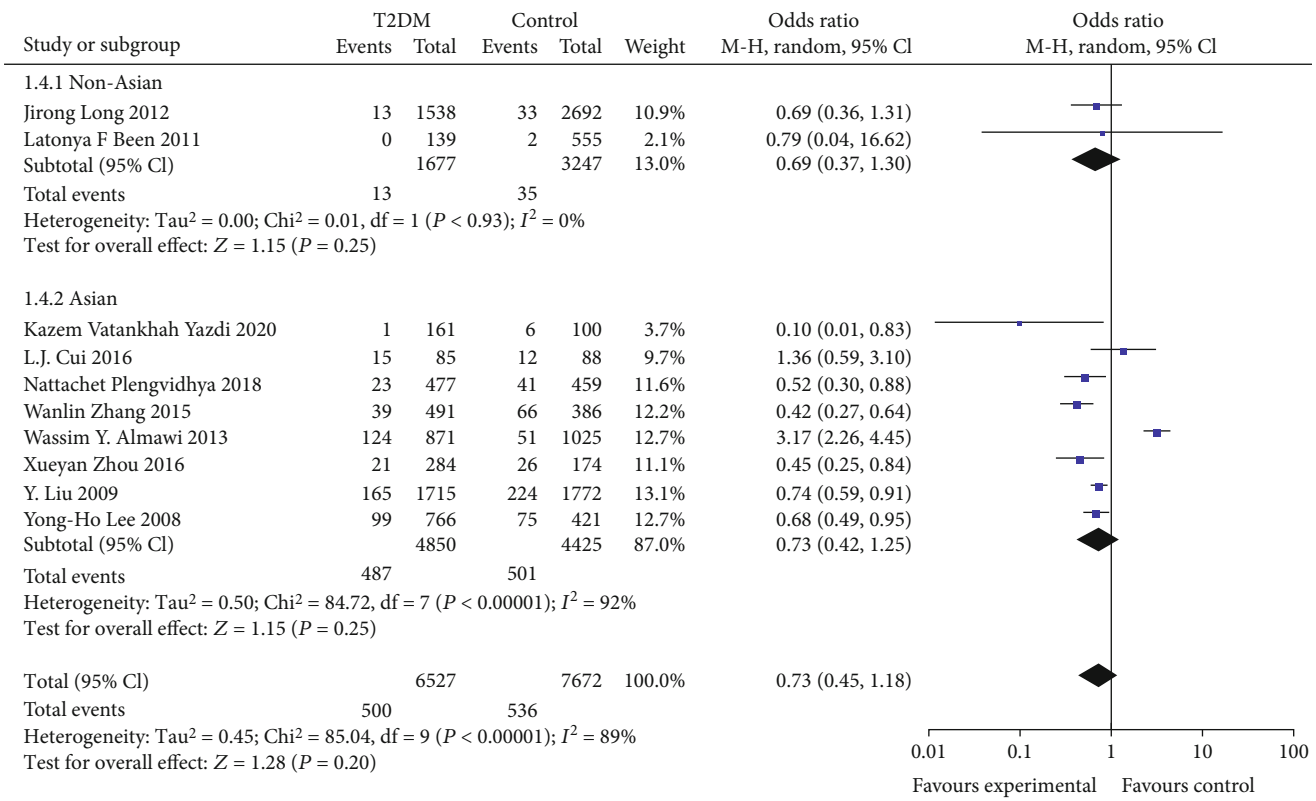


Figure 5: Forest plot of meta-analysis of the association between KCNQ12237892 locus and T2DM under the recessive model (stratified analysis).

Yu et al. conducted meta-analysis on multiple sites of KCNQ1 gene and further collected and processed on the basis of meta-analysis data; there are cases of attenuated output. The third possible reason lies in the higher conditions of data collection for this meta-analysis, which improved the data quality but also had the limitation of insufficient sample size. Of course, other possibilities are not excluded.

In conclusion, our investigation cannot prove the association of KCNQ1 rs2237892SNP with T2DM in Asian populations, and the observation of the C allele as a risk allele for T2DM in non-Asian populations may be due to small sample sizes [16, 17], taking into account that geographical or cultural barriers increase the genetic distance, functional genes or regulatory regions may be disturbed by independent sets of rare

Table 2: Meta-analysis in association between KCNQ1rs2237892C→T gene in different population.

KCNQ1	Group	A fixed-effects model			A random-effects model			Heterogeneity		
		OR (95%CL)	Z	P	OR (95%CL)	Z	P	χ^2	I^2 (%)	PQ-test
Distribute of C allelic frequency	Total	1.07 [1.01, 1.13]	2.24	0.03	1.19 [0.87, 1.62]	1.09	0.28	217.87	96	<0.00001
	Asian	1.04 [0.98, 1.10]	1.15	0.25	1.17 [0.80, 1.69]	0.81	0.42	212.68	97	<0.00001
	Non-Asian	1.25 [1.08, 1.45]	3.02	0.003	1.25 [1.08, 1.45]	3.01	0.003	0.18	0	0.67
TT vs. CC+TC	Total	0.85 [0.74, 0.96]	2.56	0.01	0.73 [0.45, 1.18]	1.28	0.20	85.04	89	<0.00001
	Asian	0.85 [0.75, 0.97]	2.36	0.02	0.73 [0.42, 1.25]	1.15	0.25	84.72	92	<0.00001
	Non-Asian	0.69 [0.37, 1.30]	1.15	0.25	0.69 [0.37, 1.30]	1.15	0.25	0.01	0	0.93

mutations, and different patterns of linkage disequilibrium may also be an influencing factor.

In our study, we did not find that the KCNQ1rs2237892 gene polymorphism was associated with T2DM risk, which is inconsistent with the results of other studies. This apparent discrepancy may be mainly due to the different genotype and allele frequencies of KCNQ1rs2237892 in populations with different clinical characteristics, geographic distribution, and ethnic origin. However, the current meta-analysis has some limitations. Large-scale studies on the association of T2DM with the KCNQ1rs2237892 locus are still lacking, and therefore, a larger sample size is needed for further studies in which consideration of all races of subjects may be beneficial to validate the exact results of such observations. These findings may fill a gap in the knowledge system of genetic variation and T2DM-related studies, and therefore, genome-wide association studies in multiple races and geographic regions are necessary.

A possible limitation of this study is that the sample size is small, and there may be bias in the results. Our later study will likely increase the sample size and further explore this issue using a stratified cross-sectional design.

5. Conclusion

We concluded that there was no significant association between the rs2237892 polymorphism of the KCNQ1 gene and the risk of T2DM in a meta-analysis of 10 case-control studies from Asia and non-Asia including a total of 7027 cases and 8208 controls.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors state that the study was conducted without any commercial or financial relationship.

Authors' Contributions

WH and JD designed this study. WH and JD searched databases and collected full-text papers. WH and JD extracted and analyzed data. JS provided guidance for statistical analysis. WH wrote the manuscript. HJ and LY reviewed the manuscript. WH and JD contributed equally to this work.

Acknowledgments

This work was supported by the Anhui Province Natural Science Foundation (1908085MG233), Quality Engineering for Research Projects of the Anhui Province (2020wyxm108 and 2020SJJXSFK1341), and National Social Science Foundation (17BGL183).

Supplementary Materials

Supplementary Figure 6: funnel plot of meta-analysis of the association between KCNQ12237892 locus and T2DM under the allele model. Supplementary Figure 7: funnel plot of meta-analysis of the association between KCNQ12237892 locus and T2DM under the allele model (stratified analysis). Supplementary Figure 8: funnel plot of meta-analysis of the association between KCNQ12237892 locus and T2DM under the recessive model. Supplementary Figure 9: funnel plot of meta-analysis of the association between KCNQ12237892 locus and T2DM under the recessive model (stratified analysis). *(Supplementary Materials)*

References

[1] W. Zhang, H. Wang, X. Guan, Q. Niu, and W. Li, "Variant rs2237892 of _KCNQ1_ Is Potentially Associated with Hypertension and Macrovascular Complications in Type 2 Diabetes Mellitus in A Chinese Han Population," *Genomics Proteomics & Bioinformatics*, vol. 13, no. 6, pp. 364–370, 2015.

[2] International Diabetes Federation, *IDF Diabetes Atlas*, International Diabetes Federation, Brussels, Belgium, 9th edition, 2019, https://diabetesatlas.org/en/sections/demographic-and-geographic-outline.html.

[3] H. Unoki, A. Takahashi, T. Kawaguchi et al., "SNPs in _KCNQ1_ are associated with susceptibility to type 2 diabetes in East Asian and European populations," *Nature Genetics*, vol. 40, no. 9, pp. 1098–1102, 2008.

[4] K. Yasuda, K. Miyake, Y. Horikawa et al., "Variants in _KCNQ1_ are associated with susceptibility to type 2 diabetes mellitus," *Nature Genetics*, vol. 40, no. 9, pp. 1092–1097, 2008.

[5] T. Erfani, N. Sarhangi, M. Afshari, D. Abbasi, H. R. A. Meybodi, and M. Hasanzad, "Kcnq1 common genetic variant and type 2 diabetes mellitus risk," *Journal of Diabetes & Metabolic Disorders*, vol. 19, no. 1, pp. 47–51, 2020.

[6] K. Vatankhah Yazdi, S. M. Kalantar, M. Houshmand et al., "Slc30a8, cdkal1, tcf7l2, kcnq1 and igf2bp2 are associated with type 2 diabetes mellitus in iranian patients"," *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, vol. Volume 13, no. 3, pp. 897–906, 2020.

[7] L. J. Cui, X. Y. Chang, L. Y. Zhu et al., "Relationship between the polymorphisms in kcnq1 and type 2 diabetes in Chinese Kazakh population," *Genetics and molecular research: GMR*, vol. 15, no. 2, pp. 1–10, 2016.

[8] J. Liu, F. Wang, Y. Y. Wu et al., "Meta-analysis of the effect of kcnq1 gene polymorphism on the risk of type 2 diabetes," *Molecular Biology Reports*, vol. 40, no. 5, pp. 3557–3567, 2013.

[9] X. X. Yu, M. Q. Liao, and Y. F. Zeng, "Associations of kcnq1 polymorphisms with the risk of type 2 diabetes mellitus: an updated meta-analysis with trial sequential analysis," *Journal of Diabetes Research*, vol. 2020, no. 27, 2020.

[10] C. X. Zhang and X. Y. Chang, "Research progress of kcnq1 gene in type 2 diabetes area," *Journal of Nongken Medicine*, vol. 34, no. 3, pp. 262–266, 2012.

[11] Y. Liu, D. Z. Zhou, D. Zhang et al., "Variants in kcnq1 are associated with susceptibility to type 2 diabetes in the population of mainland China," *Diabetologia*, vol. 52, no. 7, pp. 1315–1321, 2009.

[12] X. Zhou, J. Zhu, Z. Bao et al., "A variation in _KCNQ1_ gene is associated with repaglinide efficacy on insulin resistance in

Chinese Type 2 Diabetes Mellitus Patients," *Scientific Reports*, vol. 6, no. 1, pp. 1–11, 2016.

[13] N. Plengvidhya, C. Chanprasert, N. Chongjaroen, P. T. Yenchitsomanus, M. Homsanit, and W. Tangjittipokin, "Impact of kcnq1, cdkn2a/2b, cdkal1, hhex, mtnr1b, slc30a8, tcf7l2, and ube2e2 on risk of developing type 2 diabetes in Thai population," *BMC Medical Genetics*, vol. 19, no. 1, pp. 1–9, 2018.

[14] Y. H. Lee, E. S. Kang, S. H. Kim et al., "Association between polymorphisms in slc30a8, hhex, cdkn2a/b, igf2bp2, fto, wfs1, cdkal1, kcnq1 and type 2 diabetes in the korean population," *Journal of Human Genetics*, vol. 53, no. 11-12, pp. 991–998, 2008.

[15] W. Y. Almawi, R. Nemr, and S. H. Keleshian, "A replication study of 19 gwas-validated type 2 diabetes at-risk variants in the Lebanese population," *Diabetes Research & Clinical Practice*, vol. 102, no. 2, pp. 117–122, 2013.

[16] J. R. Long, T. Edwards, L. B. Signorello et al., "Evaluation of genome-wide association study-identified type 2 diabetes loci in African Americans," *American Journal of Epidemiology*, vol. 176, no. 11, pp. 995–1001, 2012.

[17] L. F. Been, S. Ralhan, G. S. Wander et al., "Variants in kcnq1 increase type ii diabetes susceptibility in South Asians: a study of 3, 310 subjects from India and the US," *BMC Medical Genetics*, vol. 12, no. 1, pp. 1–10, 2011.