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Advancing Type 2 Diabetes Care in General Practice in Germany:

Challenges, Strategies, and Future Directions

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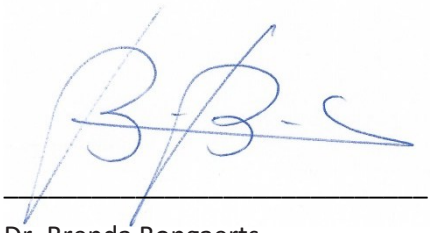

Dr. Brenda Bongaerts

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LIST OF ABBREVIATIONS

ADA: American Diabetes Association

ATC: Anatomical therapeutic chemical

CCM: Chronic care model

DDG: Deutsche Diabetes Gesellschaft (German Diabetes Society)

DEGAM: Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (German Society of General Practice and Family Medicine)

DMP: Disease management programme

DPP-4: Dipeptidyl peptidase-4

DSPN: distal sensorimotor polyneuropathy

GePaRD: German Pharmacoepidemiological Research Database

GLP-1: Glucagon-like peptide-1

HbA1c: Glycated haemoglobin

IDF: International Diabetes Federation

IFG: Impaired fasting glucose

IGT: Impaired glucose tolerance

KORA: Kooperative Gesundheitsforschung in der Region Augsburg (Cooperative Health Research in the Augsburg Region)

NGT: Normal glucose tolerance

OR: Odds ratio

SGLT-2: Sodium-glucose cotransporter-2

T2D: Type 2 diabetes

WHO: World Health Organisation

YLL: Years of life lost

YLD: Years of life lost due to disability

DEUTSCHE ZUSAMMENFASSUNG

Der Typ-2-Diabetes stellt eine der größten Herausforderungen der modernen Medizin dar. Weltweit steigt die Inzidenz weiter an, getrieben durch demografische Entwicklungen, Lebensstilfaktoren und zunehmende Urbanisierung. Damit wächst auch die Belastung für das Gesundheitssystem und insbesondere für die hausärztliche Versorgung. Vor diesem Hintergrund untersuchten die in dieser Habilitationsschrift zusammengefassten Studien zentrale Aspekte des Diabetesmanagements in der hausärztlichen Praxis. Sie untersuchten wesentliche Dimensionen der Diabetesversorgung, darunter die Wirksamkeit multifaktorieller Versorgungsmodelle, die Prävalenz und Erkennung der diabetischen Polyneuropathie, Muster der Arzneimittelabgabe, und Strategien zur Personalisierung der Versorgung.

Unsere systematische Übersichtsarbeit zur Umsetzung des multifaktoriellen Chronic Care Models (CCM) zeigte, dass Programme, die alle sechs Komponenten dieses Modells implementieren, in Europe nur selten umfassend evaluiert wurden. Die berichteten Effekte auf klinische und patienten-berichtete Endpunkte waren insgesamt moderat und variierten stark in Abhängigkeit von der Diabetesdauer. Für Deutschland fehlt bislang Evidenz, ob eine vollständige Integration des CCMs in die bestehenden Disease Management-Programme (DMPs) zusätzliche Vorteile bringen würde. Für die hausärztliche Versorgung bedeutet dies, dass multifaktorielle Ansätze insbesondere gezielt nach Krankheitsdauer oder Patientengruppe nützlich sein können. Gleichzeitig illustriert es die Notwendigkeit, DMPs weiterzuentwickeln, flexibel an die Praxisrealität anzupassen und Elemente wie strukturierte Patientenschulung oder Peer-Support stärker einzubinden.

Die Analysen aus der Kooperative Gesundheitsforschung in der Region Augsburg (KORA)-Studie zeigten eine hohe Prävalenz klinischer distaler sensomotorische Polyneuropathie (DSPN) sowohl bei Menschen mit Typ-2-Diabetes als auch bei Menschen mit Prädiabetes. Zudem blieb ein erheblicher Anteil an Betroffenen ohne Diagnose, obwohl sie regelmäßig ärztlich betreut wurden. Damit wird deutlich, dass gegenwärtige Screeningstrategien in der Primärversorgung nicht ausreichen, um das Ausmaß dieser Komplikation frühzeitig zu erfassen. Für die hausärztliche Praxis ergibt sich daraus die Notwendigkeit, strukturierte Screeningmaßnahmen stärker in den Praxisalltag zu integrieren und Barrieren wie Zeitmangel oder fehlende Schulung zu überwinden. Besonders die Fußuntersuchung, die in den Leitlinien empfohlen wird, muss konsequenter durchgeführt werden, um Folgekomplikationen wie Ulzera und Amputationen zu verhindern. Gleichzeitig ist eine Sensibilisierung der Patientinnen und Patienten für neuropathische Symptome erforderlich.

Unsere Analysen deutscher Krankenkassendaten (2012-2016) bestätigten, dass Metformin weiterhin die dominierende Erstlinientherapie darstellt, während der Einsatz von Sulfonylharnstoffen zugunsten neuerer Wirkstoffklassen abgenommen hat. Gleichzeitig zeigte die globale DISCOVER-Studie, dass

ältere Menschen mit Typ-2-Diabetes häufig eine zu intensive Therapie erhielten, vielfach mit Insulin oder Sulfonylharnstoffen trotz HbA1c-Werten deutlich unterhalb der Leitlinienziele. Dieses Muster birgt erhebliche Risiken für Hypoglykämien, Stürze und Polypharmazie. Für die hausärztliche Versorgung bedeutet dies, dass bei älteren Patientinnen und Patienten neben der Therapieintensivierung auch die De-Eskalation stärker in den Blick genommen werden muss. Leitlinien empfehlen explizit gelockerte HbA1c-Ziele bei älteren und multimorbiden Patientinnen und Patienten; ein Aspekt, der im Rahmen der DMPs künftig stärker betont und durch praxisnahe Entscheidungsinstrumente unterstützt werden sollte.

Die Analyse von HbA1c-Verläufen in der DISCOVER-Kohorte identifizierte vier unterschiedliche Trajektorien nach Beginn einer Zweitlinientherapie, die von stabil guter Kontrolle bis zu persistierend schlechter Kontrolle reichten. Diese Ergebnisse unterstreichen die Heterogenität des Typ-2-Diabetes und die Notwendigkeit individueller Therapieansätze. Unsere begleitende Literaturübersicht zur Pharmakogenetik deutete darauf hin, dass genetische Varianten die Wirksamkeit bestimmter Therapien beeinflussen können, jedoch bleibt die Evidenz aufgrund kleiner Effekte und mangelnder Replikationen begrenzt. Für die Hausarztpraxis bedeutet dies, dass personalisierte Ansätze allerdings an Bedeutung gewinnen, derzeit jedoch eher über flexible Behandlungsalgorithmen, individuell angepasste HbA1c-Ziele und patientenzentrierte Entscheidungen umgesetzt werden sollten. Auch wenn genetische Testungen bislang noch keine Rolle im Alltag spielen, ist die Sensibilisierung für die Heterogenität von Typ-2-Diabetes bereits heute für die Versorgung relevant.

Zusammenfassend unterstreicht diese Habilitationsschrift, dass die hausärztliche Versorgung von Menschen mit Typ-2-Diabetes vor komplexen Herausforderungen steht: Effekte der multifaktoriellen Versorgung variieren in Abhängigkeit der Krankheitsdauer, die DSPN als Komplikation des Diabetes bleibt häufig unerkannt, und ältere Patientinnen und Patienten sind vielfach einer riskanten Übertherapie ausgesetzt. Gleichzeitig eröffnen neue Erkenntnisse zu Krankheitsverläufen und potenziell genetischen Einflussfaktoren Perspektiven für eine stärker personalisierte Versorgung. Für die hausärztliche Praxis ergibt sich daraus ein klarer Auftrag: die Diabetesversorgung muss strukturiert und flexibel gestaltet werden, um sowohl Unter- als auch Überversorgung zu vermeiden. Zukünftig wird es entscheidend sein, praxisnahe Instrumente zu entwickeln, die Hausärztinnen und Hausärzte bei der Balance zwischen Leitlinienorientierung und patientenzentrierte Anpassungen unterstützen. Nur so lässt sich die Versorgung nachhaltig verbessern und den wachsenden Belastungen durch Typ-2-Diabetes wirksam begegnen.

1. INTRODUCTION

Type 2 diabetes represents one of the most challenging public health issues of the modern era. The disease imposes a significant burden on individuals, societies and the global health system as a whole. The increasing prevalence of type 2 diabetes and its association with numerous complications emphasise its status as a pressing healthcare priority. The chronic and systemic nature of the disease necessitates a comprehensive and multidimensional approach to patient care. There is a specific role to be played for the field of general practice, where health promotion, primary prevention of type 2 diabetes, early diagnosis and management (secondary prevention), the prevention and management of complications (tertiary prevention) and the prevention of overtreatment and unnecessary interventions (quaternary prevention) converge.

1.1 Pathophysiology of type 2 diabetes

Type 2 diabetes is a complex metabolic disorder, characterized by insulin resistance and pancreatic ß-cell dysfunction. It develops through a complex interplay of genetic predisposition, environmental factors, and lifestyle factors.

Insulin resistance

Central to type 2 diabetes is insulin resistance, a state where peripheral tissues such as muscle, liver, and adipose tissues fail to respond adequately to insulin (1). Insulin, a hormone produced by the ß-cells of the pancreas, has a key role in controlling blood glucose levels: it facilitates the uptake of glucose in these tissues for energy use or storage, and it suppresses glucose production by the liver (hepatic gluconeogenesis) (2). In the presence of insulin resistance, disruptions in molecular signalling pathways, such as the insulin receptor substrate pathway (3), lead to the impaired uptake of glucose in various organs and to an uncontrolled hepatic gluconeogenesis, which in turn results in elevated blood glucose levels (2, 4, 5). Multiple factors have been implied to contribute to insulin resistance, among which obesity and physical inactivity. Obesity-linked cytokines like tumour necrosis factor-alpha and interleukin-6 interfere with insulin signalling, making tissues less responsive to insulin (6). Furthermore, the build-up of fat in the liver or muscles, called ectopic fat accumulation, further disrupts the cell's energy homeostasis and causes oxidative stress and increased insulin resistance.

The development of insulin resistance, often in combination with a potential genetic predisposition for type 2 diabetes (7), triggers a rise in both insulin production and secretion by the pancreas, a state referred to as hyperinsulinemia.

Pancreatic ß-cell dysfunction

In parallel with the development of insulin resistance, pancreatic ß-cell dysfunction develops. The increased insulin demands, as a consequence of insulin resistance, place a sustained stress on the ß-cells and will eventually result in failure of these cells to keep up with the increased demands. Several other factors also contribute to the decline in ß-cell functioning, including the chronically elevated blood glucose levels that exert toxic effects on ß-cells (glucotoxicity) (8), the toxicity brought about by elevated levels of free fatty acids (lipotoxicity) (8), and various cellular stress pathways (9, 10). As ß-cell function deteriorates, the insulin production progressively falls and blood glucose levels further increase until, ultimately, the threshold for a diagnosis of type 2 diabetes is reached (11). By that time, normal ß-cell function has decreased to an estimated 50% of its original level and continues to decline regardless of any conventional pharmacological treatments (12, 13).

Beyond individual organs: a systemic perspective

Type 2 diabetes is a disease that goes beyond the localized dysfunctions of the pancreas and the insulin signalling pathway. It is a disease profoundly influenced by systemic processes and the so-called organ crosstalk, a complex communication and interaction between different organs and tissues in the body (14). For example, in addition to merely storing fat, adipose tissue functions as an endocrine organ releasing signalling molecules such as adiponectin and leptin, which modulate insulin sensitivity (15). In obesity, a dysregulation of these pathways magnifies metabolic disturbances. Adipose tissue as well as liver, muscle, and the pancreas interact in complex feedback loops through hormones, metabolites and inflammatory mediators, thereby making type 2 diabetes increasingly more complex than a single-organ problem.

Lifestyle and environmental drivers of type 2 diabetes

Lifestyle and environmental factors are central to the development and progression of type 2 diabetes. Unhealthy diets, physical inactivity, chronic stress, and insufficient sleep are amongst the most significant lifestyle-based risk factors for type 2 diabetes. However, since the current global epidemic of obesity is closely associated with the global rise in prevalence of diabetes, obesity is often highlighted as the primary driver (16).

Obesity is believed to contribute to the development of type 2 diabetes through a combination of mechanical, metabolic and hormonal effects. For example, adipose tissue, particularly visceral fat, releases free fatty acids into the circulation. These fatty acids impair the ability of insulin-sensitive tissue to take up glucose efficiently and they promote gluconeogenesis by the liver (17, 18). Adipose

tissue also secretes pro-inflammatory cytokines, which are hormones that interfere with insulin signalling pathways (19). The interplay between obesity and other lifestyle factors, such as poor dietary habits and physical inactivity, creates a vicious cycle that accelerates the onset of metabolic dysfunction. Still, some caution is warranted with regard to obesity as a cause of type 2 diabetes, as not all people who are obese develop type 2 diabetes and not all individuals with type 2 diabetes are obese. Evidence suggests that a high body mass index alone appears to be a weaker predictor of type 2 diabetes incidence than the presence of increased visceral obesity and/or ectopic fat (fat stored in organs such as the liver or muscles) (20-22).

Diets high in refined carbohydrates and ultra-processed foods are strongly linked to obesity and increased insulin resistance. Refined carbohydrates, which are abundantly represented in ultra-processed foods, cause rapid spikes in blood glucose levels and, consequently, an increased demand on the pancreas to produce insulin (23-25). And while saturated and trans fats have been proposed to promote lipotoxicity and systemic inflammation, thereby contributing to insulin resistance (26, 27), more recent studies question a causative role for dietary fat in type 2 diabetes (28, 29). Overall, nutritional epidemiological studies have observed varying and inconsistent relationships between various individual foods and the risk of type 2 diabetes. This reflects both the broad range of different diets consumed across the globe, and the methodological challenges inherent to the field of nutritional research, such as confounding and the Hawthorne effect (the phenomenon where people alter their behaviour because they know they are being studied) (29, 30). The modern approach to a healthy diet is therefore to focus on overall dietary patterns, like the Mediterranean diet, or on quality rather than quantity, of dietary intake (31-33). A recently published umbrella review confirmed the substantial impact of diet quality on risk of type 2 diabetes, emphasising that dietary patterns high in whole grains, fruits, and vegetables could significantly lower this risk (34).

Physical activity is another critical factor. There is a strong association between sedentary time and the risk of developing type 2 diabetes (35-37), with evidence suggesting that prolonged physical inactivity may approximately double the risk (38). Together with an insufficiently healthy diet, sedentary lifestyles promote changes in an individual's body composition, typically an increase in fat mass and a reduction in muscle mass. This reduction in muscle mass reduces the number of insulin receptors available in skeletal muscle (39), which is a major site for insulin-mediated glucose disposal. A reduction of the amount of glucose uptake subsequently increases the demands on the pancreatic ß-cells to produce more insulin (hyperinsulinemia). Various other pathogenic molecular mechanisms by which physical inactivity may lead to type 2 diabetes via insulin resistance, inflammation, mitochondrial dysfunction and metabolic disturbances have been described in the literature (40, 41).

In addition to poor diets and a sedentary lifestyle, sleep deprivation further impairs glucose metabolism (42, 43). Important in this context is the duration and quality of sleep (44). Various mechanistic pathways have been proposed, including a decreased production of insulin-sensitizing hormones like adiponectin, impaired insulin signalling, increased levels of inflammatory cytokines that contribute to insulin resistance, disruption of circadian rhythms and altered hormonal regulation through the hypothalamic-pituitary-adrenal axis (a network of interactions between the hypothalamus, pituitary gland and adrenal glands that have a role in stress responses, energy metabolism and other bodily processes) (45, 46).

Beyond individual behaviours, socio-economic status and cultural norms play a pivotal role in shaping lifestyle patterns and type 2 diabetes risk. An increased risk has been observed with socioeconomic position in high-, middle-, and low-income countries (47, 48). Lower-income populations often face barriers to accessing nutritious foods and safe spaces for physical activity. Cultural traditions and norms also influence dietary choices and physical activity levels, sometimes in ways that exacerbate the risk of developing type 2 diabetes.

Finally, environmental exposures are emerging as important contributors to type 2 diabetes risk. Air pollution, particularly the fine particulate matter, has been linked to insulin resistance and systemic inflammation (49). Similarly, persistent organic pollutants, such as polychlorinated biphenyls and dioxins, have also been implicated in the pathogenesis of type 2 diabetes through disruptions in glucose metabolism (50).

1.2 Clinical manifestations and complications of type 2 diabetes

Diagnostic criteria for type 2 diabetes

The diagnosis of type 2 diabetes is based on established international criteria, primarily outlined by the American Diabetes Association (ADA) (51), the World Health Organisation (WHO) (52), and the International Diabetes Federation (IDF) (53). In Germany, the German Diabetes Society (Deutsche Diabetes Gesellschaft; DDG) and the country's 'National Disease Management Guidelines for Diabetes' (54) follow the international recommendations closely. The criteria for diagnosis of type 2 diabetes aim to provide a standardised screening and diagnostic procedure to identify individuals with hyperglycaemia in primary care settings. They further facilitate timely intervention and the identification of individuals at high risk of diabetes-related complications, thereby supporting targeted prevention and management strategies.

Over time, the diagnostic criteria for type 2 diabetes have evolved in order to improve early detection of the condition, risk stratification, and patient outcomes. Historically, diabetes was diagnosed based on classical symptoms and elevated glucose levels in urine, but with advances in medical research the focus shifted to measurements of plasma glucose levels, which offered greater diagnostic accuracy.

By the mid-20th century, the so-called oral glucose tolerance test was established as the gold standard for the diagnosis of type 2 diabetes (the test is described in detail in chapter 2.3). In 1997, the ADA broadened the criteria and introduced fasting plasma glucose as an additional diagnostic tool, making screening for diabetes more accessible. Later, in 2010, glycated haemoglobin A1c (HbA1c) was incorporated as an alternative diagnostic criterion due to its ability to reflect average blood glucose control over the preceding three months (55, 56).

Today, the current diagnostic thresholds for the different diabetes tests according to the ADA (51) (Table 1.1) are widely adopted both internationally and in Germany. The DDG follows these standards without any major divergence in diagnostic thresholds (57).

Table 1.1: Diagnostic criteria for type 2 diabetes[*]

Diagnostic test	**Diagnostic threshold**
Fasting plasma glucose[†]	≥126 mg/dL (≥7.0 mmol/L)
Oral glucose tolerance test (2-hour value)[‡]	
Fasting preprandial value	≥126 mg/dL (≥7.0 mmol/L)
2-hour postprandial value	≥200 mg/dL (≥11.1 mmol/L)
HbA1c[§]	≥6.5% (≥48 mmol/mol)
Random plasma glucose and symptoms of hyperglycaemia	≥200 mg/dL (≥11.1 mmol/L)

[*]A diagnosis requires two abnormal results obtained at two different time points or from two different tests, unless the patient presents with clear symptoms of hyperglycaemia.
[†]Fasting is defined as having had no caloric intake for at least 8 hours.
[‡]The oral glucose tolerance test remains the most sensitive test, particularly for diagnosing early-stage diabetes or prediabetes in high-risk individuals.
[§]The HbA1c test is recommended for screening but may be less reliable in certain populations, for example those with anaemia or haemoglobinopathies.
(Table constructed by the author based on the 2025-standards for diabetes care by the American Diabetes Association (51)).

In primary care settings, the selection of a diagnostic test for type 2 diabetes depends on the clinical context, patient characteristics, and available resources. Measuring levels of fasting plasma glucose is the most widely used test due to its simplicity, minimum preparation and cost-effectiveness (56, 58). However, it has an important limitation: it may miss some cases of diabetes, particularly those with

postprandial hyperglycaemia. The HbA1c test is increasingly used in routine clinical practice as it does not require fasting and it reflects an estimate of the individual's average glucose control over the preceding two to three months. This long-term perspective makes HbA1c also a marker that is associated with the development of diabetes-related complications (56). Nevertheless, HbA1c test results can be influenced by factors unrelated to glucose metabolism, such as anaemia, chronic kidney disease, and ethnicity (59), which must be considered when interpreting results. The oral glucose tolerance test remains the more sensitive method for detecting early abnormalities in glucose metabolism, particularly in high-risk individuals, for example those with gestational diabetes, prediabetes, or metabolic syndrome. That is because it can identify an early impaired glucose tolerance before fasting glucose levels become abnormal (58, 60). The oral glucose tolerance test however, is less practical in general practice because it is time-consuming and requires multiple blood samples over a two-hour period.

While the diagnostic tests presented in Table 1.1 remain the standard for diagnosing type 2 diabetes, research on novel markers that could enhance early detection is ongoing. Some examples include 1) *continuous glucose monitoring*, which provides real-time glucose trends and helps identify postprandial hyperglycaemia missed by standard tests; 2) *1,5-anhydroglucitol*, a monosaccharide that represents a potential marker for short-term glucose fluctuations, which could be particularly useful for detecting postprandial glucose excursions; and 3) *glycated albumin*, a protein that may offer an alternative measure for glycaemic control in individuals in whom HbA1c measurements are unreliable such as those with anaemia or haemoglobinopathies (61-63). While these biomarkers hold promise, they are not yet part of routine primary care diagnostics. Further validation and cost-effectiveness studies are needed before they can be integrated into general practice (screening) protocols.

Micro- and macrovascular complications

Diabetes complications are generally classified into microvascular (affecting the small blood vessels) and macrovascular (affecting the larger arteries) diseases, both of which contribute significantly to patient outcomes and the overall healthcare burden associated with type 2 diabetes.

Microvascular complications arise from prolonged hyperglycaemia and involve damage to the small vascular system throughout the body. As a result, individuals may develop diabetic nephropathy (progressive kidney injury due to glomerular hyperfiltration, often first detected as proteinuria, which can progress to end-stage renal disease) (64), retinopathy (microvascular damage of the retina, causing vision impairment and, when left untreated, blindness) (65), and neuropathy (damage to the peripheral nerves, causing loss of senses, pain, and autonomic dysfunction, and an important risk factor of foot ulcers and amputations) (65). Overall, the primary mechanism underlying microvascular

complications is the dysfunction of the endothelial system driven by chronic hyperglycaemia. This results in oxidative stress, inflammation, and an impairment of the microcirculation (66, 67).

Macrovascular complications involve damage of larger arteries and represents the primary cause of morbidity and mortality in people with type 2 diabetes. These complications include coronary artery disease, cerebrovascular disease (stroke), heart failure, and peripheral artery disease. The main pathophysiological mechanisms include chronic insulin resistance, ongoing endothelial dysfunction, and accelerated atherosclerosis, which lead to an increased risk of (major) cardiovascular events (68). Coronary artery disease results from accelerated atherosclerosis, and increases the risk of myocardial infarction and heart failure (69), while cerebrovascular disease leads to an increased risk of stroke and cognitive decline (69). Peripheral artery disease is characterized by reduced blood supply to the lower extremities, causing pain, poor wound healing, and increasing the risk for ulcers and amputations (69).

General practitioners play a crucial role in the prevention, early detection, and management of these complications. In primary care, routine screening for microvascular complications is essential to try and prevent disease progression, for example measuring the urine albumin-to-creatinine ratio to detect nephropathy, retinal examinations to detect retinopathy, and tuning fork or monofilament testing to assess neuropathy (70, 71). At the same time, addressing cardiovascular risk factors such as arterial hypertension, dyslipidaemia, and smoking is paramount to reducing the burden of macrovascular complications.

1.3 Treatment of type 2 diabetes

Effective management of type 2 diabetes requires a multifaceted approach that combines lifestyle modifications, pharmacological treatments, and individualised care strategies tailored to each person's needs. Achieving and maintaining well-controlled blood glucose levels following a diabetes diagnosis reduce the risk of diabetes complications later in life, whereas neglected glycaemic control puts the individual at much higher risk of complications (70).

Lifestyle modification

Lifestyle modifications represent the cornerstone of diabetes management. People with type 2 diabetes are encouraged to build positive health behaviours, such as adopting a balanced and healthy diet, engaging in regular physical activity, seeking support to stop smoking, ensuring adequate sleep quality and addressing psychosocial well-being through counselling or support services (72, 73).

Key to achieving these goals is the participation in diabetes self-management, education, and support programmes. The programmes empower individuals to develop effective self-care behaviours, solve everyday health problems, make informed decisions, and actively collaborate with healthcare professionals. Structured and culturally tailored programmes that incorporate behavioural interventions have been shown to produce significant and lasting improvements in glycaemic control (74).

General practice plays an important role in advising and encouraging people to participate in such programmes and in reinforcing their benefits over time.

Pharmacological therapy

Pharmacological therapy for type 2 diabetes aims to achieve and maintain optimal blood glucose levels and reduce the risk of long-term diabetes complications. Several drug classes are available, each with distinct mechanisms of action.

Metformin, used in combination with lifestyle modifications, is since long considered the first-line therapy for people with type 2 diabetes. Metformin is a safe, inexpensive, and effective drug to reduce glucose production by the liver and improve insulin sensitivity (54, 75). Furthermore, metformin is weight neutral, does not cause hypoglycaemia and has been suggested to reduce cardiovascular mortality (76).

Sulfonylureas and meglitinides directly stimulate insulin secretion from the pancreatic ß-cells. While this is effective for lowering glycaemic levels, it inherently carries a considerable risk of hypoglycaemia and weight gain (76).

Thiazolidinediones enhance insulin sensitivity of the peripheral tissues. However, due to their associated weight gain, fluid retention and increased cardiovascular risk, thiazolidinedione use in individuals with type 2 diabetes has declined (76).

Dipeptidyl-peptidase-4 (DPP-4) inhibitors prolong the activity of the incretin hormones released from the gut, increasing insulin secretion and lowering glucagon levels. These drugs are generally well-tolerated but offer only modest glucose-lowering effects when compared to other glucose-lowering drugs (76).

Glucagon-like peptide-1 (GLP-1) receptor agonists are injectable agents that mimic the actions of endogenous GLP-1. These hormones enhance insulin secretion, slow gastric emptying, and promote satiety. Beyond potent glucose-lowering effects, GLP-1 receptor agonists have demonstrated

significant weight loss benefits and cardiovascular risk reduction, making them particularly attractive for individuals with concomitant obesity or cardiovascular disease (76-80).

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors lower blood glucose levels by reducing renal glucose reabsorption and promoting its excretion in the urine (glycosuria). Like GLP-1 receptor agonists, SGLT-2 inhibitors provide benefits beyond glycaemic control, including weight loss, blood pressure reduction, and reduction of the risk for heart failure and chronic kidney disease (76, 78, 79, 81).

Finally, insulin therapy is typically prescribed to people with advanced type 2 diabetes or those who have not managed to achieve adequate glycaemic control with other glucose-lowering drugs. Due to the high risk of hypoglycaemia, especially in older adults, patient education and their involvement in a safe and effective insulin management is important (76).

Since type 2 diabetes is often seen to progress over time, combination therapy is frequently necessary. A common approach is the addition of second-line drugs, such as GLP-1 receptor agonists or SGLT-2 inhibitors, to metformin, especially in people with co-existing obesity or cardiovascular disease (76, 82). The combination of drugs with complementary glucose-lowering mechanisms can optimise glycaemic control while minimizing drug side-effects.

Non-pharmacological therapy

In addition to lifestyle modification, bariatric surgery can be a powerful intervention to achieve glycaemic control and weight loss for individuals with severe obesity and uncontrolled type 2 diabetes. Surgical procedures such as gastric bypass and sleeve gastrectomy have been shown to not only result in significant weight loss, but also demonstrate long-term remission of diabetes in many individuals (83). Bariatric surgery is typically reserved for people with diabetes for whom lifestyle modification and pharmacological treatments have been insufficiently effective.

Personalised diabetes care

Type 2 diabetes management guidelines from major organisations, including the ADA, the European Association for the Study of Diabetes, but also the DEGAM or the DDG, emphasise a patient-centred, personalised approach to type 2 diabetes care. Personalised treatment is not only essential since type 2 diabetes is a heterogeneous disease with varying aetiology, clinical manifestation and progression, but also because of the diversity in patient backgrounds, cultural beliefs, individual values and preferences, and overall health and life expectancy. Personalised care requires an active collaboration

between healthcare professional and the patient, with clinical decisions being guided by the preferences, needs and values of the individual patient (84). This approach to care is associated with better glycaemic control, fewer diabetes-related complications, and lower hospitalization rates, ultimately lowering the economic burden on both patient and healthcare system (85). By supporting patient autonomy and fostering shared decision-making, patients have been shown to be more likely to be adherent to therapy and follow-up schedules. General practice provides an ideal setting for implementing personalised care. The continuity in the patient-provider relationship, the opportunity for regular follow-up, and the trust built over time create an environment where diabetes care can continually be tailored to the evolving needs of an individual patient.

1.4 Epidemiology of type 2 diabetes

Type 2 diabetes as a global health challenge

Type 2 diabetes is the most common manifestation of diabetes mellitus, representing about 90-95% of all diabetes diagnoses worldwide. Its prevalence has risen dramatically over recent decades, driven by demographic shifts, rapid urbanization, and widespread lifestyle changes. While type 2 diabetes was historically considered primarily a disease of high-income countries, the epidemiological landscape has shifted. Low- and middle-income countries now account for the majority of cases, largely due to increasing urbanisation, a shift to sedentary lifestyles, and nutritional changes towards diets high in refined carbohydrates, fats and highly-processed foods.

Trends and demographic factors

According to the IDF, an estimated 589 million (11.1%) adults aged 20 to 79 years were living with diabetes in 2024 (86). Men in this age range have a similar prevalence of type 2 diabetes (11.3% in 2024) to women (10.9% in 2024). The absolute numbers vary by region and are expected to rise substantially in the coming decades. Projections by the IDF suggest a rise in diabetes prevalence to 852.5 million (13%) by 2050 (86). Incidence rates also vary, with men typically being diagnosed at younger ages and a lower body mass index compared to women (87). Type 2 diabetes is estimated to decrease life expectancy by five to ten years, and almost half of all individuals with diabetes die prematurely; that is, before the age of 70 years (86, 88). In 2024, worldwide, an estimated 3.4 million people in the age of 20 to 79 years died due to diabetes or diabetes-related complications (86). Estimates for 2019 showed that mortality rates stratified by sex showed higher rates among women compared to men for the ages of 60 years and older (89). Between the ages of 30 to 59 years, mortality rates were higher in men (89). The prevalence and incidence of type 2 diabetes are influenced by

various demographic and socio-economic factors. Ageing populations in developed countries contribute to increased disease burden, whereas low- and middle-income countries face a surge in cases among younger age groups. Ethnicity also plays a crucial role, with individuals of South Asian, African, and Hispanic descent exhibiting greater susceptibility. These disparities are often compounded by limited access to healthcare and preventive resources for vulnerable populations.

In Germany, the prevalence of type 2 diabetes is in accordance with the global trends. Based on data considered representative for Germany, collected from 2008 to 2011, prevalence estimates of 7.4% in men and 7.0% in women aged 40 years and older were published (90). Mortality analyses based on statutory health insurance data from 65 million people in Germany showed that, in 2010, type 2 diabetes caused almost 140,000 excess deaths, approximately 16% of all excess deaths due to diabetes. Rates were higher in men until the age of about 75, and higher in women thereafter (91). These figures far exceed the 2.7% diabetes-related mortality reported in official death statistics, underscoring how reliance on death certificates alone underestimates the true impact of diabetes. Estimating mortality attributable to diabetes is challenging because the majority of individuals die from its complications, such as cardiovascular disease, which are frequently recorded as the underlying cause of death rather than diabetes itself.

Economic and societal implications of type 2 diabetes

The burden of diabetes typically reaches beyond that of optimising glycaemic control and results in substantial health, economic and societal costs. The economic costs of type 2 diabetes are staggering and are projected to rise alongside increasing prevalence. In 2021, global healthcare expenditures for diabetes (of which type 2 diabetes accounted for the majority of the costs) reached $966 billion, representing a threefold increase over the past 15 years (86). In addition to these direct costs, indirect costs, such as lost productivity, work absenteeism, disability, and premature mortality, put further pressure on economies. Beyond financial implications, the societal burden of diabetes is equally profound. Living with type 2 diabetes often implies a reduced quality of life, not only for patients but also for their families and caregivers. Furthermore, diabetes disproportionately affects different populations, thereby exacerbating health inequalities. Addressing these multifaceted challenges requires coordinated efforts across public health, clinical practice, and policy domains.

In Germany, the economic burden of type 2 diabetes is also substantial. In 2020, the direct costs for people with diabetes were estimated to be €7.4 billion (16). These costs included medical costs, such as hospitalization admissions, medications and the management of complications like cardiovascular disease. For indirect costs, no nationwide calculations are available. Data from the Robert Koch

Institute endorses the burden of diabetes; their analyses showed that in 2017, diabetes was responsible for 794,940 disability-adjusted life years (DALY) (17). This measure is a composite of both `years of life lost´ (YLL) due to death and `years of life lost due to disability´ (YLD).

In people with type 2 diabetes, the burden of disease was found to be predominantly attributable to YLD (67%), reflecting the chronic nature of the disease, compared to YLL (33%) due to premature mortality (17).

1.5 The integral role of general practice in type 2 diabetes care

In Germany, the field of general practice plays an indispensable role in every facet of type 2 diabetes care, from prevention and early detection to personalised treatment and long-term management. General practitioners form the cornerstone of an integrated healthcare system, addressing not only the medical but also the psychosocial needs of individuals with type 2 diabetes. This broad scope of care allows general practitioners to deliver coordinated, continuous and person-centred care.

Prevention and early diagnosis

General practitioners in Germany serve as the primary contact point for most people with type 2 diabetes, positioning them uniquely to lead diabetes prevention efforts. Through routine health check-ups, general practitioners identify and address key risk factors such as smoking, obesity, arterial hypertension, and dyslipidaemia that predispose individuals to type 2 diabetes (92). Preventive care also includes providing advice and support for lifestyle modification, such as dietary changes, increasing physical activity, and smoking cessation. These preventive measures are critical in Germany, where an ageing population and sedentary lifestyles contribute to a rising diabetes prevalence.

General practitioners also play a vital role in the early diagnosis of type 2 diabetes by recognising subtle symptoms like fatigue, polyuria, or unexplained weight loss and by routine testing of fasting plasma glucose. Diagnostic tools, such as an HbA1c test, an oral glucose tolerance test or, the repeated measurement of fasting blood glucose levels (see Table 1.1) then confirm the suspected diagnosis of diabetes. Importantly, early identification of the condition allows for a timely intervention, which can delay progression of the disease to irreversible and life-debilitating complications.

Individualised treatment and long-term management

Once diagnosed, people with type 2 diabetes rely heavily on their general practitioner to set up personalised treatment plans that align with their individual needs and preferences. In Germany, this

process is guided by evidence-based guidelines, such as those from the DEGAM or the DDG (54, 93), which provide a framework for tailoring treatment plans to the individual patient.

Treatment often involves a combination of lifestyle interventions (typically diet and exercise), oral glucose-lowering drugs, and in some cases, insulin therapy.

General practitioners practise follow-up of their patients by monitoring disease progression and screening for complications, such as nephropathy, retinopathy, neuropathy, and cardiovascular disease. Every three months, structured check-ups through the Disease Management Programmes (DMPs) include clinical measurements, targeted examinations and shared decision-making. Early detection of complications allows for a prompt referral to specialists, such as ophthalmologists or neurologists, when needed. This continuity of care ensures that all individuals with type 2 diabetes receive holistic care, avoiding gaps in treatment and improving patient outcomes.

Patient education and empowerment

A key aspect of type 2 diabetes management is patient education. Through structured education programmes, such as the DMPs mandated by Germany's statutory health insurance system, general practitioners equip patients with the knowledge and skills needed for effective self-management. These programmes include a broad range of topics such as nutritional education, the importance of regular physical activity, and techniques for self-monitoring of blood glucose levels.

Empowering people to take an active role in their own care improves adherence to treatment plans and fosters better health outcomes. For example, a patient who understands the impact of carbohydrate intake on their blood glucose levels is better equipped to make informed dietary choices, thereby reducing the risk of glycaemic excursions and avoiding both hyper and hypoglycaemia.

Coordination within a multidisciplinary framework

General practice in Germany functions as a hub of a wider interconnected healthcare network. General practitioners coordinate care with diabetologists, dietitians, podiatrists, and other specialists in order to provide comprehensive diabetes care. For example, a patient with type 2 diabetes that is complicated by peripheral diabetic neuropathy and diabetic foot syndrome may require foot care from a podiatrist, the expertise of an orthopaedic shoemaker, as well as tailored advice from a dietitian to manage body weight and blood glucose levels.

This multidisciplinary approach is particularly evident in the care of elderly patients with type 2 diabetes, who often have multiple comorbidities. In such cases, general practitioners take a central

role in managing polypharmacy, ensuring that drug-drug interactions and drug side-effects are minimized, while tailoring pharmacological and non-pharmacological therapy to the specific personal needs, preferences, and functional capacity of each individual patient. As such, treatment is ensured to be both safe and patient-centred.

Challenges and opportunities for general practice in type 2 diabetes care

Despite its critical role, general practice in Germany faces several challenges in managing type 2 diabetes. Growing patient loads and increasing administrative tasks limit the amount of time that general practitioners can spend with their patients. Additionally, the complexity of managing type 2 diabetes, particularly in individuals with comorbid conditions and polypharmacy, underscores the need for continued professional training and access to updated clinical guidelines. Opportunities to streamline care delivery lie in leveraging digital health tools. Telemedicine consultations and keeping electronic health records for example, could enhance patient management, improve coordination among care providers and support proactive monitoring of the patient.

This introduction aims to set the stage for a detailed exploration of several aspects of type 2 diabetes, encompassing its care, clinical manifestations, and treatment strategies. Special emphasis will be placed on the relevance of this research to general practice.

2. THEMES AND RESEARCH QUESTIONS OF THE UNDERLYING STUDIES

2.1 Key research aspects

The studies underlying this habilitation thesis are aimed at addressing the challenges of the various aspects in, and related to, the management of type 2 diabetes that are encountered in routine general practice. These studies explore multiple facets of diabetes care, including glycaemic control, diabetes complications, and (patterns of) pharmacological care and its implications. The key aspects of research that this work focuses on can be summarized as follows:

1. Effectiveness of providing **multifaceted type 2 diabetes care** according to the so-called "chronic care model", which is characterized by integrative, patient-centred care and a multicomponent framework for improving healthcare delivery.
2. Assessment of the prevalence of distal sensorimotor polyneuropathy in Germany, one of the most disabling microvascular **diabetes complications**, as well as the prevalence of unawareness of having this complication in people living with type 2 diabetes.
3. The strategies for **pharmacological treatment of type 2 diabetes** following a new diagnosis and following the initiation of second-line glucose-lowering therapy in older people with known type 2 diabetes.
4. **Strategies for personalised diabetes care**, including insights offered by analysing different subgroups of type 2 diabetes and the potential contributions that the field of pharmacogenetics provides to its pharmacological management.

2.2 Objectives of the included studies

The four key aspects of the research that the current thesis is based on are addressed through a total of seven studies with the following research aims:

- Multifaceted care for type 2 diabetes
    1. To evaluate the effectiveness of European chronic care programmes for type 2 diabetes mellitus, characterised by integrative patient-centred care and a multicomponent framework for enhancing healthcare delivery, in comparison to usual diabetes care.
- Diabetes complications
    2. To assess the prevalence of distal sensorimotor polyneuropathy in an older German population and to examine its relationship with prediabetes.

3. To assess the prevalence of unawareness of having distal sensorimotor polyneuropathy in people with prediabetes and type 2 diabetes in an older German population.

- Pharmacological treatment of type 2 diabetes
    4. To describe dispensation patterns of glucose-lowering drugs in people with newly diagnosed type 2 diabetes between January 2012 and December 2016 in Germany.
    5. To assess the prevalence of, and factors associated with, an inappropriately intensive pharmacological treatment in a global cohort of older individuals with type 2 diabetes and who initiated second-line glucose-lowering therapy, over a follow-up period of 24 months.
- Strategies for personalised diabetes care
    6. To identify distinct HbA1c trajectories in a global cohort of older people with type 2 diabetes starting second-line glucose-lowering therapy.
    7. To review studies examining genetic variants in people with type 2 diabetes in relation to metabolic response to treatment with the newer glucose-lowering drug classes: DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors.

2.3 Databases, methods, concepts and definitions used

For a better understanding of the seven original studies, which are summarized in chapter 3 and provided in full in Appendix 1, the following sections provide a detailed description of the study databases that were used, the concepts that were studied, and some important definitions that were used (in order of appearance in this thesis).

Concept: The chronic care model

(Refers to chapter 3.1)

The growing recognition that traditional healthcare systems were not effectively designed to manage chronic diseases led Wagner and colleagues to develop the evidence-based Chronic Care Model (CCM) (94). Wagner had observed that the increasing prevalence of chronic conditions places a substantial burden on healthcare systems, which are primarily designed for acute, episodic care. Traditional healthcare often led to fragmented, reactive, and visit-based care, whereas chronic diseases would benefit more from ongoing proactive management and patient engagement. Wagner developed the CCM to address these systemic shortcomings for chronic care, and to subsequently improve the

management of various chronic illnesses such as diabetes, arterial hypertension and cardiovascular disease (94-96).

The CCM is a primary care-based model that is based on the assumption that improvements in care require an approach that incorporates patients, healthcare providers, and system-level interventions. The model can be applied across a variety of chronic illnesses, healthcare settings and target populations, with the goal of achieving healthier patients, more satisfied care providers and cost savings (95-97). The CCM integrates six interacting components deemed essential for creating an optimal environment for effective chronic disease management. (94, 95)

1. Health system – organisation of healthcare:
   creating a culture and system that prioritises safe and high-quality care; providing leadership for securing resources, supporting care improvements, and removing barriers to care.
2. Self-management support:
   encouraging patients to play an active role in their care; facilitating patient empowerment through skills-based learning, goal setting, and problem-solving support.
3. Decision support:
   providing guidance for implementing evidence-based care; promoting provider education, decision aids, and access to clinical expertise.
4. Delivery system design:
   coordinating proactive care processes; defining roles and tasks within care teams, coordinating care across providers, and ensuring regular patient follow-up.
5. Clinical information systems:
   utilising technology such as electronic health records to organise patient data; tracking progress of care through the reporting of health metrics to patients and providers, and sharing data for optimising the coordination of care.
6. Community resources and policies:
   linking patients with external resources and support systems in the community; advocating for the inclusion of community organisations to promote health initiatives.

As such, the CCM provides a structured approach to redesigning healthcare delivery in ways that support proactive, team-based, and patient-centred care. The model has gained widespread recognition as an evidence-based framework for improving the management of various chronic diseases, and has been widely adopted and adapted across various healthcare settings and regions since its development in the 1990s. Systematic reviews and meta-analyses have demonstrated its effectiveness in improving clinical outcomes, enhancing patient satisfaction, and reducing healthcare costs. Despite its apparent success, the implementation of the CCM is not without challenges. Barriers

include limited resources in underfunded healthcare systems, resistance to organisational change and variability in the adoption of clinical information systems.

Database: The Cooperative Health Research in the Region of Augsburg (KORA) study

(Refers to chapter 3.2)

The Cooperative Health Research in the Augsburg Region (Kooperative Gesundheitsforschung in der Region Augsburg; KORA) is a large population-based study that was initiated to study the prevalence and incidence of various chronic diseases, including myocardial infarction and diabetes mellitus, in the general German population. It further aims to identify novel risk factors of these diseases. The studies included in this thesis that were performed within the framework of the KORA study, were all based on the *KORA F4 Survey* (2006-2008), which was the follow-up survey of the *KORA S4 Survey* (1999-2001) (98).

In 1999, people from the city of Augsburg (Southern Germany) and 16 towns and villages from the surrounding districts were invited to participate in the KORA S4 Survey. Within each of the selected communities, a stratified sample of ten equal strata by sex and age was drawn. Of the 6,640 people invited to participate, 2,656 were in the eligible age class of 55 to 74 years; 1,653 (62% of 2,656) completed the baseline S4 Survey between October 1999 and April 2001. Those who refused to participate were contacted by phone to obtain information on their medical history, including known diabetes and obesity. Data collection for the S4 Survey included anthropometric measurements (e.g. body weight, waist circumference, blood pressure); interviews by trained medical interviewers regarding medical history, medicine use, physical activity, lifestyle habits, and family history of diabetes; participants with known diabetes completed self-administered questionnaires about diabetes care, complications and prevention measures; fasting blood sampling for the measurement of various blood markers (e.g. HbA1c, cholesterol, triglycerides, serum creatinine); oral glucose tolerance testing in 1,353 (51% of 2,656) participants without a known diagnosis of diabetes in one of the 12 KORA study centres. The concept of an oral glucose tolerance test is described in more detail below.

In 2006-2008, the 7-year follow-up examination was conducted as the KORA F4 Survey. This round of data collection included a second oral glucose tolerance test and an extensive neurological examination. Out of the initial 1,353 participants with both complete KORA S4 survey and oral glucose tolerance test data, a total of 1,209 (89%) participated in the F4 follow-up measurements. The neurological assessment in the F4 Survey consisted of a detailed interview about the presence of

(current) pain in the feet and other parts of the body, neurological diseases and history of foot ulcers and amputations. The interview was followed by a foot inspection and a series of neurological tests, involving sensation to touch, vibration, and temperature, and the testing of ankle reflexes and sudomotor function.

All participants gave written informed consent and the study was approved by the Ethics Committee of the Bavarian Medical Association.

Concept: Oral glucose tolerance test

(Refers to chapter 3.2)

The oral glucose tolerance test is a standardised diagnostic procedure to evaluate how efficiently the body regulates blood glucose after a glucose challenge. It is particularly useful in identifying abnormalities in glucose metabolism, such as diabetes mellitus, prediabetes, or other disorders involving insulin resistance or impaired insulin secretion (see Table 1.1). The KORA study employed the oral glucose tolerance test as a key diagnostic tool in participants without a previous known diagnosis of diabetes. Its purpose was to classify participants into those having a normal glucose tolerance, prediabetes, or diabetes. Participants were considered to have previously known diabetes based on a self-reported physician diagnosis of diabetes or the self-reported use of glucose-lowering drugs.

Oral glucose tolerance tests were performed between 7:00 and 11:00 in the morning, following an overnight fast of at least 10 hours. A fasting blood sample was taken and the participant then consumed a dose of 75 g of anhydrous glucose (Dextro OGT; Boehringer Mannheim, Mannheim, Germany). A second blood sample was drawn two hours after the glucose load (98). Glucose tolerance categories were defined according to the 1999 WHO diagnostic criteria (52):

- Normal glucose tolerance (NGT):
  fasting glucose <110 mg/dL and 2-h glucose <140 mg/dL.
- Impaired fasting glucose (IFG):
  Fasting glucose ≥110 and <126 ml/dl and 2-h glucose <140 mg/dL.
- Impaired glucose tolerance (IGT):
  Fasting glucose <110 mg/dL and 2-h glucose ≥140 and <200 mg/dL.
- IFG-IGT:
  Fasting glucose ≥110 and <126 mg/dL and 2-h glucose ≥140 and <200 mg/dL.
- Diabetes (newly diagnosed):
  fasting glucose ≥126 mg/dL or 2-h glucose ≥200 mg/dL.

In KORA, participants with IFG, IGT or IFG-IGT were classified as having pre-diabetes. Furthermore, the term `overall diabetes´ comprised both participants with newly diagnosed diabetes and those with a known diabetes diagnosis.

Definition: Distal sensorimotor polyneuropathy

(Refers to chapter 3.2)

Diabetic peripheral neuropathy is a heterogeneous complication of type 2 diabetes and encompasses a wide range of abnormalities, affecting peripheral sensory and motor nerves and the autonomic nervous system (99). To date, there is no consensus on a uniform definition of diabetic neuropathy for use in observational research, making standardisation challenging.

In the studies included in this thesis that were performed within the framework of the KORA study, diabetic peripheral neuropathy was defined as a bilateral impaired foot-vibration perception and/or a bilateral impaired foot-pressure sensation, and referred to by the term *clinical distal sensorimotor polyneuropathy* (clinical DSPN). In KORA, measurements of vibration perception and pressure sensation had been performed by trained investigators and under the supervision of an experienced diabetologist, following the practical guidelines for the diabetic foot from the ADA and the International Diabetic Foot Working Group (100, 101):

- Vibration perception at the dorsal side of the left and right big toe was assessed using a calibrated 64-Hz Rydel Seiffer tuning fork. Increased thresholds were calculated according to Martina et al. (102).
- Pressure sensation was measured at the dorsal side of the left and right big toe using a 10-g monofilament (Twin-Tip, Heinsberg, Germany). If a participant perceived at least eight out of ten applications of the monofilament, pressure sensation of the foot was considered to be normal (103). Less than eight perceived applications indicated a reduced sensation.

Our choice for these two specific tests to define clinical DSPN lies in their quantitative ability to detect the insensate foot and the fact that both tests have been shown to predict future foot ulceration (104). In addition, the two tests have previously been studied as being the most accurate tools for diagnosing large-fibre peripheral polyneuropathy in people with diabetes (105). Since peripheral polyneuropathy is characterised by a bilateral appearance of the affected nerves, we included this aspect of symmetry into our definition of clinical DSPN. As such, we aimed to minimize misclassification of cases of polyneuropathy that were due to causes other than diabetes (e.g., mononeuropathy, radiculopathy).

To evaluate the diagnostic validity of our definition of clinical DSPN, we performed a validation study in a cohort of 151 in- and outpatients with type 2 diabetes (for more details, see Appendix 2). Compared to the gold standard for diagnosing peripheral polyneuropathy (nerve conduction velocity testing), our definition of clinical DSPN had an excellent discriminative ability of distinguishing individuals with and without peripheral polyneuropathy, with an area under the receiver operating characteristic curve of 0.91 (Appendix 2, Figure S1).

In the KORA study, we further defined the presence of symptomatic clinical DSPN as the presence of clinical DSPN accompanied by self-reported symptoms of burning pain or pain at rest in the lower legs or feet, and/or pain triggered by bed covers touching the skin.

Database: The German Pharmacoepidemiological Research Database (GePaRD)

(Refers to chapter 3.3)

The German Pharmacoepidemiological Research Database (GePaRD) was established by the Leibniz Institute for Prevention and Epidemiology (BIPS) in Bremen, Germany. The database is based on pseudonymised claims data from four statutory health insurance providers in Germany (106-108); i.e. three nationwide health insurance providers (DAK-Gesundheit, Handelskrankenkasse, and Techniker-Krankenkasse) and one regional provider (AOK Bremen/Bremerhaven). GePaRD currently covers information on about 25 million people from all regions of Germany who have been insured with one of the participating providers since 2004 or later. For each insured person, GePaRD records the start date and end date of the insurance period along with reasons for ending insurance coverage, such as death. The database contains information on demographic characteristics (gender, year of birth and the official 5-digit municipality code), outpatient and inpatient services (hospital stays, reasons for admission and discharge, outpatient visits and prescriptions), and diagnoses. Furthermore, GePaRD contains information on drug dispensations, including Anatomical Therapeutic Chemical (ATC) classification codes, defined daily dose, packaging size, generic and brand name. Drugs purchased over the counter and in-hospital medications, however, are not included (108). In- and outpatient diagnoses are coded according to the German modification of the International Classification of Diseases, 10th Revision, (ICD-10-GM). Yet, since insurance data is primarily intended for billing purposes and not for research purposes, certain clinical information is not routinely available in GePaRD, such as blood glucose values relevant for diabetes research or tumour stages for cancer research.

Each annual data update contains information on approximately 17% of the general population in Germany, with all geographical regions of Germany represented. GePaRD data are representative of the German general population with respect to age, sex, region of residence and medication

dispensations (108, 109). The suitability of GePaRD data for pharmacoepidemiological research has been assessed methodologically and in validation studies (108, 110, 111). As such, the database has thus far been used for a variety of pharmacoepidemiological studies, for example those that evaluated medication use in the elderly (112, 113), and studies that assessed the risks associated with taking antidepressants (110, 114-116).

Database: The DISCOVER study

(Refers to chapters 3.3 and 3.4)

The DISCOVER study programme was designed to provide a global view on the management of people with type 2 diabetes. Its primary aim was to describe the patterns of care and the clinical evolution of disease in individuals with type 2 diabetes starting a second-line glucose-lowering therapy after first-line oral treatment had failed (117, 118). In DISCOVER, initiating second-line therapy was defined as adding one or more glucose-lowering drugs to current therapy or switching between therapies. A secondary aim of the study was to describe associations between treatment patterns and various outcomes such as glycaemic control, incidence of diabetes complications, hospitalizations, and various patient-reported outcomes including quality of life, over three years of follow-up (117, 118).

The DISCOVER study is an observational, prospective study across 38 different countries; 37 in the main DISCOVER study and one (Japan) in J-DISCOVER. Countries from several regions of the world were selected, particularly those for which only limited data on type 2 diabetes management were available. Efforts were made to recruit a diverse and representative study population in each participating country for as far as possible, again, particularly in regions with sparse epidemiological and clinical data on type 2 diabetes. About a third of the invited study sites (n=778) took part and enrolled participants, which resulted in a heterogeneous DISCOVER cohort (119).

The inclusion and exclusion criteria for participant recruitment were kept to a minimum to reflect routine clinical practice. These included having a diagnosis of type 2 diabetes, being aged ≥18 years, initiating second-line therapy, and providing written informed consent. People already using injectable glucose-lowering drugs, i.e., insulin or a GLP-1 receptor agonist, were ineligible to participate as they were considered to represent a subgroup of participants with more severe disease. A standardised electronic case report form was used for data collection, and in countries like Canada, Denmark, Norway, France, and Sweden, part of the data were extracted from existing electronic medical records and health registries. Data were captured by the treating physician at baseline, 6, 12 and 24 months (±2 months) to reflect patient visits in everyday clinical practice. Collected variables included participant demographics (age, sex, duration of diabetes); clinical variables (HbA1c and other

laboratory test results); first-line glucose-lowering therapy defined as treatments the participants received before study entry; second-line glucose-lowering therapy prescribed at study baseline; and the HbA1c target value set at the time of (baseline) therapy change. Treatment at each follow-up visit was recorded, as changes in treatment could have occurred during clinical visits that were not recorded as part of DISCOVER. In line with the observational nature of the study, treatment decisions were made by the treating physician and the participant (117).

The study protocol was approved by the clinical research ethics committee in each participating country, along with the appropriate institutional review board at the individual study sites. All participants gave written informed consent.

Concept: Pharmacogenetics in type 2 diabetes

(Refers to chapter 3.4)

There is considerable variation between individuals in the way they respond to medications (120). Pharmacogenetics involves the study of how genetic variations influence individual responses to drugs. With the central idea that this genetic variation can be used to explain interindividual drug responses, the field of pharmacogenetics has emerged as a cornerstone of personalised medicine (121). In the context of type 2 diabetes, pharmacogenetics is particularly relevant due to the heterogeneity in treatment responses among individuals, which highlights the influence of underlying biological factors, including genetics (120).

Pharmacogenetics is built upon the understanding that genetic variations, most commonly single nucleotide polymorphisms (variations in DNA sequence that occurs when a single nucleotide is replaced by another), can affect pharmacokinetics (drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (drug targets and biological pathways) of a drug. These genetic variations can thus influence how individuals metabolise drugs, respond to them, and experience side effects. In type 2 diabetes care, pharmacogenetics has primarily focused on oral glucose-lowering drugs such as metformin and newer agents, like SGLT-2 inhibitors (see chapter 1.3). Genetic variability in genes encoding enzymes, transporters, and drug targets involved in these therapies has been linked to interindividual differences in both treatment efficacy and safety. This has been shown for some commonly used glucose-lowering drugs, including metformin, as illustrated in the following example.

In 2016, the Metformin Genetics consortium conducted a genome-wide association study involving 13,123 participants from different ancestral backgrounds (122). The study found a statistically significant association between the C-allele of a variant (rs8192675) of the *SLC2A2* gene and a 0.17% greater reduction in HbA1c in participants of European ancestry. The *SLC2A2* gene encodes GLUT2, a

transmembrane glucose transporter primarily expressed in the liver, pancreatic beta cells, intestinal epithelium, and renal tubular cells. GLUT2 facilitates the movement of glucose across cellular membranes, playing a key role in glucose homeostasis. The association between rs8192675 and metformin response was subsequently validated in the German Diabetes Study (123).

As a consequence of large genome-wide association studies like the one performed by the Metformin Genetics consortium, the field of pharmacogenetics is emerging, aiming to tailor treatment regimens to an individual's genetic profile and move away from the 'one-size-fits-all' approach. Tailored treatment regimens are especially relevant for type 2 diabetes, where a patient typically requires lifelong treatment, and where variability in drug response is one of the major challenges in primary care.

3. ORIGINAL STUDIES

3.1 Multifaceted care for type 2 diabetes

3.1.1 Effectiveness of the chronic care model

Bongaerts BWC, Müssig K, Wens J, Lang C, Schwarz P, Roden M, et al. Effectiveness of chronic care models for the management of type 2 diabetes mellitus in Europe: a systematic review and meta-analysis. BMJ open 2017;7(3):e013076.

Background

With the growing prevalence of chronic diseases and the ageing of populations, improvement in the quality of chronic disease management requires more than evidence on effective diagnostic procedures and treatments (124). To address this, Wagner and colleagues developed the so-called CCM in the mid-1990s (94). The CCM introduced structured components such as delivery system design, self-management support, decision support, and the use of clinical information systems to create a more effective and sustainable approach to chronic disease management (94-96). Further background information on the CCM is provided in chapter 2.3.

The literature indicates a widespread application of the CCM and, in general, positive effects on patient outcomes and processes of care (125-131). Nevertheless, reported study results are heterogeneous and the effect sizes relatively small (127, 129, 131-141). Many studies evaluated only (combinations of) selected components of the Model, which further adds to the heterogeneity in evidence regarding effectiveness of the CCM. Therefore, the aim of our review was to systematically identify European studies of type 2 diabetes management that assessed the effectiveness of interventions that addressed all six components of the CCM, and to study their effect on biochemical and patient-reported outcomes in comparison to routine diabetes care.

Methods

This systematic review was based on a predefined protocol (Appendix 3) with input from experts in diabetes care, statistical methods, and primary care (142).

We searched MEDLINE, Embase, CENTRAL, and CINAHL from January 2000 to July 2015 for (cluster-) randomised controlled trials that i) enrolled adults with type 2 diabetes; ii) tested multifaceted diabetes care interventions, designed specifically for type 2 diabetes and delivered in primary or secondary care, targeting patient, physician, and healthcare organisation; and iii) defined usual diabetes care as the control intervention.

Titles and abstracts of the subsequent search results were screened by one reviewer. Two reviewers then independently screened the full text of these articles. From those studies that were deemed eligible for inclusion in the review, one reviewer extracted study characteristics and methodology, baseline demographics of the study population, details of the intervention and control intervention, and patient outcomes, including glycaemic control, blood pressure, and quality of life. Risk of bias of the included studies was assessed using the Cochrane Risk of Bias 1 Tool, with specific attention to cluster-trial-specific issues such as recruitment bias, baseline imbalances, cluster dropout, and proper statistical adjustment (143). Both data extraction and risk of bias assessment were confirmed by a second reviewer and potential conflicts were resolved by discussion. When important study information or outcome data were missing, trial authors of the included studies were contacted.

Due to heterogeneity of the study populations and duration of the interventions, and due to only small overlap in outcomes of the individual trials, an extensive meta-analysis and meta-regression of the reported outcomes was not possible. We pooled results only for glycaemic control (HbA1c) and total cholesterol levels. Weighted mean differences (95% confidence interval (CI)) were estimated using a random-effects model for change in HbA1c and total cholesterol levels (144). Subgroup analyses were performed according to the type of diabetes diagnosis (prevalent diabetes, screen-detected diabetes, and newly diagnosed diabetes). Statistical heterogeneity was evaluated using the I^2 statistic (145).

Results

The electronic database search identified 9,464 abstracts published between January 2000 and July 2015. Eleven articles (146-156), reporting on eight unique cluster-randomised controlled trials, carried out between 1989 and 2011, were included for review (146, 148, 152-154, 156-158). In total, 9,529 participants with type 2 diabetes were enrolled, of whom 8,921 (94%) were included in our analyses.

All trials evaluated a structured multifaceted management of diabetes, focusing on all aspects of the CCM. The interventions aimed to improve the participants' cardiovascular risk profile (157, 158) and metabolic control (146-148, 152, 153, 156, 157), and to assess the effect of multifaceted care on the occurrence of cardiovascular events (148, 152, 153, 156), overall mortality (154), and risk factors for clinical complications (154). The interventions were largely delivered by general practitioners and other physicians, yet specialized nurses or practice nurses were also involved in the intervention programme as part of the practice team or to (partly) replace the physician in providing diabetes care.

Two main aspects differed among the included studies: the type of diabetes patient enrolled and the duration of the intervention. Three studies included participants with prevalent diabetes and intervened for one year (146, 157, 158), one study had enrolled participants with newly diagnosed type 2 diabetes and had a follow-up of six years (154). Four studies first initiated a diabetes screening

programme and subsequently recruited those with screen-detected diabetes to participate in the intervention study with follow-up measurements after one year (152, 156) and after five years (159). Table 3.1 presents an overview of the study characteristics and findings of these included studies.

Table 3.1: Characteristics of the included cluster-randomised controlled trials

Study	Comparison	Effect on endpoints*	Notes
Cleveringa 2008 (146)	Patient consultation by a practice nurse + use of a computerised decision support system + guideline-based care + physician support by practice nurse + interdisciplinary care by a specialist team + individualised treatment advice + patient education + physician feedback + recall system + regular patient consultations by practice nurse + physician feedback *vs* routine diabetes care	**Clinical parameters** Systolic blood pressure (+,i) Diastolic blood pressure (+,i) 10-year CHD risk (+, i) **Biochemical parameters** HbA1c (0) Total cholesterol (+, i) HDL-cholesterol (0) LDL-cholesterol (+, i) **Processes of care** HbA1c below target value§ (+,i) Systolic blood pressure below target value§ (+,i) Total cholesterol below target value§ (+,i) LDL-cholesterol below target value§ (+,i) All treatment targets reached§ (+,i)	At baseline, patients in the intervention group had higher HDL-cholesterol levels, were more often smokers and more often had a history of CHD. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control were adjusted for cluster structure.
Sönnichsen 2008 (158)	Physician education +guideline-based care + patient education + use of a clinical information system tool + interdisciplinary care by a specialist team + patient reminders + physician reminders + goal setting + shared decision-making patient and physician + regular consultations *vs* routine diabetes care	**Clinical parameters** Systolic blood pressure (0) Diastolic blood pressure (0) **Biochemical parameters** HbA1c (0) Total cholesterol (+, i) HDL-cholesterol (0) LDL-cholesterol (0) Triglycerides (0) Creatinine (0) Body mass index (+, i) **Processes of care** To the guidelines adherent: -number of eye examinations§ (+, i) -number of foot examinations§ (+, i) -provision of patient education§ (+, i) -regular HbA1c checks§ (+, i)	At baseline, patients in the intervention group had a higher BMI and higher cholesterol levels than patients in the control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control were adjusted for cluster structure and baseline values.
Frei 2010 (157)	Specialist team involving a practice nurse + practice nurse education + physician education + physician support by practice nurse + regular independent patient consultations by practice nurse + use of a clinical information system tool + guideline-based care + physician feedback + patient information leaflets + self-	**Clinical parameters** Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (0) **Biochemical parameters** HbA1c (0) Total cholesterol (0) HDL-cholesterol (0) LDL-cholesterol (+, i) Fasting blood glucose (0) **Processes of care** Number GP visits§ (0)	There were no baseline differences in patient characteristics between intervention and control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward.

	management support for patient + patient treatment groups *vs* routine diabetes care	Change in antidiabetic therapy (0) Change in antihypertensive therapy (0) Change in lipid-lowering therapy (0) **Other**	There was no evidence for a statistically significant clustering effect.
Webb 2010 (156)	Structured patient education + lifestyle advice and self-management with ongoing (bimonthly) professional support + individualised management + guideline-based care + shared decision-making patient and healthcare professional + annual screening for diabetic complications + care delivered by a specialist team (specialty doctor, diabetes nurse educator, and a dietician) + patient reminders + physician reminders *vs* routine diabetes care	**Clinical parameters** Systolic blood pressure (+, i) Diastolic blood pressure (+, i) 5-year CHD risk (+, i) 5-year CVD risk (+, i) Weight (+, i) Body mass index (+, i) Waist circumference (0) **Biochemical parameters** HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Triglycerides (0) **Processes of care** Use of anti-hypertensive drugs§ (+, i) Use of lipid-lowering drugs§ (+, i) Use of anti-platelet therapy§ (+, i) Use of metformin§ (0) Use of sulfonylurea§ (0) **Other** Health-related quality of life (0) Hypoglycaemia§ (+, i)	At baseline, more patients in the intervention group were taking anti-hypertensive medication when entering the study and had higher total and LDL-cholesterol levels. Statistical analyses were conducted by intention-to-treat. It was not reported whether or not data were missing and how missing data were handled. Comparisons between intervention and control were adjusted for cluster structure and baseline values (except quality of life which had not been measured at baseline).
Janssen 2009 (152)	Physician education + diabetes nurse education + lifestyle advice + guideline-based care + physician support by diabetes nurse + evaluation and feed-back sessions diabetes nurse + frequent patient consultations with diabetes nurse + shared decision-making patient, physician and diabetes nurse + physician reminders + patient reminders *vs* routine diabetes care	**Clinical parameters** Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (+, i) **Biochemical parameters** HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Fasting blood glucose (+, i) Triglycerides (0) **Other** Health-related quality of life (0) Hypoglycaemia§ (0)	There were no baseline differences in patient characteristics between intervention and control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control group were adjusted for age, sex, baseline values, and clustering at practice level.
Griffin 2011 (159)	This study combined the data after five years of a multifaceted care intervention from the i) Addition-Denmark study (Lauritzen et al [39]), ii) the Addition-Netherlands study (Janssen et al [38]), iii) the Addition-Cambridge study (Echouffo et al [34]), and iv) the Addition-Leicester study (Webb et al [42]) in a meta-analysis.	**Clinical parameters** Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (0) Weight (0) Waist circumference (0) CVD mortality (0) All-cause mortality (0) Myocardial infarction (0) Stroke (0) Revascularization (0) **Biochemical parameters** HbA1c (+, i)	Baseline characteristics were well matched between intervention and control group. In Denmark however, more patients were identified in practices assigned to the intervention arm than in those assigned to control arm. And in the intervention group, more patients had a history of ischemic heart disease.

		Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Triglycerides (0) Creatinine (+, c) **Processes of care** Health-related quality of life (0) Meeting target values for: HbA1c (+, i) blood pressure (+, i) total cholesterol (+, i) **Other** Hypoglycaemia§ (0) Use of any glucose-lowering drugs (+, i) Change in any anti-hypertensive drugs (+, i) Change in any cholesterol-lowering drugs (+, i)	Statistical analyses were conducted by intention-to-treat and patients with missing outcome values were excluded from the analyses. Those with missing outcome baseline values were included according to the missing indicator method. Comparisons between intervention and control were adjusted for cluster structure and baseline values.
Olivarius 2001 (154)	Patient follow-up every three months + annual screening for diabetes complications + shared decision-making patient and physician + physician feedback + goal setting + clinical guidelines + physician education + patient leaflets and folders + lifestyle advice + protocol-based care + physician recall system *vs* routine diabetes care	**Clinical parameters** Systolic blood pressure (+, i) Diastolic blood pressure (0) Weight (0) **Biochemical parameters** HbA1c (+, i) Total cholesterol (+, i) Fasting blood glucose (+, i) Triglycerides (0) Creatinine (0) **Processes of care** Number of consultations§ (+, i) Number of referrals to diabetes clinic§ (-, i) Number of hospital admissions§ (0) Use of metformin§ (+, i) Use of other glucose-lowering drugs§ (0) Use of anti-hypertensive drugs§ (0) Use of lipid-lowering drugs§ (0) **Other** Overall mortality§ (0) Severe hypoglycaemia§ (0) Diabetic retinopathy§ (0) Non-fatal myocardial infarction§ (0) Non-fatal stroke§ (0) Peripheral neuropathy§ (0) Microalbuminuria§ (0) Angina pectoris§ (0) Intermittent claudication§ (0)	At baseline, more patients in the intervention group were excluded because of severe somatic disease than in the control group. Furthermore, occupation and smoking habits differed between the two groups. Statistical analyses were conducted by intention-to-treat. It was not reported whether or not data were missing and missing data were handled. Comparisons between intervention and control group were adjusted for baseline values, duration of diabetes, age, sex, occupation, smoking habits, and clustering at physician level.

T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; CVD, cardiovascular (heart) disease; GP, general practitioner;

* +=positive effect; 0=no effect; -=negative effect; i=favouring intervention group; u=favouring control (usual care) group. The effects of the intervention are represented by the difference in change from baseline between intervention and control group. § The effect of the intervention is represented by a difference in proportions of patients at follow-up between intervention and control group.

For each trial, methodological quality was acceptable with very low rates of dropout among the enrolled participants. Details on the randomisation procedure were frequently missing, as well as information concerning concealment of allocation from general practitioners and other physicians in advance to recruitment of eligible participants.

Compared to usual diabetes care, one year of multifaceted care improved HbA1c in participants with screen-detected and newly diagnosed diabetes, but not in participants with prevalent diabetes. Across all trials the weighted mean difference in HbA1c was -0.07% (95% CI: -0.10 to -0.04), or 0.8 mmol/mol (95% CI: -1.1 to -0.4), with relatively low statistical heterogeneity (I^2=21%).

Similar to HbA1c, the effect of multifaceted care on overall cholesterol levels seemed larger in screen-detected participants than in those with prevalent diabetes. Pooled analysis showed a weighted difference in change from baseline of -0·20 mmol/L (95% CI -0·28 to -0·11) with higher heterogeneity (I^2=64%).

Improvements in blood pressure were observed across study populations, with larger improvements for the intervention arms than for the control arms, and for follow-up after one year than after five years. Pooled effects on blood pressure, as on LDL-cholesterol, were similar to those for HbA1c, albeit with greater statistical heterogeneity.

Discussion

Effects of multifaceted diabetes care in Europe were rather small and the magnitude of effects seemed to differ according to the type of diabetes patient being studied. Our analysis suggested that in comparison to usual diabetes care, multifaceted care improved HbA1c for participants with screen-detected and newly diagnosed diabetes, but not for participants with prevalent type 2 diabetes. Similar findings were observed for total cholesterol and LDL-cholesterol. The resulting improvements in blood pressure seemed less strongly related to the type of diabetes patient studied. Other outcomes, such as fasting glucose levels, triglycerides, hypoglycaemia, and cardiovascular risk, had been reported inconsistently and results varied across trials.

Overall, previous systematic reviews have reported that an integrated approach to diabetes care can indeed improve some processes of healthcare, such as screening frequencies of retinopathy, peripheral polyneuropathy and foot lesions (138, 161, 162), monitoring of HbA1c and lipid levels (162), clinical outcomes such as HbA1c (132, 138, 141, 161), blood pressure (127, 138), and lipids (127, 132).

A strength of the current study is that it is the first systematic review to provide a comprehensive overview of diabetes-care trials that evaluated the effectiveness of the all six components of the CCM combined.

3.2 Diabetes complications

3.2.1 Prevalence of distal sensorimotor polyneuropathy

Bongaerts BWC, Rathmann W, Kowall B, Herder C, Stöckl D, Meisinger C, et al. Postchallenge hyperglycemia is positively associated with diabetic polyneuropathy: the KORA F4 study. Diabetes Care. 2012;35(9):1891-3. DOI: 10.2337/dc11-2028.

Background

DSPN, a major clinical manifestation of diabetic peripheral polyneuropathy, is a severe complication of type 2 diabetes (99). It is a heterogeneous disorder encompassing a wide range of abnormalities affecting peripheral sensory and motor nerves as well as the autonomic nervous system. DSPN may cause excruciating neuropathic pain, drastically reduce quality of life, and increase mortality rates (99, 163). In elderly individuals, it may exert adverse effects on stability, gait, and sensorimotor functioning, underscoring the need for early recognition and appropriate management of the disorder (164). The underlying cause of DSPN is often difficult to determine, yet chronic hyperglycaemia is an important driver (99, 164). Whereas a relationship is underexamined (165), it has been suggested that prediabetes may imply a first stage of diabetic nerve injury (166, 167). Hence, the aim of this study was to evaluate the prevalence of DSPN in a representative sample of the older German population and examine its relationship with prediabetes.

Methods

Detailed information on the KORA Study, the concept of the oral glucose tolerance test, and the definition of clinical DSPN is provided in chapter 2.3.

The current study was performed within the framework of the KORA F4 Survey (2006-2008), which is the 7-year follow-up survey of the KORA S4 Survey (1999-2001) (98). In the F4 follow-up measurements 1,209 (89%) individuals participated. All participants underwent a neurological examination, which included a foot inspection and a series of neurological tests. We defined DSPN, as detailed in chapter 2.3, as a bilateral impaired foot-vibration perception (assessed with a calibrated 64-Hz Rydel Seiffer tuning fork) and/or a bilateral impaired foot-pressure sensation (assessed with a 10-g Twin-Tip monofilament).

Data analyses were based on cohort members with complete information on glucose tolerance status as assessed by the oral glucose tolerance test, clinical DSPN, and confounding variables (n=1,100). Multivariable logistic regression models were fitted to study associations between prediabetes,

diabetes and having clinical DSPN. Additional analyses evaluated relationships between DSPN and quartiles of HbA1c, fasting and 2-h postload glucose.

Results

Of the 1,100 participants aged 61-82 years, oral glucose tolerance data classified 577 (52%) participants as having NGT, 284 (26%) participants having prediabetes (composed of individuals with IFG and/or IGT) and 239 (22%) as having diabetes (composed of individuals with known and undiagnosed diabetes). Details are provided in Table 3.2.

Table 3.2: Adjusted odds ratios* and 95% confidence intervals for clinical distal sensorimotor polyneuropathy† according to oral glucose tolerance status; KORA F4 (2006-2008)

	Clinical DSPN		OR	95% CI
	No	Yes		
Oral glucose tolerance status				
NGT	513	64	1.00	Reference
Prediabetes (total)	243	41	1.22	0.78-1.90
isolated IFG	52	3	0.33	0.10-1.13
isolated IGT	156	27	1.26	0.76-2.08
IFG-IGT	35	11	2.82	1.29-6.10
Diabetes (total)	190	49	1.54	1.01-2.42
Known diabetes	138	39	1.77	1.10-2.87
Undiagnosed diabetes	52	10	1.22	0.57-2.61

DSPN: distal sensorimotor polyneuropathy, OR: odds ratio, CI: confidence interval, NGT: normal glucose tolerance, IFG: impaired fasting glucose, i-IGT: isolated impaired glucose tolerance, HbA1c: glycated haemoglobin

* All models were adjusted for age (years), sex, height (cm), waist circumference (cm), diastolic blood pressure (mm Hg), level of physical activity (low/high) and alcohol consumption (low, moderate, high).

† Defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation.

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The highest prevalence of clinical DSPN among participants with prediabetes was observed for those with IFG-IGT (23.9%, 95% CI: 12.6-38.8), and among participants with diabetes for those with known diabetes (22.0%, 95% CI: 16.2-28.9). Neuropathic complications, such as absent ankle reflexes and foot ulcers, were observed more frequently in these two subgroups, and accordingly, the prevalence of

symptomatic clinical DSPN was the highest in these subgroups also; 15.2% (95% CI: 6.3-28.9) in the IFG-IGT group and 13.6% (95% CI: 8.9-19.5) in the known diabetes group.

Adjusted logistic regression models did not convincingly show a positive association for the participants with prediabetes overall. However, a 2.82-fold increase in odds ratio (OR) (95% CI: 1.29-6.10) for having clinical DSPN was observed for the subgroup with IFG-IGT, compared to participants with normal glucose tolerance (Table 3.2). For the overall group of participants with diabetes, a positive association with having clinical DSPN was seen, which was largely attributable to the participants with known diabetes (OR: 1.77, 95% CI: 1.10-2.87) compared to participants with normal glucose tolerance.

For quartiles of fasting blood glucose and HbA1c, no evident relationship with prevalent clinical DSPN was observed. For quartiles of 2-h postload blood glucose however, we found a J-shaped relationship with the prevalence of clinical DSPN.

Discussion

In the present population-based study we observed a similar prevalence of clinical DSPN in participants with IFG-IGT and those with known diabetes. Among the participants with prediabetes, only for those with IFG-IGT an evident positive relationship with DSPN was seen. Participants with IFG-IGT thus appear to represent a high-risk group for clinical DSPN, which underscores the need for careful monitoring and early preventive strategies in primary care. Moreover, a J-shaped relationship was observed between 2-h postload glucose levels and clinical DSPN, whereas fasting glucose and HbA1c showed no associations. These findings suggest that postprandial glucose concentrations, even within the normal range, may play an important role in the development of diabetic polyneuropathy.

A major strength of our study is the use of the oral glucose tolerance test to facilitate the classification of both distinct prediabetes subgroups and undiagnosed diabetes. Another important strength involves the validation of our definition of clinical DSPN against nerve velocity conduction in an independent cohort of external patients, showing excellent diagnostic performance. Study limitations include the cross-sectional design that prevents assumption of causality, and the potential misclassification of DSPN due to smoking or diseases such as cancer and acute myocardial infarction, which are known to cause neurological damage.

3.2.2 Unawareness of having distal sensorimotor polyneuropathy

Bongaerts BWC, Rathmann W, Heier M, Kowall B, Herder C, Stöckl D, et al. Older subjects with diabetes and prediabetes are frequently unaware of having distal sensorimotor polyneuropathy: the KORA F4 study. Diabetes Care. 2013;36(5):1141-6. DOI: 10.2337/dc12-0744

Background

Of all diabetes complications, DSPN causes the highest number of hospital admissions. Also, being the main cause of foot ulcers, DSPN is responsible for 50-70% of all non-traumatic amputations following ulceration (169). DSPN not only causes substantial morbidity, it also significantly reduces the quality of life for the individual patient and increases the risk of death (163, 164). According to the German National Disease Management Guidelines for neuropathy in people with diabetes, screening should take place at diagnosis and yearly thereafter (57). Notwithstanding, in the absence of symptoms, neurological tests and physical examinations of the feet of people with diabetes are rarely performed. Even in the presence of neuropathic pain, the pain often remains unrecognized and, hence, untreated (170-172). Data on the prevalence of underdiagnosed DSPN are sparse, yet the existing evidence suggests it is substantial (173, 174). The current study therefore evaluated the prevalence of unawareness of having clinical DSPN among older adults with diabetes or prediabetes in Germany.

Methods

Detailed information on the KORA Study, the concept of the oral glucose tolerance test, and the definition of clinical DSPN is provided in chapter 2.3.

The current study was based on the 7-year KORA F4 follow-up examination (2006-2008) of the KORA S4 Survey (1999-2001). For 177 participants of the 1,209 who participated in the follow-up survey, a previous diagnosis of diabetes could be validated. Of the remaining participants, 923 successfully completed an oral glucose tolerance test to determine glycaemic status. During data collection, participants with known diabetes specifically, were asked the question “When has a physician examined your feet lately?”, with answering options a) within the past 12 months; b) more than 12 months ago; c) not ever; and d) I don’t know. As an indication for ever having had one’s feet examined, answers a and b were considered confirmatory of a foot examination and answer c was considered non-confirmatory.

All participants subsequently underwent a neurological examination of which the first part comprised a detailed interview addressing the presence of pain in the feet and other parts of the body, any known neurological diseases, and a history of foot ulcers and amputations. The second part comprised a foot inspection and a series of neurological tests. We defined the presence of clinical DSPN as a bilateral

impairment of foot-vibration perception and/or a bilateral impairment of foot-pressure sensation (see chapter 2.3). Furthermore, participants were asked if a physician had ever told them that they were suffering from nerve damage, neuropathy, polyneuropathy, or diabetic foot. Participants meeting our study definition of clinical DSPN were classified as being unaware of their disorder if they had answered this question with "no."

Our statistical analyses were of descriptive nature. For participants who were either aware or unaware of having clinical distal sensorimotor polyneuropathy, we compared age- and sex-adjusted differences in characteristics.

Results

Of the 1,100 participants with complete KORA F4 data, 154 (14%) had clinical DSPN according to our study definition. Only 14 (9% of 154) of them were classified as being aware of having this disorder and as many as 140 (91% of 154) as being unaware (Table 3.3). Among 177 participants with known diabetes, 39 (22%) had clinical DSPN, of whom a subsequent 77% were unaware of having this disorder (Table 3.3).

Table 3.3: Prevalence of clinical distal sensorimotor polyneuropathy, according to glucose tolerance status; KORA F4 (2006-2008)

	Clinical DSPN*		
	n	**Prevalence of clinical DSPN* (95% CI)**	**Unawareness of clinical DSPN†**
Total study population (n=1,100)	154	14.0% (12.0-16.2)	91%
Normal glucose tolerance (n=577)	64	11.1% (8.6-13.9)	98%
Isolated-impaired fasting glucose (n=55)	3	5.5% (1.1-15.1)	100%
Isolated-impaired glucose tolerance (n=183)	27	14.8% (10.0-20.7)	89%
Impaired fasting glucose - impaired glucose tolerance (n=46)	11	23.9% (12.6-38.8)	91%
Newly diagnosed diabetes (n=62)	10	16.1% (8.0-27.7)	100%
Known diabetes (n=177)	39	22.0% (16.2-28.9)	77%

CI: confidence interval, DSPN: distal sensorimotor polyneuropathy

* Defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation.

† Defined by a disaffirmative answer to the question "Has a physician ever told you that you have nerve damage, neuropathy, polyneuropathy or diabetic foot?" in combination with the presence of clinical DSPN.

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Participants classified as being aware of having clinical DSPN, were more likely to have known diabetes, complaints of current pain, paraesthesia and numbness in their feet, foot ulcers and absent ankle reflexes, compared to participants classified as being unaware of having clinical DSPN.

Information on having ever had a foot examination by a physician was collected for the 177 participants with known diabetes only. Excluding 10 participants with missing data, 113 out of 167 (68%) reported to have ever had their feet examined (Table 3.4). As many as 78% of these foot examinations had taken place within the past year, 22% had been done over a year ago and 8% of participants could not remember. Almost a quarter of the participants indicated to never have had a foot examination. Of the 38 participants with known diabetes, clinical DSPN, and available neurological data, 29 (76%) were unaware of having DSPN, and a subsequent 18 (62% of 29) of them indicated ever having had a foot examination by a physician. Thirteen of these 18 (72%) foot examinations had been performed in the past year.

Table 3.4: Performance of a foot exam by a physician in participants with known diabetes; KORA F4 (2006-2008)

Foot examination by a physician*	All subjects with known diabetes (N=167)	Subjects with known diabetes		
			Subjects with clinical DSPN†	
		No clinical DSPN† (N=129)	Aware of having clinical DSPN‡ (N=9)	Unaware of having clinical DSPN§ (N=29)
Yes	113 (68%)	88 (68%)	7 (78%)	18 (62%)
Within last 12 months	88 (78%)	71 (81%)	4 (57%)	13 (72%)
More than 12 months ago	25 (22%)	17 (19%)	3 (43%)	5 (28%)
No	41 (24%)	32 (25%)	1 (11%)	8 (28%)
Unknown	13 (8%)	9 (7%)	1 (11%)	3 (10%)

DSPN: distal sensorimotor polyneuropathy

* Participants were asked “When has a physician examined your feet lately?” Answering options a) within the past 12 months, and b) longer than 12 months ago, were combined to indicate that a foot examination had ever taken place. Answering option c) not ever, indicated that a foot examination had never taken place and option d) I don’t know, indicated an unknown status regarding the performance of a foot examination.

† DSPN was defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation.

‡ As defined by a confirmative answer to the question “Has a physician ever told you that you have nerve damage, neuropathy, polyneuropathy or diabetic foot?” in combination with the presence of DSPN.

§ As defined by a disaffirmative answer to the question “Has a physician ever told you that you have nerve damage, neuropathy, polyneuropathy or diabetic foot?” in combination with the presence of DSPN.

Finally, for a group of 154 participants information on diabetes duration was available. Of the 49 participants living with diabetes for ≤5 years, 30 (61% of 49) reported to have ever had their feet examined. For the 105 participants living with diabetes for more than five years, this involved 75 (71% of 105) people.

Discussion

This cross-sectional analysis of the population-based KORA F4 Survey indicated that a large proportion of participants with known diabetes were unaware of having clinical DSPN. While 68% of participants with known diabetes reported having ever had their feet examined, among those with DSPN according to our definition (n=25), as many as 18 (72%) of them were unaware of having clinical DSPN.

Our findings align with the main message from two previously published studies on the prevalence of undiagnosed DSPN (173, 174), in which DSPN was undiagnosed in over 50% of the study population of people with diabetes. Furthermore, the current results support the literature, of that time, sketching a general picture of inadequate practices of preventive foot care in type 2 diabetes (170, 172, 176-179).

Study limitations should be taken into account when interpreting the findings. First, the data on foot examinations, as well as that on having ever been told by a physician to be having nerve damage, polyneuropathy or diabetic foot, rely on self-report and, hence, are subject to recall bias. Second, since there is no uniform consensus on the diagnosis of diabetic DSPN, we cannot rule out the presence of misclassification bias. Strengths of this study include the collection of (neurological) survey data by trained interviewers, the use of different bedside tests for peripheral sensory functioning, and the performance of a validation study that indicated that the diagnostic performance of our clinical DSPN definition was excellent (168).

In conclusion, our findings suggest an inadequate attention to diabetic foot prevention and insufficient adherence to the clinical guidelines for diabetes care, necessary for the prevention of severe foot complications.

3.3 Pharmacological treatment of type 2 diabetes

3.3.1 Treatment patterns of type 2 diabetes in Germany

Bongaerts B, Kollhorst B, Kuss O, Pigeot I, Rathmann W. Dispensation Patterns of Glucose-Lowering Drugs in Newly Diagnosed Type 2 Diabetes: Routine Data Analysis of Insurance Claims in Germany. Experimental and Clinical Endocrinology & Diabetes. 2022;130(09):587-95. DOI: 10.1055/a-1702-5151

Background

Hyperglycaemia in newly diagnosed type 2 diabetes is a strong predictor of requiring early intensification of glucose-lowering treatment (180). Overall, studies indicate that well-controlled blood glucose levels following a diabetes diagnosis reduce the risk of diabetes-related complications later in life (181), while neglected HbA1c control puts a person at much higher risk of developing complications (182, 183).

In Germany, representative nationwide data on glucose-lowering prescription patterns in people with type 2 diabetes are lacking. Previous research has utilized the IMS Disease Analyser database, which comprises data from a sample of general and internal medicine practices in Germany (184). However, since German citizens are free to change their treating physician at any time, these data rarely capture full treatment histories, and thus only allow analysis of people with prevalent diabetes. Another study was conducted using data from two German diabetes registries containing information from outpatient clinics throughout the country (185). These hospital-based datasets, too, have the drawback of only allowing analysis of people with a prevalent diagnosis of diabetes. By contrast, data from Germany's statutory health insurance companies have the potential to offer a more comprehensive nationwide overview of outpatient diabetes treatment, covering details on the diagnosis of type 2 diabetes as well as on the prescription and dispensation of medications.

Therefore, the objective of the current study was to describe the dispensation patterns of glucose-lowering drugs among people with newly diagnosed type 2 diabetes in Germany between January 2012 and December 2016.

Methods

The current study was performed using data from the German Pharmacoepidemiological Research Database (GePaRD). Detailed information on this database is provided in chapter 2.3.

In brief, GePaRD contains the pseudonymized claims data from four statutory health insurance providers in Germany (106-108). The database includes information on demographics, in- and outpatient services and diagnoses, and details on drug dispensations.

Eligible for inclusion in the current study were adult persons, newly diagnosed with type 2 diabetes between 1 January 2012 and 31 December 2016. To ensure the selection of incident cases only, we excluded people who did not have continuous insurance in the three years preceding their diagnosis of type 2 diabetes, who had a diagnosis of any other type of diabetes (e.g., type 1 diabetes, gestational diabetes), or who had already been dispensed a glucose-lowering drug. To ensure sufficient follow-up data, we only included individuals with at least one year of continuous insurance after their diabetes diagnosis.

First-line glucose-lowering treatment was defined as the first-ever glucose-lowering therapy a person received, which could be either monotherapy or combination therapy with multiple glucose-lowering drugs. Second-line and subsequent-line treatment was defined as a change in therapy by either switching to another drug (class), discontinuing of one or more drugs, or adding of one or more drugs to the previous-line regimen. People without any glucose-lowering drug dispensation in the first year after diagnosis were presumed to be managed with non-pharmacological interventions (e.g., lifestyle changes) only.

We analysed the dispensation patterns of first-line glucose-lowering therapies initiated in the year after diabetes diagnosis and patterns of second-line therapies dispensed in the year after first-line treatment.

Results

Of all adults insured in GePaRD between January 1, 2012 and December 31, 2016, a total of 356,647 (2.2%) met our inclusion criteria. The mean age of this population with newly diagnosed type 2 diabetes was 63.5 (SD 13.4) years and 50.7% were female.

In the 31.6% of individuals treated pharmacologically in the year after diagnosis, metformin monotherapy was most frequently dispensed (73.1%), followed by dual therapy of metformin and DPP-4 inhibitors (6.4%), and monotherapy with DPP-4 inhibitors (2.9%). Of all possible first-line therapies, GLP-1 receptor agonists and SGLT-2 inhibitors contributed to only 2% of first-line regimens. Over the study period of 2012-2016, we observed changes in dispensation frequencies of first-line therapies. First, dispensation of sulfonylureas and combination therapies with sulfonylureas decreased by more than 50%. Second, while dispensations with DPP-4 inhibitors were already amongst the most frequent ones, we observed an increase of up to 10.6% in dispensations of certain combination therapies with

DPP-4 inhibitors. These included the combined treatment with insulin and that with metformin and SGLT-2 inhibitors.

After a median of five months (interquartile range: 3 – 8), 22,579 people (20.0% of those treated pharmacologically) initiated second-line therapy in the year following the initiation of first-line treatment. This percentage was highest among the first-line monotherapy users (51.2%) and involved a switch to dual therapy in 60.3% of them. Overall, the most frequently dispensed second-line therapy was a combined treatment with metformin and DPP-4 inhibitors (21.4%), followed by metformin monotherapy (16.7%) and monotherapy with either insulin or DPP-4 inhibitors (both 12.0%).

In general, there were no evident differences in treatment dispensations between men and women or between people living in West- versus East-Germany. We also did not observe clear differences in dispensed treatment frequencies between individuals with and without baseline macrovascular disease.

Discussion

Data from German statutory health insurance providers (2012 to 2016) showed that the majority of people with newly diagnosed type 2 diabetes were dispensed metformin monotherapy (73.1%), consistent with guideline recommendations. Over time, dispensation of sulfonylureas and their combinations markedly decreased, while DPP-4 inhibitors, as monotherapy or in combination, were dispensed more frequently. The observation that GLP-1 receptor agonists and SGLT-2 inhibitors were rarely dispensed likely reflected their later entry to the market, their higher costs, and the limited evidence on cardiovascular effects during the study period.

A total of 20.0% of the included study population initiated second-line glucose-lowering treatment within one year of starting first-line therapy, most often with dual therapy with metformin and DPP-4 inhibitors. Treatment prescription patterns were similar across sexes, regions and baseline status of macrovascular complications. The proportion of people without pharmacological treatment (68.4%) was high compared to earlier studies, likely reflecting the initial focus on lifestyle management in people with a new diagnosis of diabetes.

Strengths of our study include the large, representative GePaRD database and the use of pharmacy dispensation data, which minimizes recall bias. Limitations include the lack of inpatient dispensation data, the inability to verify if dispensed drugs were actually taken in adherence to therapy, and the uncertainty around non-pharmacological therapy, since diet and lifestyle changes are not reimbursed in Germany and therefore, not documented in the database.

3.3.2 Potential overtreatment of older adults with type 2 diabetes

Bongaerts B, Arnold SV, Charbonnel BH, Chen H, Cooper A, Fenici P, et al. Inappropriate intensification of glucose-lowering treatment in older patients with type 2 diabetes: the global DISCOVER study. BMJ Open Diabetes Research and Care. 2021;9(1):e001585.A

Background

Guidelines generally recommend an HbA1c of ≤7.5% in otherwise healthy older adults with type 2 diabetes, and ≤8.5% in those with complex comorbidities (186, 187). Higher targets may be appropriate since older people are at higher risk of hypoglycaemia and related complications, such as falls, fractures, cognitive decline, vascular events, and mortality (188-191). Intensive HbA1c targets often lead to complex treatment regimens and polypharmacy, which, especially in older adults, are associated with adverse drug events, drug-drug interactions, and poor adherence (192). Therefore, guidelines recommend individualised treatment with simple regimens and drugs that pose a low risk for hypoglycaemia.

Evidence from Europe and the USA, however, indicate that guidelines are not always followed and that many older people with type 2 diabetes are being potentially overtreated (193-197). This may lead to high rates of hypoglycaemia-related hospitalizations. Data on overtreatment in low- and middle-income countries remain scarce. We therefore aimed to investigate the proportion of older patients (aged ≥65 years) who were potentially being overtreated (HbA_{1c} level <7.0%) using data from the global DISCOVER study. Factors associated with potential overtreatment and the use of glucose-lowering medications associated with a high risk of hypoglycaemia (insulin, sulfonylureas, and meglitinides) were also assessed.

Methods

The current study was performed using data from the global DISCOVER programme. Detailed information on this database is provided in chapter 2.3.

In brief, DISCOVER is a 3-year observational study programme of 15,992 people with type 2 diabetes initiating second-line glucose-lowering therapy in 38 countries (117, 118). Adult participants were enrolled between 2014 and 2016. Data for the current study was collected at baseline, and at 6, 12, and 24 months using standardised electronic case report forms, and included variables such as age, sex, BMI, diabetes duration, and first-and second-line glucose-lowering treatments. First- and second-line therapy were defined as the initial regimen before study entry and the regimen at baseline, respectively. Also, treatment at each follow-up visit was recorded, since participants may have changed treatment at other routine clinical visits that were not part of DISCOVER.

Our statistical analyses comprised the cohort of 3,344 older participants (≥65 years) with baseline HbA1c data (22). Inappropriate intensive treatment was defined as HbA1c <7.0% at baseline or follow-up. Insulin, sulfonylureas, and meglitinides were classified as high-risk drugs. Using hierarchical regression analysis, we subsequently examined which (baseline) covariates were associated with an inappropriately intensive treatment or using high-risk medications.

Results

Of the 3,344 older patients in our analytic cohort, aged ≥65 years and having baseline HbA1c data, 785 (23.5%) had an HbA1c below 7.0% when initiating second-line glucose-lowering therapy (at baseline). Of these potentially inappropriately intensified participants, 252 (32.1%) received second-line treatment with high-risk glucose-lowering drugs. At 6, 12, and 24 months of follow-up, HbA1c <7.0% was observed in 55.2%, 54.2%, and 53.5% of participants, respectively, of whom one-third were treated with high-risk drugs at each time point of follow-up (Figure 3.1).

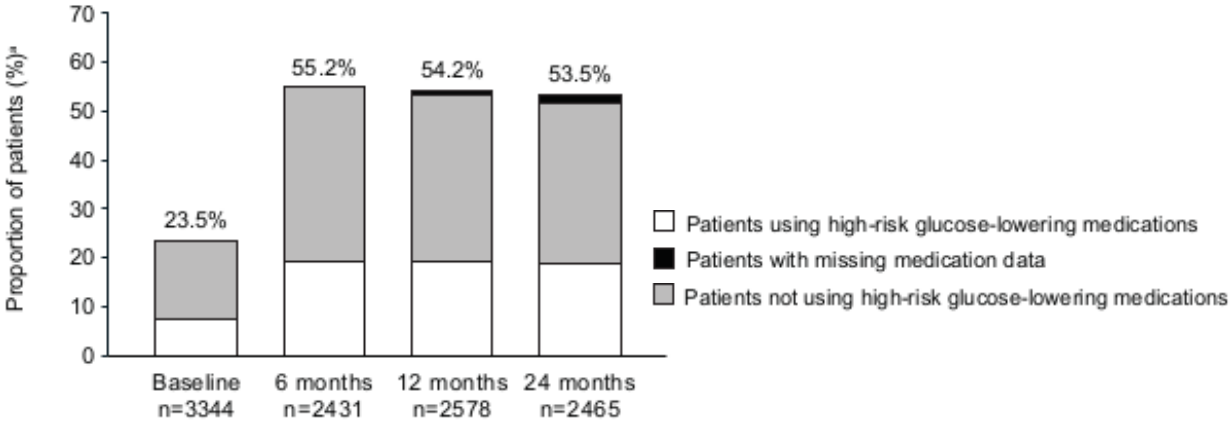

Figure 3.1: Proportion of older patients (aged ≥65 years) with HbA1c level of <7.0% treated with or without high-risk glucose-lowering medications (insulin, sulfonylureas, and/or meglitinides).
(Figure adapted from Bongaerts B et al. (198). Open access under CC BY-NC 4.0 license).

The proportion of patients with HbA1c <7.0% was highest in high-income countries, whereas the use of high-risk drugs was most frequent in middle-income countries.

Longer duration of diabetes and the use of high-risk drugs at 12 months were associated with a lower odds of having an HbA1c <7.0% (OR 0.89, 95% CI: 0.83-0.95 and OR 0.51, 95% CI: 0.43-0.61, respectively). High country income was associated with a greater odds of having an HbA1c <7.0% (OR 1.05, 95% CI: 1.00-1.09).

At 12 months, the proportion of people receiving treatment with a sulfonylurea was lower in participants with an HbA1c <7.0% (29.5%) than in those with an HbA1c ≥7.0% (42.4%), as was the case for insulin treatment (2.3% versus 10.9%). Higher BMI, shorter diabetes duration, and HbA1c <7.0% were associated with a lower odds of receiving high-risk glucose-lowering therapy (OR 0.83, 95% CI: 0.76-0.91; OR 0.91, 95% CI: 0.86-0.98; and OR 0.52, 95% CI: 0.44-0.62, respectively) while higher country income was also associated with a reduced odds of receiving high-risk glucose-lowering drugs (OR 0.86, 95% CI: 0.78-0.95).

Discussion

In this large global cohort, about one-quarter of older participants with type 2 diabetes and HbA1c <7.0% at the time of initiating second-line glucose-lowering treatment, and about half of participants had an HbA1c <7.0% during follow-up, suggesting potentially inappropriate treatment intensification. Because all participants were initiating second-line treatment, some decline in HbA1c after baseline was expected, yet the proportion of patients tightly controlled remained high, indicating that physicians may not always recognize inappropriate intensification of therapy.

Intensive glycaemic control was most frequent in high-income countries, likely reflecting stricter treatment targets, greater monitoring, and wider access to care. One-third of tightly controlled participants were treated with high-risk drugs, particularly in middle-income countries where newer therapies with drug classes such as DPP-4 inhibitors and GLP-1 receptor agonists, may be less available or affordable. This highlights both inequality in diabetes care and the global opportunity to adopt more individualised treatment strategies to minimize hypoglycaemia risk in older adults.

Our findings are consistent with previous reports from Europe and the USA (193-197). They also underline the risk of polypharmacy in older adults with type 2 diabetes, where achieving low HbA1c often requires multiple drugs, which raises the potential for adverse drug events. Education on treatment simplification and individualised targets could help reduce potential overtreatment.

Strengths of the DISCOVER study include its large, diverse cohort of participants and standardised data collection across the different countries. Limitations include the observational design, the possibility for selection bias towards more advanced treatment centres, and a limited number of hypoglycaemia outcomes to be analysed in association with potential overtreatment. Moreover, defining inappropriate control as HbA1c <7.0% may have misclassified some otherwise healthy older participants without comorbidities, who may benefit from tighter glycaemic targets.

3.4 Strategies for personalised diabetes care

3.4.1 Type 2 diabetes subgroups

Bongaerts B, Kuss O, Bonnet F, Chen H, Cooper A, Fenici P, et al. HbA1c trajectories over 3 years in people with type 2 diabetes starting second-line glucose-lowering therapy: The prospective global DISCOVER study. Diabetes, Obesity and Metabolism. 2023;25(7):1890-9.

Background

Several classes of glucose-lowering therapies are available for type 2 diabetes, enabling physicians to follow individualised treatment approaches (74, 199-201). Evidence-based treatment requires knowledge of how people are likely to respond to therapy over time, and the statistical technique of latent class growth modelling has previously been used to identify a large subgroup of people with type 2 diabetes with a similar favourable pattern of glycaemic control after treatment (202, 203). While many people maintain stable good control of their blood glucose, subgroups with poor glycaemic control differ between studies, likely due to variations in populations and regimens (183, 204-206). To date, no study has focused exclusively on HbA1c trajectories in people with type 2 diabetes after their initiation of second-line diabetes treatment.

Using data from the DISCOVER study programme, we therefore aimed to identify distinct HbA1c trajectories in adults with type 2 diabetes starting second-line glucose-lowering therapy.

Methods

The current study was performed using data from the global DISCOVER programme. Detailed information on this database is provided in chapter 2.3.

In brief, DISCOVER is a 3-year observational study programme of 15,992 people with type 2 diabetes initiating second-line glucose-lowering therapy in 38 countries (117, 118). Enrolment of adult participants took place between 2014 and 2016. Data were collected at baseline (start of second-line therapy), and at 6, 12, and 24 months using standardised electronic case report forms. Variables included demographics such as age, sex, BMI, diabetes duration, HbA1c, and glucose-lowering treatments. Data were recorded by physicians as part of routine care and collection of clinical measures was not mandatory.

Participants were included in our trajectory analyses if they had baseline HbA1c and at least two follow-up measurements. Latent class growth modelling was used to identify HbA1c trajectories from baseline to 36 months. The Bayesian Information Criterion was used to help assess the optimal number

of trajectory groups, with higher values indicating a better model fit (207, 208). Logistic regression models examined the odds of participants being assigned to different HbA1c trajectory groups according to baseline covariates. Multiple imputation handled missing covariate data using iterative sequential regression.

Results

Of the 14,691 eligible participants, 9,295 (63%) had at least three or more HbA1c measurements (including a baseline measurement) and were included in our analyses. Latent class growth modelling identified four HbA1c trajectory groups (Figure 3.2). Most participants (72.4%) showed stable good glycaemic control; with mean HbA1c 7.6% at baseline, falling to 6.8% at 6 months and remaining stable below 7.0% thereafter. Another 18.0% had stable moderate glycaemic control, with HbA1c falling from 8.9% to 8.3% but remaining above the internationally recommended targets of <7.0%. A smaller group (6.7%) showed highly improved glycaemic control, with HbA1c dropping from 11.7% to 7.8% by 6 months and 7.3% by 12 months, remaining stable thereafter. The final 2.9% had stable poor glycaemic control with HbA1c only decreasing from 11.6% at baseline to 10.9% after 6 months, followed by only a small and gradual decrease to 10.4% by 36 months.

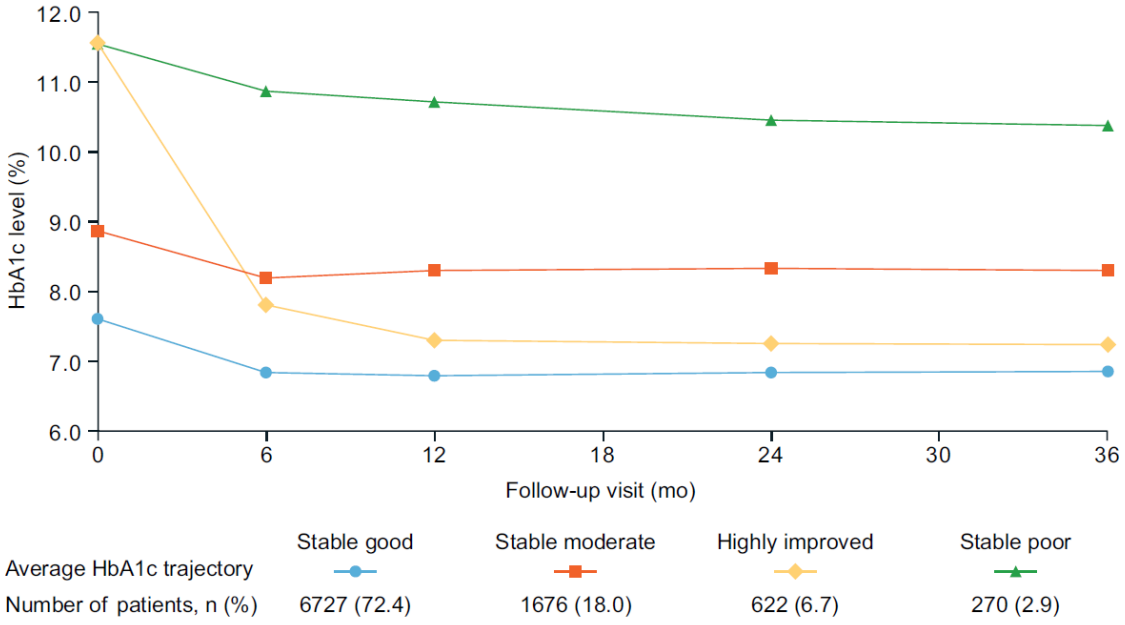

Figure 3.2: Mean HbA1c trajectories of participants assigned to each trajectory group. Stable good group (72.4% of the cohort): a decrease in HbA1c level over the first 6 months followed by stable average HbA1c levels < 7.0% for the remainder of follow-up. Stable moderate group (18.0% of the cohort): a decrease in HbA1c level over the first 6 months followed by stable levels for the remainder of follow-up; however, the mean HbA1c level at 36 months remained on average > 7.0%. Highly improved group (6.7% of the cohort): a steep decrease in HbA1c

level between baseline and 6 months before remaining stable for the remainder of follow-up. Stable poor group (2.9% of the cohort): a high baseline HbA1c with a small decrease in HbA1c level over time; however, the mean HbA1c level at 36 months remained high.
(Figure adapted from Bongaerts B, et al. (209) Open access under CC BY-NC 4.0 license).

At baseline, mean age ranged from 52.3 years in the stable poor group to 59.3 years in the stable good group. The proportion of women varied, from 41.3% in the highly improved group to 51.9% in the stable poor group. BMI was similar across groups, while diabetes duration ranged from 3.2 years to 4.8 years. Microvascular comorbidities were reported in about 21-26% of participants across groups. Injectable glucose-lowering drugs were most often used in the stable poor group, while oral monotherapy or dual therapy had the highest frequency of use in the stable good group. Group distribution varied substantially by region across the globe.

Regression models showed that older age (≥65 years) and being treated in a high-income country increased the likelihood of belonging to the stable good control group. Compared to participants receiving monotherapy, those receiving three or more oral glucose-lowering drugs or injectable agents was associated with being in the stable moderate, highly improved or stable poor groups.

In the stable good group, the use of dual oral therapy predominated with 70% at baseline and 56% at 36 months. In the stable moderate group, dual therapy use declined from 54% at baseline to 29% at 36 months, while the use of ≥3 oral therapies and injectable agents increased. In the highly improved group, dual therapy fell from 56% at baseline to 38% at 36 months, met by a rise in the use of three or more oral therapies. In the stable poor, dual therapy use dropped from 47% at baseline to 13% at 36 months. This was largely compensated for by an increase in the use of injectable agents (from 19% to 59%). Metformin was the most commonly prescribed drug across all trajectory groups.

Discussion

Our analyses identified four distinct HbA1c trajectories in a cohort of adults with type 2 diabetes after initiation of second-line therapy. Most participants achieved stable good glycaemic control, but nearly one-fifth of participants showed moderate or poor glycaemic control during follow-up.

Our findings align with previous studies showing large subgroups with stable HbA1c near target values, though proportions varied by populations studied (183, 202, 206). The use of dual glucose-lowering therapy dominated in the stable good group, while injectable agents were increasingly prescribed in the stable poor group, consistent with high HbA1c values driving treatment intensification. Younger age and microvascular comorbidities were more common in the stable poor group, suggesting a more severe metabolic phenotype and/or poor treatment adherence. In contrast, older age and treatment

in high-income countries were associated with stable good glycaemic control, likely reflecting better access to glucose-lowering therapies and diabetes care. Metformin use remained high across all HbA1c trajectory groups, which underscores its central role in the treatment of type 2 diabetes. Our findings underscore, once more, the importance of personalised treatment strategies and warrant further research into behavioural, genetic and socioeconomic factors that can influence HbA1c trajectories.

Strengths of this study include its large and diverse population of adults with type 2 diabetes. The standardised data collection enabled the comparison of results between countries and regions. Study limitations include the observational design, and the fact that not all participants had complete data available.

3.4.2 Genetic susceptibility to pharmacological therapy

Rathmann W, Bongaerts B. Pharmacogenetics of novel glucose-lowering drugs. Diabetologia. 2021;64:1201-12

Background

There is considerable variation in individual responses to glucose-lowering drugs in type 2 diabetes (120). Genetic variants may help explain these differences and allow for stratification of subgroups of people with diabetes that respond particularly well to specific therapies (120). Pharmacogenetics remains an emerging field, with new studies on gene variants affecting individual responses to newer glucose-lowering therapies, such as DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors (210). Further background information on the concept of pharmacogenetics in type 2 diabetes is provided in chapter 2.3. The current review focuses on gene variants influencing metabolic responses to treatment with novel glucose-lowering drugs, including glycaemic effects, weight change, and related traits. Our review draws mainly on studies in people with type 2 diabetes although important studies performed in people without diabetes will also be considered. A narrative review was chosen given the limited number of heterogeneous studies and the lack of replication studies, making meta-analysis not possible.

Methods

A MEDLINE literature search for pharmacogenetic studies was conducted from database inception up to 12 August 2020, by using a predefined search algorithm. Out of the 2,663 identified articles, 37 duplicates were removed and titles and abstracts of the remaining 2,626 publications were scanned. To identify further relevant articles, we also screened the reference lists of included articles. The

characteristics and main results of these pharmacogenetic studies are summarized in tables (see Appendix 1). We described narratively which genes have been found to be associated with therapeutic responses for each of the three novel glucose-lowering drugs (DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors).

Results

In total, 22 studies were retrieved from the literature (MEDLINE). Below, only a few illustrative examples of gene variants associated with diabetes treatment response are given. Please refer to Appendix 1 for the full overview.

Variants of the *GLP-1 receptor* gene (*GLP1R*) were associated with altered responses to DPP-4 inhibitors. For example, the rs6923761 variant of *GLP1R* was related to a smaller reduction in HbA1c in adults with type 2 diabetes after six months of treatment with sitagliptin, vildagliptin, or linagliptin. (211, 212). Similarly, a genetic variant of the *KCNQ1* gene, coding for a potassium channel which plays a role in type 2 diabetes via insulin release, was found to be linked with a smaller reduction in HbA1c after six months of DPP-4 inhibitor therapy (213).

Concerning glucose-lowering treatment with GLP-1 receptor agonists, *GLP1R* variants have also been studied. In people with type 2 diabetes and obesity and treated with liraglutide, being a carrier of the A allele of the rs6923761 variant (GA/AA genotypes) was associated with a larger reduction in weight of almost three kg, when compared with being a carrier of GG genotype (214).

The evidence for SGLT-2 inhibitor treatments is limited. A study of variants in the *SLC5A2* gene, encoding the SGLT-2 protein that contributes to renal glucose reabsorption, did not observe a relevant difference in HbA1c response to treatment with empagliflozin (215). A *PNPLA3* variant, encoding the PNPLA3 protein that is involved in fat metabolism in the liver, was found to modify liver fat responses in people with type 2 diabetes and non-alcoholic fatty liver disease after treatment with dapagliflozin and omega-3 fatty acids (216).

Discussion

Only a small number of studies have examined genetic variants and responses to novel glucose-lowering drugs, focusing mainly on glycaemic outcomes (HbA1c) and body weight. For DPP-4 inhibitors and GLP-1 receptor agonists, most research has targeted gene variants in drug-related pathways (e.g., *GLP1R, KCNQ1)*. *GLP-1R* variants were linked to reduced glycaemic treatment responses, though the findings for weight change under treatment with GLP-1 receptor agonist were inconsistent. For SGLT-2 inhibitors drugs, which act independently of diabetes pathophysiology, most work has focused on genes involved in renal glucose reabsorption (e.g., *SLC5A2*), but no clinically relevant effects have been observed.

Overall, current evidence is hampered by small sample sizes, small genetic effects and limited statistical power, inconsistent statistical methodology, inadequate adjustment for confounders and effect modifiers, and, most importantly, a lack of replication studies. Robust, well-powered studies and meta-analyses are needed to validate individually reported associations. To date, research has relied mainly on candidate gene approaches, which offer only limited insights. Genome-wide association studies, in that respect, may hold more promise to provide novel insights. However, the identification of distinct subgroups of type 2 diabetes may also be a requirement for pharmacogenetic studies to be successfully used for a stratified individualised prescription of glucose-lowering therapy.

4. DISCUSSION

General practitioners in Germany serve as primary coordinators of diabetes management for their patients. They are not only responsible for the medical aspects, such as diagnosis, treatment initiation, monitoring, and prevention of complications, but also for supporting their patients in areas like education, self-management, and shared decision-making. Within the framework of structured DMPs, general practitioners are responsible for implementing evidence-based care strategies, ensuring treatment aligns with clinical guidelines while adapting their care to the unique medical and psychosocial needs of the individual patient.

This discussion section therefore contextualizes the findings of the original studies included in this thesis to the broader real-world challenges and opportunities of diabetes care in German general practice. By examining the implications for general practice, this discussion addresses both practical and systemic factors that influence diabetes care delivery, including the feasibility of personalised treatment approaches and directions for future research. Given the central role of general practitioners in long-term diabetes management, this discussion aims to address how the evolving landscape of type 2 diabetes treatment may be integrated into primary care settings to improve patient outcomes.

4.1 Summary of the key findings

Multifaceted care for type 2 diabetes

(Article No. 1)

The systematic review of the CCM in Europe provided a comprehensive overview of diabetes care trials that evaluated the combined implementation of all six components of this model for chronic care. The review highlights that there is an important lack of such studies. While the CCM is proposed to improve the quality of (diabetes) care, and ultimately, patient outcomes, our systematic review indicated that the included programmes have not been as successful as expected. Improvements in both clinical and patient-reported outcomes were rather small and their magnitude seemed to differ according to the type of diabetes patient being studied.

Diabetes complications

(Articles No. 2 and 3)

The KORA study emphasised a similar, yet high, prevalence of DSPN in older adults with a known diagnosis of diabetes and those with both IFG and IGT. This may indicate that risk of diabetic neuropathy may already be elevated before diabetes is fully established. The KORA study further highlighted that over two-thirds of the participants with known diabetes were unaware of having clinical DSPN. Of the participants with known diabetes, only 68% reported having had a foot examination by a physician, 80% of which had been performed within the last 12 months.

Pharmacological treatment of type 2 diabetes

(Articles No. 4 and 5)

Analysis of German statutory health insurance data (2012 to 2016) revealed that metformin was the predominant first-line therapy for people newly diagnosed with type 2 diabetes, consistent with current national and international guidelines. Over time, there was a marked reduction in the use of sulfonylureas, replaced by newer drug classes like DPP-4 inhibitors and GLP-1 receptor agonists. The global DISCOVER study, however, highlighted a concerning pattern of substantial overtreatment in older people with type 2 diabetes. More than half of the study population maintained HbA1c levels below the recommended target values, yet continued treatment with insulin, sulfonylureas and meglitinides; drugs that pose a high risk for hypoglycaemia.

Strategies for personalised diabetes care

(Articles No. 6 and 7)

In the global DISCOVER study, four distinct HbA1c trajectories were identified among people with type 2 diabetes initiating second-line glucose-lowering therapies. While mean HbA1c levels decreased between baseline and six months in all four identified groups, longer-term control up to 36 months diverged. The first and largest group (72.4% of participants) showed stable good levels of glycaemic control over the remainder of follow-up and the second group (18.0%) showed stable moderate levels of glycaemic control. The third group (2.9%) showed stable poor levels of glycaemic control, while the fourth group (6.7% of participants) showed highly improved glycaemic control between baseline and six months and stable control over the rest of follow-up. A separate literature review of 22 studies investigated the role of pharmacogenetics in type 2 diabetes. The review showed that genetic variants, such as those of the GLP-1 receptor gene, may influence a person's response to glucose-lowering therapies. Although some associations were reported, the overall evidence base remains sparse.

The relevance to personalised medicine remained limited as a result of small genetic effect sizes, small sample sizes, inadequate statistical analyses, and lack of replication studies.

4.2 Implications for clinical practice

While chapter three of this thesis provides only a summary of the more general discussion section of each of the seven included articles (available in full in Appendix 1), the current section specifically addresses the implications of the described research for diabetes care in general practice.

Multifaceted care for type 2 diabetes

The findings from our systematic review of the primary care-based CCM underscore the challenges regarding its practical applicability in routine diabetes care practices. For general practitioners in Germany, these findings may highlight several key considerations for the delivery of multifaceted diabetes care within primary care settings.

One important consideration is that the effectiveness of multifaceted care appears to vary according to diabetes duration. Our review found that CCM-based interventions were most effective in participants with screen-detected or newly diagnosed diabetes, while benefits were limited in those with long-standing type 2 diabetes. This finding suggests that general practitioners may need to adjust their approaches according to disease duration, offering additional or alternative strategies for people with established diabetes compared to people with a recent diagnosis. Another important consideration concerns the German context. The absence of trials performed in Germany raises questions about the applicability of CCM-based interventions within the German DMPs for type 2 diabetes. While these programmes already incorporate some elements of the CCM, there is limited evidence on whether fully integrating all six components would further improve patient outcomes. As an example, a current pragmatic randomised controlled trial will address the effectiveness of peer-support groups and telephone-based coaching as additional elements to the German DMPs to enhance patient self-management (217). Another key consideration for German chronic disease management is the role of health literacy and patient engagement. Baumert et al. reported that German people with type 2 diabetes, particularly women and older people, often rate the quality of their diabetes care as “moderate” (218). Moreover, people rated the quality of diabetes care to be poorer with increasing population size in their residential area. These results reinforce the need for a patient-centred approach in primary care, where general practitioners can play an active role in supporting and advancing patient self-management using approaches such as structured education, motivational interviewing and shared decision-making.

From an organisational perspective, our review also pointed out challenges in standardising and evaluating complex interventions across different healthcare settings. German general practice is quite heterogeneous, with wide variations in practice size, staff and resources. While projections of diabetes prevalence suggest its burden will continue to rise in Germany (219), growing demands will be placed on general practitioners. This underlines the importance of integrating CCM-principles into primary care in a way that is scalable and adaptable to the different practice environments.

Finally, our review findings showed that effects on long-term cardiovascular and microvascular outcomes remain unclear. Evidence from the Steno-2 study (220) demonstrated that multifactorial interventions can significantly lower cardiovascular- and mortality risks over time. However, similar long-term benefits have yet to be replicated in real-world primary care settings, indicating the need for further research.

Diabetes complications

The findings from our analyses in the KORA F4 Study on clinical DSPN underscore the critical role of general practitioners in the prevention and early detection of diabetes-related complications. The high prevalence of undiagnosed clinical DSPN among both individuals with IFG-IGT (prediabetes) as well as with diabetes indicates that current screening efforts in primary care may not fully capture the burden of this debilitating condition. This is particularly relevant for general practitioners, since they serve as the first point of contact for most people with type 2 diabetes and have a responsibility in implementing structured chronic disease management strategies (221, 222). Furthermore, our observation that individuals with IFG-IGT appeared to be at a comparable risk for DSPN as those with established diabetes, suggests that prediabetes, which is often monitored less intensively than overt diabetes, may in fact require greater attention in routine primary care. Given that DSPN is a strong predictor for diabetic foot ulcers, early identification of prediabetes and attention to foot care at this stage may be an important step in preventing of later-stage complications (223, 224). While the general practitioner remains central in screening and managing clinical DSPN, effective prevention measures may also require the timely referral to specialists or coordination of multidisciplinary care for patients at particularly high risk (225).

The KORA F4 Study further indicated that a significant proportion of people with diabetes and clinical DSPN remained undiagnosed with DSPN, despite receiving regular diabetes care. This suggests that, despite guideline recommendations that emphasise foot care and regular foot examinations, systemic and practical barriers in general practice hamper adherence to the guidelines. Such barriers may include time constraints during consultations, limited training of general practitioners and their practice teams regarding neurological examination techniques, and a prioritisation of other diabetes-

related issues during consultations, such as patients' lifestyle, glycaemic control, or cardiovascular risk management. The high rates of undiagnosed DSPN highlight a broader issue relevant for the management of other diabetes-related complications, too, namely, that complications with an insidious onset and gradual progression may not receive adequate attention until significant symptoms present. Increasing the awareness of long-term diabetes complications among both patients and physicians could reinforce and optimise the comprehensive and systematic screening efforts in routine diabetes care and help ensure earlier detection and intervention.

Pharmacological treatment of type 2 diabetes

The findings from the studies we performed within the German GePaRD database (226) and the global DISCOVER cohort (198) on glucose-lowering treatment of people of type 2 diabetes offer insights relevant for general practice, particularly as they touch upon dispensation trends, adherence to national and international guidelines, and challenges in providing individualised care.

One important observation concerns the shift in dispensing from sulfonylureas to DPP-4 inhibitors. This change aligns with concerns about risk of hypoglycaemia, weight gain, and cardiovascular safety, all factors that are increasingly emphasised in modern diabetes care (76, 201). For general practice in Germany, this trend reflects the broader goals of the DMPs for diabetes, which emphasise evidence-based and individualised treatment (227). Unfortunately, since our study was not designed to uncover patterns between dispensation behaviour and patient characteristics such as prevalent macrovascular disease or depression, we were not able to draw any conclusions on the potential drivers of prescribing behaviour. Another key observation was that over two-thirds of people newly diagnosed with type 2 diabetes did not receive pharmacological treatment within the first year. While this may reflect a guideline-driven approach prioritising lifestyle interventions before starting pharmacotherapy, we found that the relatively high percentage of people receiving non-pharmacological therapy in the year after their diagnosis were on average five years older, were less often obese, were more often diagnosed with dyslipidaemia and taking statins, and less often had the German nationality compared to those who did receive pharmacological treatment. While it remains unclear how well people receiving non-pharmacological therapy for type 2 diabetes are monitored in general practice, there is a risk that suboptimal glycaemic control remains unaddressed longer than intended, particularly if follow-up is inconsistent.

Another major finding from our studies was the high proportion of older adults with type 2 diabetes who are potentially overtreated, with many of them continuing on intensive glucose-lowering therapy despite already having an HbA1c below 7.0% (198). For older adults, strict glycaemic control can be harmful, as aggressive therapy increases the risk of hypoglycaemia, falls, and polypharmacy-related

complications (228, 229). This issue is highly relevant for general practitioners, who are often the primary prescribers and long-term care coordinators for older people with type 2 diabetes. Despite guideline recommendations to relax glycaemic target values for older patients with poor health and multiple coexisting chronic diseases, or with moderate functional or cognitive decline (230), de-intensification of therapy remains underutilized (231, 232). Several factors may explain this. Literature suggests that general practitioners and other healthcare professionals who treat people with diabetes may face (practical) challenges in adjusting pharmacotherapy to patient complexity (232, 233). These challenges may include limited consultation time, underreporting of hypoglycaemia by patients, a lack of clear decision-support tools for individualised de-intensification of treatment, and patients and their families', as well as doctors', ambivalence regarding deprescribing. A patient's expectations and concerns about treatment withdrawal subsequently require general practitioners to engage in careful shared-decision-making.

The question remains whether Germany's structured DMPs for diabetes sufficiently address the potential need for treatment de-intensification in older adults. While the DMPs focus on monitoring metabolic control, cardiovascular risk factors and diabetes complications, there may be less emphasis on identifying and addressing overtreatment (227). This presents an opportunity for further refinement of these programmes to integrate systematic medication reviews and deprescribing strategies for older patients at risk of hypoglycaemia and polypharmacy.

Strategies for personalised diabetes care

The increasing recognition that type 2 diabetes is a heterogeneous disease (234, 235), underlined by our study within the global DISCOVER cohort characterizing distinct HbA1c trajectories following the initiation of second-line therapy (209), has the potential to increase the focus on personalised treatment in general practice. In Germany, DMPs for type 2 diabetes are designed to provide structured, guideline-based care (227, 236), but they largely rely on standardised treatment algorithms that may not fully account for the heterogeneity in treatment responses observed in real-world settings. The findings from our study on HbA1c trajectory analyses suggest that certain patients, such as those with persistent poor glycaemic control despite treatment intensification, may represent a metabolically distinct subgroup that could benefit from earlier therapeutic adjustments or alternative strategies to improve adherence. Similar suggestions about guidance of treatment decisions and avoidance of premature treatment intensifications, in those who might benefit from alternative strategies, have been posed previously (237, 238). With regard to German DMPs, these insights underscore the need for a greater flexibility in treatment protocols.

In German general practice, shared decision-making between physicians and patients is an important tool for treatment individualization (239), and there are conceivable practical barriers to implementing subgroup-based treatment strategies, including limited consultation time and lack of access to advanced phenotyping tools (240). Also, pharmacogenetic testing to aid the selection of an optimal diabetes treatment for the individual patient is not yet part of routine primary care. Although genetic stratification for optimising treatment has not yet demonstrated clear clinical benefit (241), genotyping costs are currently high and decision-support tools for integrating genetic markers into the choice of a specific glucose-lowering drug based on individual patient characteristics are not yet available (242).

Although the immediate clinical implications of identifying distinct diabetes subtypes and pharmacogenomics are still evolving, opportunities for optimising diabetes treatment already exist through the integration of more flexible treatment algorithms that allow for individualised glycaemic targets and treatment de-intensification in older or frail people with type 2 diabetes. Yet, current DMPs strongly emphasise standardisation and may not explicitly account for diabetes heterogeneity (227, 239). While structured protocols improve the quality of care overall, the challenge for general practice is to balance the adherence to guidelines with personalised care, ensuring that patients receive a therapy that is aligned with their metabolic profile, comorbidities, and their personal needs and treatment goals.

4.3 Implications for future research

In line with the structure in the previous section 4.2, the current section will address the implications of the studies described in chapter 3 for future research, with specific focus on general practice.

Multifaceted care for type 2 diabetes

The findings from our systematic review of the primary care-based CCM highlight several research priorities that are directly relevant to general practice in Germany. At present, there is no trial explicitly evaluating multifaceted care according to the CCM within the setting of German general practice. This represents a clear research gap and future research should investigate how structured, multicomponent care models compare with care provided according to standard DMPs. Attention should be placed, among other aspects, on healthcare utilization, cost-effectiveness, and long-term patient outcomes. Given that the burden of diabetes-related morbidity in Europe will steadily increase in the coming years (243), future longitudinal studies should assess whether structured care programmes not only provide benefits in terms of glycaemic control, but also long-term patient

outcomes such as reducing complications and increasing quality of life. Given the high healthcare costs associated with diabetes, the need for cost-effective strategies is emphasised (244). Studies should therefore explore whether implementing the full CCM in German DMPs is financially sustainable and whether such an approach could lead to measurable cost savings in terms of, for example, reductions in hospitalizations and complications. Finally, given that our review has indicated that effectiveness of the CCM varied depending on diabetes duration, future research should further explore which (combinations of) components of the CCM provide optimal care for people at different stages of type 2 diabetes.

Diabetes complications

Our studies into the prevalence of (unknown) clinical DSPN in Germany suggest several directions for future research in clinical practice. While regular foot examinations are already recommended as part of German DMPs for diabetes, our findings suggest that adherence to these recommendations is variable and that many cases of DSPN remain undetected in routine practice.

Future research could therefore investigate whether, for example, structured protocols for foot examinations, additional training for general practitioners and their practice teams, or digital reminders within electronic medical records might improve the detection rates for clinical DSPN. To better understand the reasons for underdiagnosis, future studies could explore the practical barriers that may prevent general practitioners from consistently conducting foot examinations. These barriers may include competing priorities, lack of confidence in using specific diagnostic tools, and limited consultation time. Qualitative research methods, such as interviews and focus groups with general practitioners, could provide valuable insights into the challenges faced in (German) primary care and inform strategies for overcoming them. Finally, the high proportion of undiagnosed clinical DSPN suggests that both physicians and patients with diabetes may not fully recognize the importance of this complication. This calls for research opportunities to explore if, for example, educational programmes, workshops or continuing medical education activities improve general practitioners' awareness and knowledge of diabetic polyneuropathy, and with that, adherence to screening guidelines. On the patients' side, studies could investigate if and how patient education campaigns can increase awareness of diabetes complications in patients and, consequently, positively influence the self-reporting of symptoms or the participation in foot care to improve early detection rates of clinical DSPN.

Pharmacological treatment of type 2 diabetes

Several key priorities for future research emerged from our research on pharmacological treatment patterns and overtreatment. These priorities specifically address prescribing practices in general practice, barriers to therapy de-intensification, and strategies to optimise personalised care. Future research should not only continue to monitor trends in dispensation or prescription of pharmacological glucose-lowering treatment, but also evaluate the long-term effects of these treatments in primary care settings. While the DMPs for diabetes in Germany emphasise patient-centred care, open questions for research remain as to whether treatment intensification and, equally important, treatment de-intensification strategies are systematically applied in routine general practice (245). Also, future studies should explore in more detail how general practitioners make decisions about increasing or reducing treatment intensity in (older) people, and whether clinical inertia influences (de)-prescribing practices. Like our study, many studies in the existing literature have pointed to the problem of persistent overtreatment despite the well-documented risks of severe hypoglycaemia and polypharmacy in older patients. Future research should therefore evaluate the effectiveness of educational programmes for general practitioners and other healthcare professionals managing diabetes, that are aimed at increasing the awareness of safe glycaemic targets and deprescribing practices. Also, studies could investigate how various clinical decision-support tools, such as electronic prompts, risk calculators, and structured deprescribing checklists, could have a role in optimising personalised treatment and (de)prescribing behaviour (246).

Strategies for personalised diabetes care

The findings from our study on HbA1c trajectories and the growing literature on distinct diabetes subgroups, call for further investigation into how stratified treatment strategies can be implemented in primary care settings, both in Germany and the rest of the world.

Observational studies conducted in real-world general practice settings could help determine whether stratifying people with diabetes based on metabolic characteristics indeed leads to better treatment adherence, lower rates of treatment intensification, and improved glycaemic control. Or, for that matter, if incorporating HbA1c trajectory monitoring in primary care would lead to improved treatment decision-making and to greater patient engagement and adherence. Moving towards more personalised diabetes care will inevitably face general practice with practical challenges, such as time constraints, lack of training, and the need for good digital tools to support individualised treatment decisions. Further research should explore these challenges. Implementation studies should investigate whether general practitioners can effectively integrate HbA1c trajectory analysis or subgroup classification into routine consultations, and how these approaches align with patient

preferences and the realities of primary care. The role of clinical decision-support systems that incorporate data-driven risk stratification should also be evaluated (242).

Regarding pharmacogenetics, current evidence does not yet lend strong support for its routine use in general practice. Nevertheless, future studies should investigate how genetic markers could be integrated into clinical workflows in a feasible and cost-effective manner (241). In addition, it needs to be explored how primary care could play a role in identifying patients who might benefit from genetic testing to help guide the choice of diabetes therapy, particularly for newer agents such as GLP-1 receptor agonists and SGLT-2 inhibitors. Finally, raising awareness among general practitioners about heterogeneity of type 2 diabetes should be a research priority. At present, many educational interventions focus on diabetes management as a whole, with little emphasis on the practical application of stratified treatment approaches in primary care. Research should explore whether targeted training programmes can improve physician confidence in tailoring diabetes treatment, and whether patient engagement strategies such as personalised care plans, can improve long-term treatment adherence and health outcomes (247).

4.4 Concluding remarks

For general practitioners in Germany, the findings from our review on effectiveness of the CCM highlight both opportunities and considerable challenges in optimising diabetes care for their patients. While multifaceted care models have the potential to improve outcomes, their full and successful integration into German general practice requires further research. Key areas that need to be addressed include how these models work in terms of patient subgroup differentiation, the role of behavioural interventions, monitoring long-term outcomes, and the question of economic feasibility. To ensure sustainable and effective management strategies for the growing population of people with type 2 diabetes, it will be essential to address the gaps in adapting multicomponent care models to the everyday reality of primary care settings. Achieving this will require coordinated efforts from research, healthcare management as well as health policy.

Our studies on clinical DSPN highlight the critical role of the general practitioner in identifying and managing diabetes-related complications. While German diabetes care guidelines recommend an annual foot examination, there nevertheless exists a high prevalence of undiagnosed DSPN. Understanding the underlying practical barriers in general practice and raising awareness of complications among physician and patient themselves could imply improvements not only for the detection of diabetic neuropathy, but also of other diabetes complications. These insights emphasise

the importance of systematic, structured screening strategies for complications in routine primary care.

The studies we performed on patterns of pharmacological treatment of type 2 diabetes in Germany showed a shift in dispensation patterns towards safer drug classes. On a global level, however, there remains a persistence of overtreatment of older adults with diabetes, with many continuing intensive therapies despite already having blood glucose levels below the recommended targets. For general practitioners, these findings reinforce the need for patient-centred therapy choices that particularly balance the benefits of glycaemic control against the risk of hypoglycaemia and polypharmacy. Future research should prioritise implementation studies on de-intensification, physician education on the risks of overtreatment, and the integration of clinical decision-support tools in routine care. Understanding how prescribing trends truly align with guideline recommendations will be a key step in optimising diabetes management in primary care.

The identification of distinct diabetes subgroups, whether based on HbA1c trajectories or other metabolic features, has the opportunity to transform diabetes care in general practice in Germany. Future research is then required to focus on evaluating real-world strategies for implementing these findings, particularly in the time-constrained setting of primary care. General practitioners are in a unique position to integrate patient-specific factors into diabetes management, but systematic barriers, such as the limited availability of decision-support tools and rigid guideline structures, need to be addressed before personalised diabetes care can be routinely implemented in general practice. Future research should focus on how stratified diabetes care models can be effectively introduced in primary care, how general practitioners can apply these strategies in routine consultations, and whether pharmacogenetics will eventually become a viable tool for guiding treatment selection. Overcoming these practical barriers and developing reliable decision-support systems will be crucial for moving type 2 diabetes care towards a more personalised precision-medicine approach in Germany.

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APPENDIX 1: Seven original studies

The following section lists and reprints the original publications of the current habilitation thesis. Publication 4 is reproduced with the kind permission of the respective journal publishers. Publications 2 and 3 are open access articles published under the CC BY-NC 3.0 license and publications 1, 5, 6 and 7 under the CC BY-NC 4.0 license.

Publication 1: Bongaerts BWC, Müssig K, Wens J, Lang C, Schwarz P, Roden M, et al. Effectiveness of chronic care models for the management of type 2 diabetes mellitus in Europe: a systematic review and meta-analysis. BMJ open. 2017;7(3):e013076. DOI: 10.1136/bmjopen-2016-013076 (IF: 2.4 in 2017).

Publication 2: Bongaerts BWC, Rathmann W, Kowall B, Herder C, Stöckl D, Meisinger C, et al. Postchallenge hyperglycemia is positively associated with diabetic polyneuropathy: the KORA F4 study. Diabetes Care. 2012;35(9):1891-3. DOI: 10.2337/dc11-2028. DOI: 10.2337/dc11-2028 (IF: 7.7 in 2012).

Publication 3: Bongaerts BWC, Rathmann W, Heier M, Kowall B, Herder C, Stöckl D, et al. Older subjects with diabetes and prediabetes are frequently unaware of having distal sensorimotor polyneuropathy: the KORA F4 study. Diabetes Care. 2013;36(5):1141-6. DOI: 10.2337/dc12-0744. DOI: 10.2337/dc12-0744 (IF: 8.6 in 2013).

Publication 4: Bongaerts B, Kollhorst B, Kuss O, Pigeot I, Rathmann W. Dispensation Patterns of Glucose-Lowering Drugs in Newly Diagnosed Type 2 Diabetes: Routine Data Analysis of Insurance Claims in Germany. Experimental and Clinical Endocrinology & Diabetes. 2022;130(09):587-95. DOI: 10.1055/a-1702-5151. DOI: 10.1055/a-1702-5151 (IF: 1.8 in 2022).

Publication 5: Bongaerts B, Arnold SV, Charbonnel BH, Chen H, Cooper A, Fenici P, et al. Inappropriate intensification of glucose-lowering treatment in older patients with type 2 diabetes: the global DISCOVER study. BMJ Open Diabetes Research and Care. 2021;9(1):e001585.A. DOI: 10.1136/bmjdrc-2020-001585 (IF: 4.2 in 2021).

Publication 6: Bongaerts B, Kuss O, Bonnet F, Chen H, Cooper A, Fenici P, et al. HbA1c trajectories over 3 years in people with type 2 diabetes starting second-line glucose-lowering therapy: The prospective global DISCOVER study. Diabetes, Obesity and Metabolism. 2023;25(7):1890-9. DOI: 10.1111/dom.15050 (IF: 5.4 in 2023).

Publication 7: Rathmann W, Bongaerts B. Pharmacogenetics of novel glucose-lowering drugs. Diabetologia. 2021;64:1201-12. DOI: 10.1007/s00125-021-05402-w (IF: 10.4 in 2021).

BMJ Open

Effectiveness of chronic care models for the management of type 2 diabetes mellitus in Europe: a systematic review and meta-analysis

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ABSTRACT

Objectives: We evaluated the effectiveness of European chronic care programmes for type 2 diabetes mellitus (characterised by integrative care and a multicomponent framework for enhancing healthcare delivery), compared with usual diabetes care.

Design: Systematic review and meta-analysis.

Data sources: MEDLINE, Embase, CENTRAL and CINAHL from January 2000 to July 2015.

Eligibility criteria: Randomised controlled trials focussing on (1) adults with type 2 diabetes, (2) multifaceted diabetes care interventions specifically designed for type 2 diabetes and delivered in primary or secondary care, targeting patient, physician and healthcare organisation and (3) usual diabetes care as the control intervention.

Data extraction: Study characteristics, characteristics of the intervention, data on baseline demographics and changes in patient outcomes.

Data analysis: Weighted mean differences in change in HbA1c and total cholesterol levels between intervention and control patients (95% CI) were estimated using a random-effects model.

Results: Eight cluster randomised controlled trials were identified for inclusion (9529 patients). One year of multifaceted care improved HbA1c levels in patients with screen-detected and newly diagnosed diabetes, but not in patients with prevalent diabetes, compared to usual diabetes care. Across all seven included trials, the weighted mean difference in HbA1c change was −0.07% (95% CI −0.10 to −0.04) (−0.8 mmol/mol (95% CI −1.1 to −0.4)); I^2=21%. The findings for total cholesterol, LDL-cholesterol and blood pressure were similar to HbA1c, albeit statistical heterogeneity between studies was considerably larger. Compared to usual care, multifaceted care did not significantly change quality of life of the diabetes patient. Finally, measured for screen-detected diabetes only, the risk of macrovascular and mircovascular complications at follow-up was not significantly different between intervention and control patients.

Conclusions: Effects of European multifaceted diabetes care patient outcomes are only small. Improvements are somewhat larger for screen-detected and newly diagnosed diabetes patients than for patients with prevalent diabetes.

Strengths and limitations of this study

- This is the first systematic review providing a comprehensive overview of studies that have evaluated the effectiveness of multifaceted diabetes care programmes addressing all their components together, rather than separately.
- The focus in this systematic review was on European multifaceted diabetes care programmes only, to meet the need for efficient and established programmes to providing optimal chronic care due to the burden of increasing diabetes prevalence in Europe.
- There is an important lack of studies which evaluate the effectiveness of implementing all chronic care model-components simultaneously.
- Overall, the studies included in this systematic review provided insufficient details to fully understand the intensity of the intervention, and there was only little overlap in the wide range of outcome measures evaluated.

INTRODUCTION

Chronic disease management relies on the assumption that providing optimal chronic care requires changes of patients and professionals with regard to behaviour, culture, and communication.[1 2] Indeed, with ageing of the population and the growing prevalence of chronic diseases, initiatives to improving quality of chronic care require more than evidence about effective diagnostic procedures and treatments in comparison to acute disorders.[3] Aimed at describing essential elements for improving outcomes in care of chronic diseases, the chronic care model (CCM) was developed in the mid-1990s and

was further refined in 1997.[2 4 5] This primary care-based model is based on the assumption that improvements in care require an approach that incorporates patients, healthcare providers and system level interventions.[4 6] The CCM comprises six interrelated components deemed essential for providing high-quality care to patients with chronic disease: (1) healthcare organisation (ie, providing leadership for securing resources and removing barriers to care), (2) self-management support (ie, facilitating skills-based learning and patient empowerment), (3) decision support (ie, providing guidance for implementing evidence-based care), (4) delivery system design (ie, coordinating care processes), (5) clinical information systems (ie, tracking progress through reporting outcomes to patients and providers and (6) community resources and policies (ie, sustaining care by using community-based resources and public health policy).[7]

The current literature indicates a widespread application of the CCM to multiple illnesses, and various studies have provided a rigorous evaluation of its individual components.[5 8–14] In general, these studies have reported positive effects on patient outcomes and processes of care. The reported effect sizes, however, are relatively small, and many outcomes are flawed by a considerable level of statistical heterogeneity.[10 13–25]

An aspect that complicates the assessment of effectiveness of chronic care programmes is their inherent multicomponent nature.[14 20 25] While some authors found that the total number of CCM elements incorporated in the interventions did not influence patient outcomes,[9 10] others concluded that interventions containing more than one CCM component were more successful at improving the quality of care than single-component interventions.[11 24 26 27]

To date, no summative reviews have evaluated to which extent the complete CCM—thus all six components combined in interventions—improves diabetes care.

As such, the aim of the current review was to systematically identify studies of diabetes care assessing the effect of interventions addressing all six components of the CCM. We subsequently aimed to pool the effect of these models on biochemical outcomes (HbA1c, cholesterol levels, blood pressure, body mass index (BMI), fasting glucose, triglyceride and creatinine levels), patient-reported outcomes (health-related quality of life) and diabetes complications (macrovascular and microvascular complications, hypoglycaemia, cardiovascular risk, medication use and processes of care) in adult patients with type 2 diabetes compared to usual diabetes care by means of a meta-analysis.

METHODS

Our systematic review was based on a protocol with input from experts in diabetes care, statistical methods and primary care. The protocol was composed according to the PRISMA-P guidelines (see online supplementary file S1).[28]

Data sources and searches

We identified studies by searching MEDLINE, Embase, CINAHL and CENTRAL from January 2000 until July 2015. Search syntaxes were developed in consultation with the Cochrane Metabolic and Endocrine Disorders Group by adapting and combining published search strategies from previous systematic reviews on chronic (diabetes) care management.[10 12] Given that the CCM—and its terminology—had been introduced in the late 1990s, we restricted the search to publications from January 2000 onwards. In addition, reference lists of eligible studies and systematic reviews on multifaceted diabetes care were searched by hand to identify additional studies. The full MEDLINE search strategy is available in the online supplementary file S2.

Study selection

One reviewer (BWCB) identified potentially relevant studies for inclusion by screening title and abstract of all citations that resulted from our literature search. Two reviewers (BWCB and WR) then screened the full text of these articles. Only randomised controlled trials were considered eligible for inclusion. Non-randomised studies were excluded, as were studies written in a language other than English. Since this systematic review was part of a large European project on managed diabetes care that aimed at developing chronic care management standards and guidance for Europe,[29] we further excluded all non-European CCM trials. Trials eligible for inclusion had to comply with the following inclusion criteria.

Type of participants

Individuals, regardless of gender and ethnicity, diagnosed with type 2 diabetes and with or without comorbidities.

Type of intervention

Previous systematic reviews on multifaceted chronic care have reported that randomised-controlled-trial-interventions are generally described poorly and incomprehensively, which complicates mapping the individual elements of the intervention to the six CCM components. To avoid mapping difficulties, we have reformulated the following inclusion criteria for the interventions: The intervention had to be described as a multifaceted CCM or programme that (1) was designed specifically for individuals with type 2 diabetes, (2) was based on guidelines, (3) provided multidisciplinary care, (4) addressed patient empowerment, (5) provided quality management (eg, patient registry systems, recording of process measurements and adherence to guidelines, achievement of treatment goals), (6) was delivered in primary or secondary care and (7) had a minimum duration of 6 months. The control intervention had to

be defined as usual diabetes care as recommended in that particular country (eg, regular follow-up with the required health professional and a full diabetes annual review).

Type of outcome measures

We considered three categories of outcome measures: (1) biochemical outcomes, including HbA1c, cholesterol levels, blood pressure, BMI, fasting glucose, triglyceride and creatinine levels, (2) patient-reported outcomes, including health-related quality of life, and (3) diabetes complications, including macrovascular and microvascular complications, hypoglycaemia, cardiovascular risk, medication use and processes of care.

Any disagreements between the two reviewers regarding the inclusion or exclusion of studies were resolved by consensus.

Data extraction and quality assessment

Using a standard structured data abstraction form, one reviewer (BWCB) performed the data extraction which was confirmed by a second reviewer (WR). The extracted data included study design, length of intervention/follow-up, sample size, inclusion and exclusion criteria, mean or median age of the included sample, percentage males, study setting (ie, primary or secondary care), intervention details and mean differences in change for various outcomes. When important information or outcome data were missing, trial authors of the included studies were contacted. When unavailable, the particular data were not included in the analyses.

The standard Cochrane EPOC Risk of Bias Tool was used to assess risk of bias for each of the selected studies.[30] Since all included studies were cluster-randomised controlled trials, additional attention was given to potential sources of bias specific to cluster-randomised trials: (1) recruitment bias: did recruitment of diabetes patients take place before or after randomisation of the clusters?, (2) did the intervention and control group differ in baseline characteristics?, (3) did any of the clusters drop out during follow-up?, (4) was clustering accounted for in the statistical analyses? If a certain domain could not be classified as 'high' or 'low' risk of bias due to inadequate reporting, it was deemed 'unclear' risk of bias.

Data synthesis and analysis

Owing to heterogeneity of the study populations and duration of the interventions, and owing to the small overlap in outcomes of the individual trials, an extensive meta-analysis and meta-regression of all reported outcome variables was not possible. The available data only allowed to statistically pool the results for HbA1c concentrations and total cholesterol levels. Review Manager (RevMan 5.2.0; the Cochrane Collaboration) was used to compute the weighted mean difference in change in HbA1c and total cholesterol between intervention and control groups, employing the generic inverse variance method. To incorporate between-study and within-study variance, we used a random effects model for estimating the weighted mean differences in change between intervention and control group across the included trials.[31] Mean differences were pooled separately for the different types of diabetes patients (prevalent, screen-detected and newly diagnosed), and subsequently for the entire patient population. The consistency of the findings across the studies was assessed using forest plots. We evaluated statistical heterogeneity by calculating the I^2 statistic, a measure independent of the number of studies and effect size metric.[32] All outcome variables other than HbA1c and total cholesterol, we analysed descriptively.

RESULTS

Figure 1 summarises the identification of relevant studies and the numbers of excluded and included studies. The search of the electronic databases identified 9464 abstracts of studies published between January 2000 and July 2015. After excluding duplicate citations (n=1227) and studies unrelated to the current review''s topic (n=7801), we considered 436 articles for full-text review. Of these, 424 studies failed to meet our explicit inclusion criteria. In total, 12 articles met our inclusion criteria and were included in the current review.[33–44] No relevant studies were retrieved by hand-search.

Study characteristics

The 12 included articles[33–44] reported on eight unique cluster randomised controlled trials,[33 35 39–41 43–45]

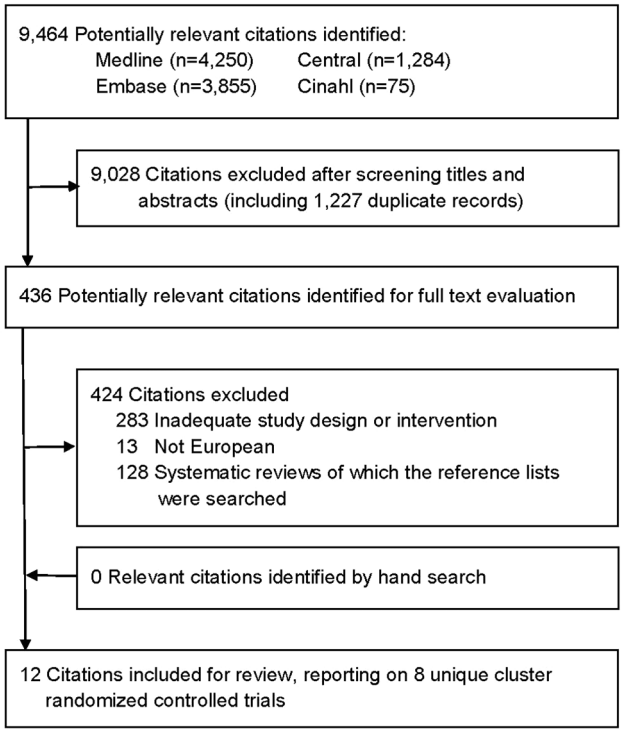

Figure 1 Flow chart summarising the identification of studies for inclusion in the review.

carried out between 1989 and 2011. Two of these trials, Addition-Denmark[40] and Addition-Cambridge,[35] had not individually reported any follow-up results in sequel to their study protocols. Their 5-year data however were pooled in the Addition-Europe study[46] together with the 5-year data of the Addition-Netherlands[39] and Addition-Leicester[43] trials. For the remainder of the 'Methods' section, we will describe the design features and assess risk of bias for the Addition-Denmark and Addition-Cambridge trials based on their published protocol, yet for the 'Results' section we will have to resort to the pooled five-year data from the Addition-Europe study. This means that although we identified eight unique trials,[33 35 39–41 43–45] there are just seven publications to extract data from.[33 39 41 43–46]

All trials had recruited either general practitioners or physician practices which represented the cluster level (level of randomisation). In one study,[45] however, first-level clusters were formed by district (characterised as urban, rural and mixed) and second-level clusters by the physicians. The total number of patients with type 2 diabetes enrolled by the physicians amounted to 9529, of whom 8921 (94%) had been included in the analyses.

The objective of each trial was the structured multifaceted management of diabetes, and the interventions were aimed at improving the patients' cardiovascular risk profile[44 45] and metabolic control,[33 35 39 40 43 44] and assessing the effect of multifaceted care on the occurrence of cardiovascular events,[35 39 40 43] overall mortality[41] and risk factors for clinical complications.[41] Interventions focused on all aspects of the CCM including more regular and frequent consultations, annual screening for diabetes complications, patient education/advice, guideline-based clinical treatment and physician education, regular/annual feedback reports to physicians, referrals, record keeping, formation of multidisciplinary (primary care provider) teams, delegation of routine diabetes tasks to a trained practice nurse, patient and physician reminders and patient–physician communication and decision-making. The interventions were largely delivered by general practitioners and physicians, yet specialised nurses or practice nurses were also involved in the intervention-programme as part of the practice team and to (partly) replace the physician in providing diabetes care.[33 35 39 40 43 44]

Two main aspects differed among the trials: the type of diabetes patient enrolled and the duration of the intervention. Three trials[33 44 45] had included patients with prevalent diabetes and intervened for 1-year. The average diabetes duration in these studies ranged from 5.8 to 9.5 years. One trial[41] had enrolled patients with newly diagnosed type 2 diabetes and assessed outcome measures after 6 years of intervention. Finally, there were four trials[35 39 40 43] that first had initiated a diabetes screening programme and subsequently had recruited those with screen-detected diabetes to participate in the intervention study. Follow-up measurements were assessed at 1-year and at 5 years. Table 1 presents an overview of interventions and findings of the included publications. Tables 2 and 3 present the baseline patient characteristics for the trials that recruited patients with prevalent diabetes[33 44 45] and for the trials that recruited patients with screen-detected[39 43 46] and newly diagnosed diabetes,[41] respectively.

Data quality assessment

Figure 2 summarises the risk of bias for the trials included in this review. Although the Addition-Denmark[40] and the Addition-Cambridge[35] trials had not published 1-year data, they did provide 5-year data for the Addition-Europe meta-analysis[46] and were thus included in the risk of bias assessment. However, since not having published actual trial data, we could not assess the domains of incomplete outcome data, selective reporting and other bias, which resulted in the occurrence of blanks in figure 2.

Seven trials had at least one domain judged as unclear risk of bias. Five trials had at least one domain judged as high risk of bias. Only one study[44] had explicitly described that their physicians were unaware of being allocated to the intervention or control group when recruiting eligible patients. For the remaining studies, prior knowledge of treatment allocation cannot be ruled out (recruitment bias). Furthermore, the Addition studies[35 39 40 43] were the only trials in which patients remained unaware of group assignment throughout the study.

In four studies,[35 39 40 43] outcome assessment was performed completely blinded for patient allocation. In one study,[45] only laboratory outcomes were assessed blinded, whereas clinical outcomes were obtained by contacting the general practitioner, introducing possible bias. No substantial baseline differences between the intervention and control groups existed with regard to the outcomes of interest.

Biochemical outcomes

All studies had assessed biochemical outcomes at follow-up, including HbA1c level, blood lipid levels, blood pressure and BMI.

HbA1c levels

All studies assessed HbA1c values at follow-up. For six[33 39 43–46] of the seven study populations glycaemic control at baseline was moderate to good, as expressed by the mean HbA1c concentrations ranging from 7.0 to 7.8% (53 to 62 mmol/mol). The three trials with prevalent type 2 diabetes patients[33 44 45] observed no statistically significant difference in change in HbA1c levels between the intervention and control group after 1-year of intervention (figure 3). There was no statistical heterogeneity between these three trials (I^2=0%) and the weighted mean difference in change between intervention and control groups was −0.06% (95% CI −0.13 to 0.01) (−0.7 mmol/mol (95% CI −1.4 to 0.1)), in favour of the intervention group. Using a similarly short

Table 1 Characteristics of the included cluster randomised controlled trials

Study	Comparison	Effect on end points*	Notes
Cleveringa *et al.* (2008)[33]	Intervention: Patient consultation by a practice nurse +use of a computerised decision support system +guideline-based care+physician support by practice nurse+interdisciplinary care by a specialist team +individualised treatment advice+patient education +physician feedback+recall system+regular patient consultations by practice nurse+physician feedback versus Usual diabetes care (not further specified)	*Biochemical outcomes* HbA1c (0) Total cholesterol (+, i) HDL-cholesterol (0) LDL-cholesterol (+, i) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) 10-year CHD risk (+, i) *Diabetes complications and processes of care* HbA1c below target value† (+, i) Total cholesterol below target value† (+, i) LDL-cholesterol below target value† (+, i) Systolic blood pressure below target value† (+, i) All treatment targets reached† (+, i)	At baseline, patients in the intervention group had higher HDL-cholesterol levels, were more often smoker and more often had a history of CHD. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between the intervention and control group were adjusted for cluster structure.
Sönnichsen *et al.* (2008)[45]	Intervention: Physician education+guideline-based care+patient education+use of a clinical information system tool+interdisciplinary care by a specialist team +patient reminders+physician reminders+goal setting +shared decision-making patient and physician +regular consultations versus Usual diabetes care (not further specified)	*Biochemical outcomes* HbA1c (0) Total cholesterol (+, i) HDL-cholesterol (0) LDL-cholesterol (0) Systolic blood pressure (0) Diastolic blood pressure (0) Body mass index (+, i) Triglycerides (0) Creatinine (0) *Diabetes complications and processes of care* To the guidelines adherent: – number of eye examinations† (+, i) – number of foot examinations† (+, i) – provision of patient education† (+, i) – regular HbA1c checks† (+, i)	At baseline, patients in the intervention group had a higher BMI and higher cholesterol levels than patients in the control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between the intervention and control groups were adjusted for cluster structure and baseline characteristics.
Frei *et al.* (2010)[44]	Intervention: Specialist team involving a practice nurse +practice nurse education+physician education +physician support by practice nurse+regular independent patient consultations by practice nurse +use of a clinical information system tool +guideline-based care+physician feedback+patient information leaflets+self-management support for patient+patient treatment groups versus Usual diabetes care (not further specified)	*Biochemical outcomes* HbA1c (0) Total cholesterol (0) HDL-cholesterol (0) LDL-cholesterol (+, i) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (0) Fasting blood glucose (0) *Patient-reported outcomes* *Diabetes complications and processes of care* Number GP visits† (0) Change in antidiabetic therapy (0) Change in antihypertensive therapy (0) Change in lipid-lowering therapy (0)	There were no baseline differences in patient characteristics between intervention and control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between intervention and control group were adjusted for cluster structure and baseline characteristics.

Continued

Table 1 Continued

Study	Comparison	Effect on end points*	Notes
Webb *et al.* (2010)[43]	Intervention: Structured patient education+lifestyle advice and self-management with ongoing (bimonthly) professional support+individualised management +guideline-based care+shared decision-making patient and healthcare professional+annual screening for diabetic complications+care delivered by a specialist team (specialty doctor, diabetes nurse educator, and a dietician)+patient reminders+physician reminders versus Usual diabetes care (not further specified)	*Biochemical outcomes* HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (+, i) Weight (+, i) Waist circumference (0) Triglycerides (0) 5-year CHD risk (+, i) 5-year CVD risk (+, i) *Patient-reported outcomes* Health-related quality of life (0) *Diabetes complications and processes of care* Hypoglycaemia† (+, i) Use of antihypertensive drugs† (+, i) Use of lipid-lowering drugs† (+, i) Use of antiplatelet therapy† (+, i) Use of metformin† (0) Use of sulfonylurea† (0)	At baseline, more patients in the intervention group were taking antihypertensive medication when entering the study and had higher total and LDL-cholesterol levels. Statistical analyses were conducted by intention-to-treat. It was not reported whether or not data were missing and how missing data were handled. Comparisons between intervention and control group were adjusted for cluster structure and baseline characteristics (except quality of life which had not been measured at baseline).
Janssen *et al.* (2009)[39]	Intervention: Physician education+diabetes nurse education+lifestyle advice+guideline based care +physician support by diabetes nurse+evaluation and feed-back sessions diabetes nurse+frequent patient consultations with diabetes nurse+shared decision-making patient, physician and diabetes nurse +physician reminders+patient reminders versus Usual diabetes care (not further specified)	*Biochemical outcomes*HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (+, i) Fasting blood glucose (+, i) Triglycerides (0) *Patient-reported outcomes* Health-related quality of life (0) *Diabetes complications and processes of care* Hypoglycaemia† (0)	There were no baseline differences in patient characteristics between the intervention and control group. Statistical analyses were conducted by intention-to-treat and for missing follow-up data the last observation was carried forward. Comparisons between the intervention and control group were adjusted for baseline characteristics, and clustering at practice level.
Griffin *et al.* (2011)[46]	This study combined the data after five years of a multifaceted care intervention from the (1) Addition-Denmark study (Lauritzen *et al*[40]), (2) the Addition-Netherlands study (Janssen *et al*[39]), (3) the Addition-Cambridge study (Echouffo *et al*[35]) and (4) the Addition-Leicester study (Webb *et al*[43]) in a meta-analysis.	*Biochemical outcomes* HbA1c (+, i) Total cholesterol (+, i) LDL-cholesterol (+, i) HDL-cholesterol (0) Systolic blood pressure (+, i) Diastolic blood pressure (+, i) Body mass index (0) Weight (0) Waist circumference (0) Triglycerides (0)	Baseline characteristics were well matched between intervention and control group. In Denmark however, more patients were identified in practices assigned to the intervention arm then in those assigned to control arm. And in the intervention group, more patients had a history of ischaemic heart disease. Statistical analyses were conducted by intention-to-treat and patients with missing outcome values at baseline were excluded from the analyses. Those with missing outcome

Continued

Table 1 Continued

Study	Comparison	Effect on end points*	Notes
		Creatinine (+, c) *Patient-reported outcomes* Health-related quality of life (0) *Diabetes complications and processes of care* All-cause mortality (0) CVD mortality (0) Myocardial infarction (0) Stroke (0) Revascularisation procedures (0) Hypoglycaemia† (0) Meeting target values for: HbA1c (+, i) Blood pressure (+, i) Total cholesterol (+, i) Use of any glucose-lowering drugs (+, i) Change in any antihypertensive drugs (+, i) Change in any cholesterol-lowering drugs (+, i)	baseline values were included according to the missing indicator method. Comparisons between intervention and control group were adjusted for cluster structure and baseline characteristics.
Olivarius *et al.* (2001)[41]	Intervention: Patient follow-up every three months +annual screening for diabetes complications+shared decision-making patient and physician+physician feedback+goal setting+clinical guidelines+physician education+patient leaflets and folders+lifestyle advise +protocol based care+physician recall system versus Usual diabetes care (not further specified)	*Biochemical outcomes* HbA1c (+, i) Total cholesterol (+, i) Systolic blood pressure (+, i) Diastolic blood pressure (0) Weight (0) Fasting blood glucose (+, i) Triglycerides (0) Creatinine (0) *Diabetes complications and processes of care* Overall mortality† (0) Severe hypoglycaemia† (0) Diabetic retinopathy† (0) Non-fatal myocardial infarction† (0) Non-fatal stroke† (0) Peripheral neuropathy† (0) Microalbuminuria† (0) Angina pectoris† (0) Intermittent claudication† (0) Number of consultations† (+, i) Number of referrals to diabetes clinic† (−, i) Number of hospital admissions† (0) Use of metformin† (+, i) Use of other glucose-lowering drugs† (0) Use of antihypertensive drugs† (0) Use of lipid-lowering drugs† (0)	At baseline, more patients in the intervention group were excluded because of severe somatic disease than in the control group. Furthermore, occupation and smoking habits differed between the two groups. Statistical analyses were conducted by intention-to-treat. It was not reported whether or not data were missing or how missing data were handled. Comparisons between intervention and control group were adjusted for cluster structure and baseline characteristics.

*+=positive effect; 0=no effect; −=negative effect; i=favouring intervention group; u=favouring control (usual care) group. The effects of the intervention are represented by the difference in change from baseline to follow-up between the intervention and control group.
† The effect of the intervention is represented by a difference in proportions of patients at follow-up between the intervention and control group.
CHD, coronary heart disease; CVD, cardiovascular (heart) disease; GP, general practitioner; T2DM, type 2 diabetes mellitus.

Table 2 Baseline patient characteristics of the included cluster randomised controlled trials studying patients with prevalent diabetes

	Cleveringa *et al*[33] *		Sönnichsen *et al*[45] †		Frei *et al*[44] ‡	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
N	1699	1692	649	840	162	164
Follow-up duration (years)	1	1	1	1	1	1
Type of diabetes patients	Prevalent diabetes		Prevalent diabetes		Prevalent diabetes	
Country	Netherlands		Austria		Switzerland	
Baseline patient characteristics						
Age (years)	65.2±11.3	65.0±11.0	65.4±10.4	65.5±10.4	65.7±10.4	68.3±10.6
Sex (% men)	48.2	49.8	51.0	53.1	54	60
Ethnicity (% Caucasian)	97.7	97.6	–	–	–	–
Diabetes duration (years)	5.8±5.7	5.4±5.8	7.0±6.5		9.5±7.4	10.3±7.8
Current smoking (% yes)	**22.6**	**16.6**	13.4		14	9
Body mass index (kg/m^2)	30.0±5.3	30.2±5.3	**30.4±5.1**	**29.7±4.9**	30.5±5.3	30.7±5.9
Systolic blood pressure (mm Hg)	149±22	149±21	141±19	139±17	140±18	138±17
Diastolic blood pressure (mm Hg)	83±11	82±11	83±11	82±10	83±10	79±10
UKDPS CHD risk (%)	22.5±16.5§	21.7±15.8§	–	–	–	–
HbA1c (%)	7.1±1.3	7.0±1.1	7.46±1.53	7.34±1.31	7.8±1.5	7.6±1.1
Total cholesterol (mmol/L)	5.0±1.0	4.9±1.1	**5.15±1.14**	**5.02±1.09**	5.0±1.2	4.7±1.1
HDL-cholesterol (mmol/L)	**1.36±0.36**	**1.32±0.35**	1.35±0.39	1.32±0.36	1.2±0.3	1.3±0.4
LDL-cholesterol (mmol/L)	2.8±0.92	2.8±0.95	2.87±0.96	2·87±0·91	2·8±1·1	2·5±1·1
Fasting glucose (mmol/L)	8·0±2·4	7·8±2·2	–	–	8·4±2·5	7·7±2·2
Creatinine (μmol/L)	87.5±27.7	85.9±22.5	84.9±30.9	84.9±34.5	–	–
Triglycerides (mmol/L)	1.8±1.1	1.8±1.3	2.14±1.82	2.00±1.73	–	–
Urinary albumin (mg/L)	–	–	–	–	–	–
Quality of life: PCS¶					43.9±10.9	
Quality of life: MCS¶					50.1±11.3	
History of myocardial infarction (%)	**47.1**	**63.3**	8.4		–	–
History of stroke (%)			7.0		–	–
Diabetic retinopathy (%)	2.9	3.3	-	-	9.3	8.1
Peripheral neuropathy (%)	–	–	–	–	18.6	13.4

Values are mean±sd, or percentages. Bold font indicates that the particular baseline characteristic differed statistically significantly between the intervention and control group.
*The information on BMI, fasting glucose, creatinine, triglycerides and retinopathy was obtained through contacting the authors.
†The information on diabetes duration, smoking, history of myocardial infarction and history of stroke was obtained from the publication describing baseline characteristics of the total study population and stratified by sex (Flamm *et al*[60]).
‡The quality of life summary scores for the physical and mental component were obtained from the publication describing baseline characteristics of the total study population (Frei *et al*[61]). Peripheral neuropathy is represented by 'pathological foot status' and diabetic retinopathy is represented by 'annual eye exam: pathological'.
§Values concern the 10-year UKDPS CHD risk.
¶Quality of life was assessed with the 36-item Short Form Health Survey (SF-36).
CHD, coronary heart disease; MCS, Mental Component Summary Score; PCS, Physical Component Summary Score; UKPDS, UK Prospective Diabetes Study.

intervention period, yet studying patients with screen-detected type 2 diabetes, the Addition-Leicester trial[43] observed a significant difference in change in HbA1c between the two trial arms of −0.20% (95% CI −0.32 to −0.08) (−2.2 mmol/mol (95% CI −3.4 to −0.9)). Whereas the Addition-Netherlands authors[39] did not report the actual difference in HbA1c change between the two groups, they stated in their paper that the improvement in HbA1c was significantly better in the intervention group, compared to the control group. The pooled 5-year data from all four Addition-trials[46] showed a somewhat smaller, yet significantly greater improvement in HbA1c concentration in intervention patients, compared to control patients (−0.08% (95% CI −0.14 to −0.02)) (−0.9 mmol/mol (95% CI −1.5 to −0·2)) (figure 3). Finally, the effect of multifaceted care in Danish patients with newly diagnosed diabetes[41] after 6 years of intervention was comparable to that in screen-detected patients after 5 years of intervention[46] (−0.06% (95% CI −0.08 to −0.03)) (−0.7 mmol/mol (95% CI −0.9 to −0.3)).

Pooling all seven trials, multifaceted care improved HbA1c concentration with −0.07% (95% CI −0.10 to −0.04) (−0.8 mmol/mol (95% CI −1.1 to −0.4)) (figure 3). Statistical heterogeneity across the seven trials was small to moderate (I^2=21%).

Cholesterol levels

Figure 4 presents the mean differences in change in total cholesterol levels for all seven trials. Of the three trials that studied prevalent diabetes patients, only the Dutch trial[33] observed multifaceted care to significantly

Table 3 Baseline patient characteristics of the included cluster randomised controlled trials studying patients with screen-detected and newly diagnosed diabetes

	Webb *et al*[43]		Janssen *et al*[39]		Griffin *et al*[46]		Olivarius *et al*[41]	
	Intervention	**Control**	**Intervention**	**Control**	**Intervention**	**Control**	**Intervention**	**Control**
N	146	199	255	243	1678	1379	649	614
Follow-up duration (years)	1	1	1	1	5	5	6	6
Type of diabetes patients	Screen-detected diabetes		Screen-detected diabetes		Screen-detected diabetes		Newly diagnosed diabetes	
Country	UK		Netherlands		UK, Netherlands, Denmark		Denmark	
Baseline patient characteristics								
Age (years)	59.4±10.0	60.0±10.0	60.1±5.4	59.9±5.1	60.3±6.9	60.2±6.8	65.5 (55.3–74.0)	65.3 (56.3–73.5)
Sex (% men)	56.9	58.3	51.8	56.0	58.5	57.3	52.4	53.1
Ethnicity (% Caucasian)	52.7	62.3	98.0	98.7	95.8	93.4	–	–
Diabetes duration (years)	0	0	0	0	0	0	0	0
Current smoking (% yes)	15.2	10.2	26.3	21.4	26.9	27.8	**35.5**	**34.5**
Body mass index (kg/m^2)	31.0±5.9	31.5±5.7	31.2±5.1	30.4±4.6	31.6±5.6	31.6±5.6	29.4 (26.2–33.0)	28.8 (26.0–32.3)
Systolic blood pressure (mm Hg)	145.7±18.5	148.4±20.5	166±23	163±23	148.5±22.1	149.8±21.3	150 (130–164)	148 (130–160)
Diastolic blood pressure (mm Hg)	87.8±10.4	89.5±10.7	90±11	89±10	86.1±11.1	86.5±11.3	85 (80–90)	85 (80–90)
UKPDS CHD risk (%)	8.5±5.8†	9.3±7.1*	–	–	–	–	–	–
HbA1c (%)	7.2±1.5	7.3±1.8	7.3±1.6	7.4±1.7	7.0±1.6	7.0±1.5	10.2 (8.6–11.6)	10.2 (8.7–11.9)
Total cholesterol (mmol/L)	**5.3±1.2**	**5.6±1.3**	5.6±1.1	5.6±1.1	5.5±1.1	5.6±1.2	6.2 (5.4–7.1)	6.2 (5.5–7.2)
HDL-cholesterol (mmol/L)	1.2±0.4	1.2±0.3	1.1±0.4	1.1±0.3	1.2 (1.0–1.5)	1.2 (1.0–1.5)	–	–
LDL-cholesterol (mmol/L)	**3.2±1.0**	**3.5±1.0**	3.7±1.0	3.7±1.0	3.4±1.0	3.5±1.0	–	–
Fasting glucose (mmol/L)	–	–	7.8±2.3	8.1±2.8	–	–	13.8 (10.7–17.0)	13.7 (10.7–17.0)
Creatinine (μmol/L)	–	–	–	–	83.4±17.1	84.9±18.6	90 (81–101)	88 (79–100)
Triglycerides (mmol/L)	2.1±1.9	2.1±1.4	1.9±1.0	2.0±1.6	1.6 (1.2–2.3)	1.7 (1.2–2.4)	2.03 (1.44–2.91)	1.98 (1.39–2.95)
Urinary albumin (mg/L)	–	–	–	–	–	–	11.7 (6.0–32.5)	11.8 (5.7–27.5)
Quality of life: PCS†	39.0 (37.4–40.5)	38.5 (37.1-40.0)	No summary scores reported		–	–	–	–
Quality of life: MCS†	38.2 (35.2–41.2)	39.2 (36.5–41.9)	No summary scores reported		–	–	–	–
History of myocardial infarction (%)	15.8*	10.6‡	–	–	6.8	6.1	6.6	7.7
History of stroke (%)			–	–	2.9	1.9	3.5	4.2
Diabetic retinopathy (%)	–	–	–	–	–	–	5.0	4.5
Peripheral neuropathy (%)	–	–	–	–	–	–	18.8	19.7

Values are mean±sd, or median (IQR) or percentages. Bold font indicates that the comparison between the intervention and control group was statistically significant.
*Values concern the 5-year UKDPS CHD risk.
†Quality of life was assessed with the 12-item Short Form Health Survey (SF-12) in the study by Webb *et al*, and with the 36-item Short Form Health Survey (SF-36) in the study by Janssen *et al*.
‡Defined as 'pre-existing CVD', including myocardial infarction, stroke and angina.
CHD, coronary heart disease; MCS, Mental Component Summary Score; PCS, Physical Component Summary Score; UKPDS, UK Prospective Diabetes Study.

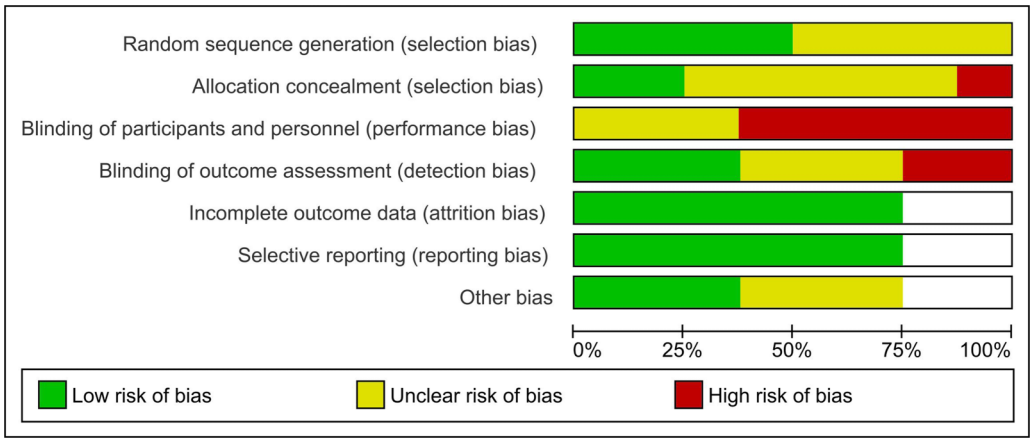

Figure 2 Risk of bias graph. Review authors' judgements about each risk of bias item presented as percentages across all included studies. Studies included are Cleveringa *et al* (2008);[33] Sönnichsen *et al* (2008),[45] Frei *et al* (2010),[44] Olivarius *et al* (2001),[41] Janssen *et al* (2009),[39] Webb *et al* (2010),[43] Lauritzen *et al* (2000)[40] and Echouffo *et al* (2009).[35] The studies from Lauritzen and Echouffo were included in the risk of bias assessment since their 5-year follow-up data had been included in the Addition-Europe meta-analysis by Griffin *et al*.[46] As the Addition-Europe publication only reported pooled data, no comprehensive overview of results was available for the studies by Lauritzen and Echouffo, which resulted in the blanks in the risk of bias graph.

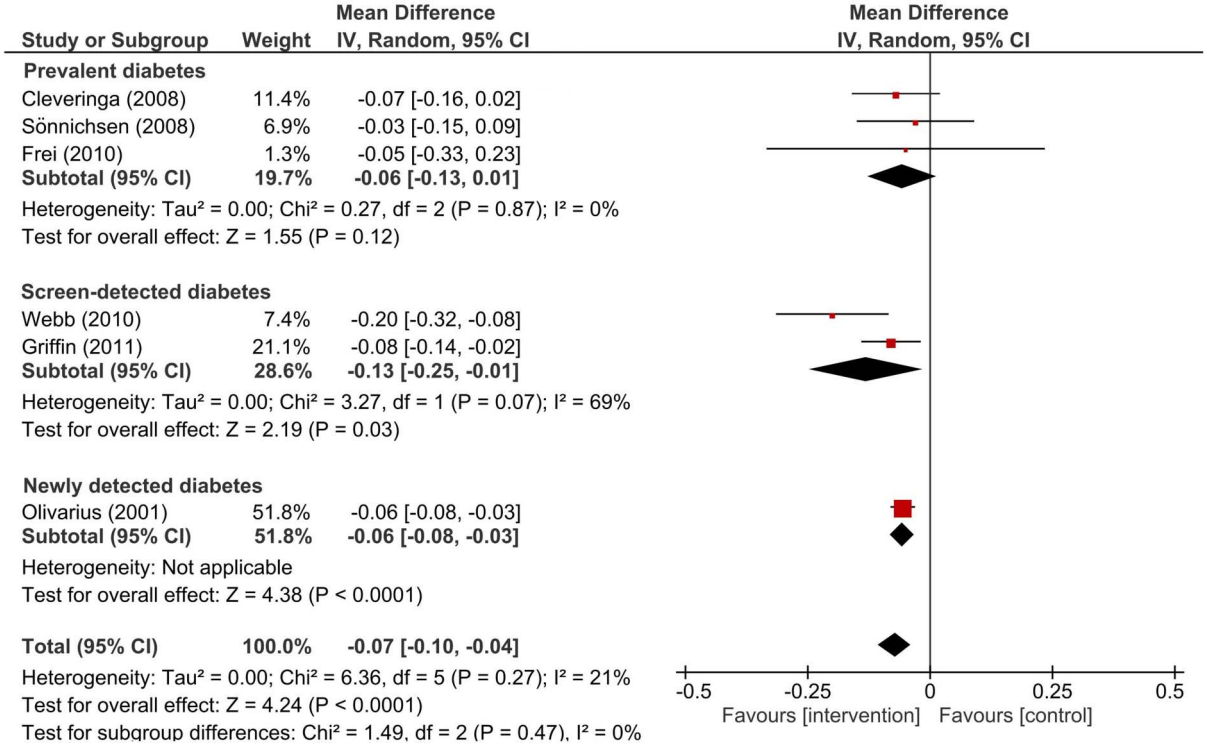

Figure 3 Mean difference in change (95% CI) in HbA1c levels (%) after multifaceted care between intervention and control groups. Results are stratified by type of diabetes patient. IV, generic inverse variance method. The three studies including patients with prevalent diabetes has an intervention duration of 1-year. The methodology for calculating the difference in change between intervention and control group that Cleveringa *et al*.[33] have used (subtracting the HbA1c change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the HbA1c change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa *et al*.,[33] we have recalculated their HbA1c results according to the methodology used by the other studies. The study of Webb *et al*.[43] had an intervention duration of one year and the study of Griffin *et al*.[46] combined the 5-year intervention data from all four Addition studies, including the five-year data from Webb *et al*.[43] The study including patients with newly detected diabetes had an intervention duration of six years.

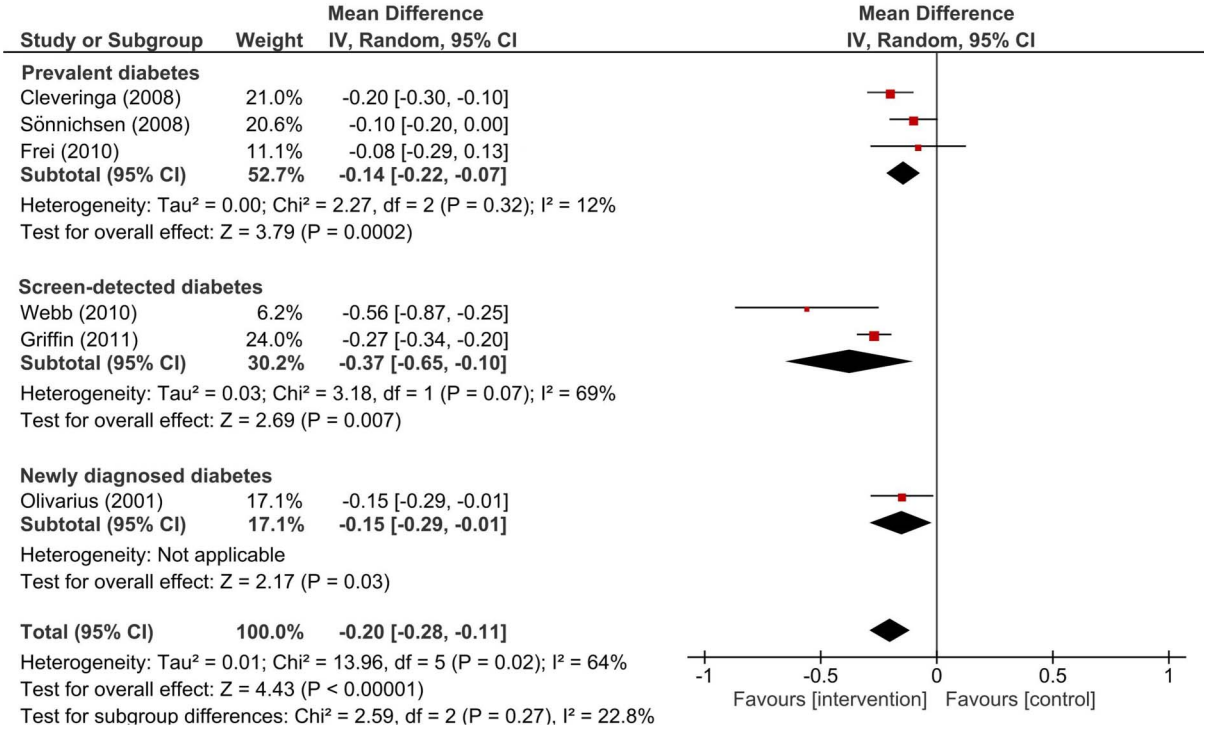

Figure 4 Mean difference in change (95% CI) in total cholesterol levels (mmol/L) after multifaceted care between intervention and control groups. Results are stratified by type of diabetes patient. IV, generic inverse variance method. The three studies including patients with prevalent diabetes has an intervention duration of 1-year. The methodology for calculating the difference in change between intervention and control group that Cleveringa et al.[33] have used (subtracting the HbA1c change over time for the control group from the change over time for the intervention group) was the opposite of that used by the other trials (subtracting the HbA1c change over time for the intervention group from the change over time for the control group). Since this would result in a misleading visual presentation of the findings from Cleveringa et al.,[33] we have recalculated their HbA1c results according to the methodology used by the other studies. The study of Webb et al.[43] had an intervention duration of one year and the study of Griffin et al.[46] combined the 5-year intervention data from all four Addition studies, including the five-year data from Webb et al.[43] The study including patients with newly detected diabetes had an intervention duration of six years.

improve total cholesterol concentrations. In the remaining two studies,[44 45] cholesterol levels were similar between intervention and control arm. Statistical heterogeneity across the three studies was low (I^2=12%) and their weighted mean difference in change between intervention and control groups amounted to −0.14 mmol/L (95% CI −0.22 to −0.07). Similar to HbA1c, the effect of multifaceted care on cholesterol seemed larger in screen-detected patients than in patients with prevalent diabetes. After 1-year of intervention, Addition-Leicester[43] found a mean difference in change between the intervention and control group of −0.56 mmol/L (95% CI −0.87 to −0.25). The pooled 5-year data from all four Addition trials also showed a significantly greater improvement in total cholesterol levels in intervention patients, compared to control patients (−0.27 mmol/L (95% CI −0.34 to −0.20)). Finally, in Danish patients with newly diagnosed diabetes,[41] 6 years of multifaceted care had caused cholesterol levels to improve (−0.15 mmol/L (95% CI −0.29 to −0.01)).

Pooling all trials, the effect of multifaceted care on improvement of total cholesterol resulted in a weighted difference in change between intervention and control patients of −0.20 mmol/L (95% CI −0.28 to −0.11); I^2=64%.

In addition to improvements in total cholesterol levels, HDL-cholesterol levels appeared to be unaffected by multifaceted care in patients with prevalent diabetes.[33 44 45] LDL-cholesterol levels on the other hand did improve (see online supplementary figure S1 and S2). The Dutch[33] and the Swiss[44] study found significantly better improvements in LDL-cholesterol for the intervention group, when compared to the control group. The Addition-Netherlands[39] and Addition-Leicester[43] studies observed that multifaceted care significantly improved LDL-cholesterol levels after 1-year, while HDL-cholesterol remained largely unchanged. Similar results were reported for 5 years of intervention by the Addition-Europe study.[46] The Danish study[41] with newly diagnosed diabetes patients had not measured HDL and LDL-cholesterol levels.

Blood pressure

Two[33 44] out of the three trials with patients with prevalent diabetes reported a difference in change in diastolic

and systolic blood pressure, both being in favour of the intervention group (see online supplementary figures S3 and S4). Better improvements in blood pressure were also seen in intervention patients with screen-detected diabetes, compared to control patients.[39 43 46] Improvements after 1-year of intervention[43] were larger than those after 5 years of intervention.[46] In patients with newly diagnosed diabetes[41] 6 years of multifaceted care significantly improved systolic, but not diastolic, blood pressure when compared to usual diabetes care. Similar to HbA1c and total cholesterol, the results for blood pressure were stronger for patients with screen-detected and newly diagnosed diabetes than for those with prevalent, long-standing diabetes.

Body mass index

With regard to the studies on prevalent diabetes, only the Austrian study[45] found a significant difference in change in BMI between the intervention group and control group after 1-year of intervention (see online supplementary figure S5). In screen-detected diabetes patients,[39 43] multifaceted care resulted in a significantly higher reduction in BMI, compared to usual diabetes care. Furthermore, Addition-Leicester[43] reported a higher reduction in BMI and body weight (kg) for the intervention group compared to the control group, but observed no difference in reduction of waist circumference. After an intervention duration of 5 years, the pooled reduction in weight and waist circumference, but not in BMI, in screen-detected diabetes was significantly higher in the intervention group compared to the control group.[46] The Danish trial[41] with newly diagnosed diabetes patients observed no difference in weight change after 6 years of intervention, yet BMI had not been measured.

For further biochemical outcomes, see online supplementary file S3 and figures S6–S8.

Patient-reported outcomes

The effect of a multifaceted care intervention on the patients' quality of life accounted for the only patient-reported outcome assessed by the included trials.

Health-related quality of life

Quality of life was reported by five[33 39 43 44 46] of the seven trials, most of which had used the 36-item Short Form Health Survey (SF-36) to assess the different domains of health-related quality of life. In patients with prevalent diabetes,[33 44] significant changes over time were absent for all scores of the SF-36 subscales for the intervention and control arms. A superior effect of multifaceted care was observed only on the SF-36 subscale 'health change' in the Dutch trial with prevalent diabetes patients.[33] For the two Addition studies reporting results after 1-year of intervention,[39 43] as for the pooled 5-year data by Addition-Europe,[46] no significant changes in the physical and mental summary scores of the SF-36, or the abbreviated SF-12 version that was used in the Addition-Leicester trial,[43] could be demonstrated.

Diabetes complications

Only few trials had reported diabetes complications, including cardiovascular disease and mortality. Closely related to the prevention and occurrence of complications, some studies evaluated the effect of their intervention on processes of care, such as reaching target values for HbA1c and receiving regular eye and foot examinations.

Macrovascular and microvascular complications

Macrovascular and microvascular diabetes complications during follow-up were reported by the two studies[41 46] with the longer intervention periods. The Addition-Europe study[46] had assessed myocardial infarction, stroke, coronary and peripheral revascularisation procedures, cardiovascular death and total mortality and non-traumatic amputation in screen-diagnosed diabetes patients. Although the estimated HRs for these events all favoured the intervention group, none of the estimates reached statistical significance. In newly diagnosed diabetes patients,[41] multifaceted care had not resulted in differences between intervention and control group regarding the risk of diabetic retinopathy, peripheral neuropathy, microalbuminuria, non-fatal myocardial infarction and stroke, angina pectoris or intermittent claudication at 6 years.

Processes of care

Only three studies assessed processes of care or process quality measures.[33 45 46] The Dutch study[33] with prevalent diabetes patients observed that multifaceted care resulted in significantly more patients reaching treatment targets (18.9%) than usual diabetes care (13.4%) (treatment targets were defined as HbA1c ≤7% (53 mmol/mol), systolic blood pressure ≤140 mm Hg, total cholesterol ≤4.5 mmol/L and LDL-cholesterol ≤2.5 mmol/L). Process quality measures at 1-year, defined as the percentage of patients receiving guideline-adherent foot-examinations, eye-examinations and HbA1c-examinations, were reported by the Austrian study with prevalent diabetes patients[45] to be significantly higher in the intervention group. The pooled 5-year results from the four Addition studies[46] showed that in both trial arms more patients had values below target thresholds for HbA1c (<7% (53 mmol/mol)), blood pressure (≤135/85 mm Hg) and cholesterol level (<4.5 mmol/L), yet proportions were higher in the intervention group than in the control group.

For further diabetes complications and related outcomes, see online supplementary file S3.

DISCUSSION

This review assessed the effectiveness of chronic disease management models for type 2 diabetes on the

improvement of patient outcomes, in Europe. In general, the effects of multifaceted care on patient outcomes were rather small and their magnitude seemed to differ according to the type of diabetes patient being studied. Our analysis suggested that in comparison to usual diabetes care, multifaceted care improves HbA1c levels for patients with screen-detected diabetes and patients with newly diagnosed diabetes, but not for patients with prevalent type 2 diabetes. Similar findings were observed for total cholesterol, LDL-cholesterol, BMI and body weight. The resulting improvements in blood pressure seemed less strongly related to the type of diabetes patient studied. Other outcomes, such as fasting glucose levels, triglycerides, quality of life and diabetes complications, had been reported inconsequently, and results varied widely across the included trials.

The few cluster randomised controlled trials that we identified from the literature were relatively heterogeneous with regard to the individual components of the implemented intervention, duration of the intervention, type of diabetes patient and reported outcomes. For each trial, methodological quality was acceptable and there were very low rates of dropout among the enrolled patients. Still, details on the randomisation procedure were frequently missing as well as information concerning concealment of allocation from general practitioners and physicians in advance to recruitment of eligible patients. Since the currently performed meta-analysis included only a small number of trials, caution is warranted not to overinterpret its results. The χ^2 statistic for example, indicating homogeneity of the effect of the intervention on HbA1c and total cholesterol, has low power when based on only few, and small-sized, studies.[47] When interpreting the data, we thus prefer to look at the direction of the individual effect estimates and CIs, rather than let the calculated statistics guide our conclusions. As such, given the current literature, it is not possible to draw an unequivocal conclusion about the effectiveness of chronic multifaceted care on diabetes patient outcomes.

Overall, previous systematic reviews have reported that an integrated approach to diabetes care versus usual diabetes care may improve clinical and biochemical outcomes,[9 10 19 20 23 24 48] including HbA1c levels, blood pressure and blood lipid concentrations. Those reviews that included a meta-analysis reported mean differences in HbA1c reduction between intervention and control groups ranging from −0.14% (95% CI −0.25 to −0.05) to −0.5% (95% CI −0.6 to −0.3). Mean differences in total cholesterol have only been estimated by one meta-analysis, which reported a reduction of −0.24 mmol/L (95% CI −0.41 to −0.06) in favour of the intervention group.[10] This study also reported a mean difference in diastolic blood pressure reduction of −1.3 mm Hg (95% CI −0.21 to −0.6) and a mean difference in systolic blood pressure reduction of −2.2 mm Hg (95% CI −3.5 to −0.9), comparable with the summary estimate for systolic blood pressure from Elissen *et al* (−2.8 mm Hg (95% CI −4.7 to −0.9)).[20] All other outcomes of multifaceted care interventions were described narratively. Improvements have been observed for frequency of retinopathy screening,[20 48 49] screening for peripheral polyneuropathy and foot lesions,[20 48 49] proteinuria measurements[49] and the monitoring frequency of lipid and HbA1c levels.[49] In addition, there seems to be an economic benefit of integrated diabetes care.[50] Yet, other systematic reviews have found no impact on patients outcomes and processes of care[18 25 49] or have disputed the clinical relevance of statistically significant findings.[19] A comparison of the reported effect estimates with our summary estimates for HbA1c and total cholesterol warrants caution, given the varying number of CCM elements the estimates were based on, the heterogeneity among the included diabetes patients, the different restrictions to geographical region and the number of included studies in each review.

The novelty of the current systematic review is that it provides a comprehensive overview of diabetes care trials that have evaluated the effectiveness of the all the six components of the CCM combined, instead of one or more components. Overall, we found there is an important lack of studies which evaluate the implementation of all six CCM-components simultaneously. In the current literature, findings on the issue of whether multifaceted chronic care is to be preferred over single-faceted care are conflicting.[9–12 24–26 51] However, improving the management of a complex disease like diabetes is a challenging goal which, we believe, may not be achieved by targeting single care aspects only. Another novel aspect of the current review is the focus on state-of-the-art diabetes management in Europe only. The narrow view relates to the enormous burden that type 2 diabetes represents in Europe, in individual and in societal terms.[52] The prevalence of diabetes in Europe is expected to increase from 59.8 million adults in 2015 to 71.1 million in 2040.[53]

As reflected by recent guidelines for the management of patients with type 2 diabetes,[54] healthcare providers have increasingly focused at improving and controlling cardiovascular risk factors to improve patient outcomes, including hyperglycaemia, overweight or obesity, elevated blood pressure and dyslipidemia. Results from the Steno-2 trial support the view that even in high-risk patients with type 2 diabetes multifaceted care has the potential to reduce the risk of complications and mortality.[55] Randomising 160 patients with type 2 diabetes and persistent microalbuminuria to an intensive multifactorial treatment and conventional therapy, the authors found that the multifactorial treatment was associated with a lower risk of cardiovascular events after 13.3 years of follow-up, as well as with a lower risk of death from cardiovascular disease, compared to conventional treatment. And while the CCM has been proposed as a tool to improve the quality of diabetes care and, subsequently, patient outcomes, the current review indicates that at least the existing programmes have not been as

successful in this respect as intended. The challenge thus remains to translate results from landmark studies like Steno-2, into primary care, where the majority of type 2 diabetes patients are being treated.

When aiming to improve chronic healthcare, it has been proposed that only assessing the effects of a multifaceted care intervention on patient outcomes is not sufficient. In order to gain insights into why and when certain interventions are effective, it is also important to focus on barriers and facilitators to the implementation process of the intervention and their effect on the interplay between intervention and outcomes.[56] This latter aspect is usually not evaluated or reported on by randomised controlled trials implementing a multifaceted care intervention.[57] As such, it has not yet been possible to analyse the relationships between context, mechanisms and outcomes of multifaceted diabetes care interventions and to subsequently provide meaningful insights into how these have influenced the outcomes achieved.[57]

There are some limitations of our work that need to be considered. First, many studies provided insufficient detail in their methods section to fully understand the intensity of (specific components of) the intervention. This complicated our appraisal of whether all components of the CCM were fully covered. Also, the different interventions that the trials have used to represent a given component of the CCM have possibly resulted in some heterogeneity across the trials. In addition to the insufficiently described interventions, standards for usual diabetes care were not elaborated on in any of the trials. Online versions of diabetes care guidelines were found to be published in the country's native language and represented current versions only. However, most European countries define their standards according to the recommendations made by the joint task force convened by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[54 58] Indeed, identified guidelines from the Netherlands, Austria, and the UK did comply with the ADA/EASD recommendations. We do therefore not expect that practices of usual diabetes care in the individual trials have differed to the extent of causing a significant increase in heterogeneity. Second, whereas the aim of the current review was to investigate the effectiveness of CCMs in Europe, the trials available for this review only represented the Western part of Europe. Countries with the highest prevalence of diabetes lie in Eastern Europe, that is, Turkey, Montenegro, Macedonia and Serbia.[52] The top-three countries in Western Europe with the highest diabetes prevalence are Germany, Spain and Italy,[52] none of which were represented in this review. And third, the procedure of selecting relevant studies for the current review was largely performed by only one person. However, two reviewers subsequently screened the full text of all potentially relevant papers such that the final decision on inclusion was based on two opinions.

In conclusion, the available scientific evidence regarding the effectiveness of multifaceted chronic care programmes for type 2 diabetes in older patients in Europe is low. In general, the current findings support the concept of the CCM, yet the improvements in patient outcomes and processes of care are only small. While key aspects of type 2 diabetes can be improved by a multifactorial intervention, it is not yet clear if these improvements will subsequently lower diabetes-related complications, such as cardiovascular disease and overall mortality. Furthermore, the effect of the interventions seemed, at least partly, to depend on the type of diabetes patient, which could suggest effect modification by disease duration and/or disease severity. Another aspect that could add to the differences in effectiveness between the individual interventions is the degree in which they facilitate changes in social behaviour. This implies that more attention in trials should be spent to factors like adherence to treatment strategies, level of self-management skills and patients' knowledge on their disease. These traits need to be positively affected before an improvement in clinical measures can even occur,[1] yet studies generally reveal little on person-centred factors. And finally, there is a lack of knowledge (on information) on effective methods to address important pragmatic questions about improvement of care, for example, which specific mechanism or procedure of a CCM works, for which patients and under which circumstances?[59] Future research would need to incorporate the measurement of context, mechanisms and outcomes of multifaceted care into study designs in order to deliver the full extent of insights needed to improve chronic diabetes care and, ultimately, patient outcomes.

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Contributors BWCB designed the review by writing the review protocol, identified studies for inclusion, extracted and interpreted the data and drafted and revised the article. KM contributed to the review protocol and to the discussion. He further revised the draft paper for intellectual content. JW involved in conception of the review and he contributed to the review protocol, to interpretation of the data and to the discussion. Furthermore, JW revised the draft paper for intellectual content. CL contributed to the review protocol and to the discussion, and she revised the draft paper for intellectual content. PS conceived and initiated the review, contributed to the review protocol and contributed to the interpretation of the data, to the discussion and to revision of the draft paper. MR involved in conception of the review and revised the draft paper for intellectual content. WR contributed to the review protocol, identified studies for inclusion, extracted and interpreted the data and revised the draft paper for intellectual content. All authors approved the final completed article.

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Postchallenge Hyperglycemia Is Positively Associated With Diabetic Polyneuropathy

The KORA F4 study

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OBJECTIVE—To assess the prevalence of distal sensorimotor polyneuropathy (DSPN) in an older population and to examine its relationship with prediabetes.

RESEARCH DESIGN AND METHODS—Glucose tolerance status was determined in 61- to 82-year-old participants (n = 1,100) of the population-based Cooperative Health Research in the Region of Augsburg (KORA) F4 Survey (2006–2008). Clinical DSPN was defined as bilaterally impaired foot-vibration perception and/or foot-pressure sensation.

RESULTS—Prevalence of clinical DSPN was similar in subjects with known diabetes (22.0%) and subjects with combined impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (23.9%). Among prediabetic subgroups, IFG-IGT, but not isolated-IFG and -IGT, was associated with a higher risk of clinical DSPN, compared with normal glucose tolerance. A J-shaped association was observed between clinical DSPN and quartiles of 2-h postchallenge glucose, but not with fasting glucose and HbA_{1c} levels.

CONCLUSIONS—Subjects with IFG-IGT and known diabetes had a similar prevalence of clinical DSPN. Elevated 2-h postload glucose levels appeared important for disease risk.

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Distal sensorimotor polyneuropathy (DSPN) is an important complication of type 2 diabetes. It is still unclear whether nerve disorders are already manifest in subjects with prediabetes (1).

The aim of the current study was to evaluate the prevalence of DSPN in a representative sample of the older population and to study the association between prediabetes and DSPN. In addition, we examined the relationship between glucose (fasting and 2-h postload) and HbA_{1c} levels and the disorder.

RESEARCH DESIGN AND METHODS

The current study is performed using the follow-up data of the Cooperative Health Research in the Region of Augsburg (KORA) S4 Survey (1999–2001): the KORA F4 Survey (2006–2008) (2). Of the 1,209 participants, 923 participants subsequently completed an oral glucose tolerance test (OGTT) (according to World Health Organization criteria) (3), and self-reported diabetes was validated for 177 participants. Clinical DSPN was defined as bilaterally impaired foot-vibration perception (tuning fork) and/or bilaterally impaired foot-pressure sensation (10-g monofilament). Details on a validation study of the DSPN definition are provided in the Supplementary Data online.

Age- and sex-adjusted differences in characteristics were evaluated for the different categories of glucose tolerance using ANOVA. Multivariate logistic regression models were fitted to study associations between diabetes, prediabetes (combined impaired fasting glucose [IFG] and impaired glucose tolerance [IGT], isolated IFG [i-IFG], and isolated IGT [i-IGT]), and the presence of clinical DSPN. In addition, relationships between glucose concentrations, HbA_{1c}, and clinical DSPN were studied. Analyses were performed with STATA (version 11; StataCorp, College Station, TX).

RESULTS

The results are based on 1,100 participants with complete information on glucose tolerance status, clinical DSPN, and other covariables. The study population included 577 subjects with normal glucose tolerance (NGT), 55 with i-IFG, 183 with i-IGT, 46 with IFG-IGT, 62 with undiagnosed diabetes, and 177 with known diabetes. Participants with known and undiagnosed diabetes were physically less active and had a larger waist circumference, a higher prevalence of hypertension, and prior cardiovascular events compared with subjects with NGT.

The prevalence of clinical DSPN was similar among participants with IFG-IGT (23.9% [95% CI 12.6–38.8]) and those with known diabetes (22.0 [16.2–28.9]). Prevalence in subjects with NGT, i-IFG, i-IGT, and undiagnosed diabetes was 11.1 (8.6–13.9), 5.5 (1.1–15.1), 14.8 (10.0–20.7), and 16.1 (8.0–27.7), respectively. Subjects with clinical DSPN were slightly older, taller, and physically less active than subjects without DSPN and had a larger waist circumference and higher HbA_{1c} levels.

The total prediabetic group did not show statistically significantly increased odds of having clinical DSPN compared

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with the NGT group (Table 1). When the subgroups were examined separately, a positive association was observed between IFG-IGT and clinical DSPN (odds ratio [OR] 2.82 [95% CI 1.29–6.10]). Compared with NGT subjects, participants with diabetes (undiagnosed and diagnosed) had increased odds of having clinical DSPN (1.54 [1.01–2.42]). This elevated risk was largely attributable to subjects with known diabetes, given that no association was observed for subjects with undiagnosed diabetes.

A J-shaped relationship was observed between quartiles of 2-h postload blood glucose and the presence of clinical DSPN (Table 1). There was no relationship between quartiles of fasting blood glucose and quartiles of HbA_{1c} levels and the disorder. In addition, there was no association between (components of) metabolic syndrome and clinical DSPN (data not shown).

CONCLUSIONS—The present population-based study showed a similar prevalence of clinical DSPN in participants with IFG-IGT and those with known diabetes. Among the prediabetic subgroups, only IFG-IGT was positively associated with having clinical DSPN, while the total prediabetic group was not related to having the disorder. A J-shaped relationship was observed between quartiles of 2-h postload glucose and the presence of clinical DSPN. No associations were seen with fasting glucose and HbA_{1c} levels.

In the current literature, the prevalence of DSPN varies between 18 and 42% for populations with known diabetes (4,5) and between 4 and 19% for populations with prediabetes (6–10). The prevalence found in the current study for both diabetic groups is in concordance with the literature. Published prevalences for subjects with prediabetes, or IGT only, ranged from 5 to 16% (4,7,11,12). The proportion of clinical DSPN that we found in subjects with IGT is in line with these observations. Occurrence of DSPN in IFG was reported less frequently (11–13) yet was within a range of 5.7–11.3% comparable with our study estimate. Prevalence of clinical DSPN in individuals suffering from IFG-IGT has not been published before. Our findings indicate that participants with IFG-IGT were similar to participants with diabetes regarding characteristics and frequency of clinical DSPN. Consequently, subjects with IFG-IGT represent a high-risk group for DSPN.

Considering glycemia, 2-h postload glucose concentrations appeared more important for DSPN risk than fasting glucose levels. Risk of clinical DSPN was increased at postload glucose concentrations that were still within the normal range of the glycemic metabolism according to the World Health Organization (3). Previous studies show similar curvilinear relationships between 2-h postload glucose concentrations and risk of (cardiovascular) mortality (14,15). Altogether, these results suggest an important role of postprandial glucose levels, including those below the diagnostic threshold, in the development of diabetes complications.

The current study has some limitations. Since there is no uniform consensus on a definition of DSPN for use in epidemiological studies, we may have under- or overestimated the true prevalence of DSPN. However, a validation study of our clinical DSPN definition showed excellent diagnostic performance (see Supplementary Data online). Additional adjustment of our analyses for other risk factors of DSPN (smoking and diseases causing neurologic damage) did not change the results. Finally, stratified analyses resulted in some small subgroups.

An important methodological strength of the current study, as opposed to other previous population-based studies, is the use of the OGTT. This enables studying the entire spectrum of glucose disorders through identification of subjects with undiagnosed diabetes and prediabetes. Another strength of the study is the use of different neurologic bedside tests, facilitating a relatively accurate definition of clinical DSPN.

Replication of the present findings in large, well-defined, population-based

Table 1—*Adjusted ORs* and 95% CIs for clinical DSPN† according to oral glucose tolerance status and blood concentrations: KORA F4 (2006–2008)*

	Clinical DSPN			
	No	Yes	OR	95% CI
Oral glucose tolerance status				
NGT	513	64	1.00	Reference
Prediabetes (total)	243	41	1.22	0.78–1.90
i-IFG	52	3	0.33	0.10–1.13
i-IGT	156	27	1.26	0.76–2.08
IFG-IGT	35	11	2.82	1.29–6.10
Diabetes (total)	190	49	1.54	1.01–2.42
Known diabetes	138	39	1.77	1.10–2.87
Undiagnosed diabetes	52	10	1.22	0.57–2.61
Blood concentrations				
Fasting glucose (mg/dL)‡§				
Quartile 1	222	31	1.00	0.57–1.76
Quartile 2	195	29	1.00	Reference
Quartile 3	191	27	0.96	0.53–1.71
Quartile 4	200	28	0.82	0.43–1.54
2-h postload glucose (mg/dL)‖§				
Quartile 1	212	27	1.64	0.84–3.20
Quartile 2	208	16	1.00	Reference
Quartile 3	197	36	2.91	1.51–5.62
Quartile 4	191	36	3.64	1.56–8.48
HbA_{1c} (%)¶				
Quartile 1	281	32	0.74	0.45–1.21
Quartile 2	292	48	1.00	Reference
Quartile 3	156	21	0.82	0.46–1.45
Quartile 4	217	53	1.15	0.70–1.87

*All models were adjusted for age (years), sex, height (cm), waist circumference (cm), diastolic blood pressure (mmHg), level of physical activity (low/high), and alcohol consumption (low, moderate, high). †Defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation. ‡The quartile borders for fasting glucose levels are quartile 1: 66–91 mg/dL; quartile 2: 92–97 mg/dL; quartile 3: 98–104 mg/dL; and quartile 4: 105–168 mg/dL. §Patients with known diabetes (n = 177) were excluded because they did not need to undergo an OGTT and, hence, have inadequate fasting and no postload glucose blood samples. ‖The quartile borders for 2-h glucose values are quartile 1: 49–99 mg/dL; quartile 2: 100–119 mg/dL; quartile 3: 120–149 mg/dL; and quartile 4: 150–275 mg/dL. ¶The quartile borders for HbA_{1c} levels are quartile 1: 4.7–5.4%; quartile 2: 5.5–5.7%; quartile 3: 5.8–5.9%; and quartile 4: 6.0–12.1%.

studies may shed light on the developmental mechanism of DSPN and on identifying high-risk individuals.

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B.W.C.B. performed data analyses and wrote the manuscript. W.R. planned the study, contributed to data analyses, and wrote the manuscript. B.K., C.H., D.S., and C.M. reviewed and edited the manuscript. D.Z. planned the study, contributed to data analyses and discussion, and reviewed and edited the manuscript. W.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Older Subjects With Diabetes and Prediabetes Are Frequently Unaware of Having Distal Sensorimotor Polyneuropathy

The KORA F4 Study

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OBJECTIVE—Distal sensorimotor polyneuropathy (DSPN) is a severe complication of type 2 diabetes. This study aimed to assess the prevalence of unawareness of DSPN in prediabetes and diabetes in a sample of the older population of Augsburg, Germany.

RESEARCH DESIGN AND METHODS—Glucose tolerance status was determined in 61- to 82-year-old participants of the population-based KORA F4 Study (2006–2008) (n = 1,100). Clinical DSPN was defined as the presence of bilaterally impaired foot-vibration perception and/or bilaterally impaired foot-pressure sensation. DSPN case subjects were considered unaware of their condition when answering "no" to the question, "Has a physician ever told you that you are suffering from nerve damage, neuropathy, polyneuropathy, or diabetic foot?"

RESULTS—Clinical DSPN was prevalent in 154 (14%) participants, 140 of whom were unaware of their disorder. At a prevalence of 23.9% (95% CI 12.6–38.8), participants with combined impaired fasting glucose and impaired glucose tolerance had the highest prevalence of DSPN. Of these, 10 of 11 (91%) were unaware of having clinical DSPN. Participants with known diabetes had an equally high prevalence of DSPN [22.0% (16.2–28.9)], with 30 of the 39 (77%) DSPN case subjects unaware of having the disorder. Among subjects with known diabetes who reported to have had their feet examined by a physician, 18 of 25 (72%) clinical DSPN case subjects emerged unaware of having DSPN.

CONCLUSIONS—Our findings showed a high prevalence of unawareness of having clinical DSPN among the prediabetic and diabetic groups and an insufficient frequency of professional foot examinations, suggesting inadequate attention to diabetic foot prevention practice.

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Diabetic peripheral neuropathy is a severe complication of type 2 diabetes related to chronic hyperglycemia and the presence of cardiovascular risk factors (1). Symmetrical distal sensorimotor polyneuropathy (DSPN), the most common form of peripheral neuropathies in patients with diabetes, is a heterogeneous disorder covering a wide range of abnormalities that affect peripheral sensory and motor nerves as well as the autonomic nervous system (2). Of all diabetes complications, DSPN is responsible for the highest number of hospital admissions and, being the foremost cause of foot ulcers, for 50–75% of all nontraumatic amputations after ulceration (3). Next to substantial morbidity, DSPN leads to reduced quality of life and an increased risk of mortality (1,4).

In recognition of the importance of early detection and prevention of DSPN, American (5), British (6), and German (7) national guidelines for diabetes care state that all patients with type 2 diabetes should be screened for clinical DSPN at the time of their diabetes diagnosis and yearly thereafter. Screening is to be performed using simple clinical tests, such as vibration perception, pressure sensation, assessment of ankle reflexes, and pinprick sensation. Still, several reports have indicated that in primary care practice, where most of the diabetic patients are being treated, screening for polyneuropathy was underused (8–11). Neurologic tests and physical examination of the feet are being carried out rarely in asymptomatic diabetic patients, and neuropathic pain often remains unrecognized and untreated (12). To date, there are only sparse data on the prevalence of undiagnosed DSPN (13,14). Although the two studies differed in methodology, both observed that over one-half of their study sample of diabetic patients had undiagnosed DSPN. The aim of the current study was to examine the prevalence of unawareness of having clinical DSPN among older prediabetic and diabetic individuals from a population-based sample in Germany.

RESEARCH DESIGN AND METHODS

The Cooperative Health Research in the Region of Augsburg (KORA) was initiated to study the prevalence and incidence of various chronic diseases in the general population, including diabetes, and to identify novel risk factors of these diseases. The current study is based on the follow-up examination of the KORA S4 Survey that was conducted in 1999–2001. The study

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design and subject enrollment have previously been described in detail (15). Briefly, 2,656 men and women aged 55–74 years were randomly selected from the region of Augsburg in the south of Germany to participate in the KORA S4 Survey. From the 2,564 eligible subjects, 1,653 (64%) completed the survey and a subsequent 1,353 subjects without known diabetes successfully completed an oral glucose tolerance test (OGTT). In 2006–2008, the 7-year follow-up examination (F4 Survey) of this cohort took place, including a second OGTT. Of the initial 1,353 subjects, a total of 1,209 (89%) participated in the follow-up measurements. For 177 participants, a previous diagnosis of diabetes could be validated, and a further 923 participants successfully completed the OGTT, resulting in a total sample size of 1,100 (81%) subjects. All participants gave written informed consent, and the study was approved by the ethics committee of the Bavarian Medical Association.

Measurements and interviews

Height, weight, waist circumference, and systolic and diastolic blood pressure were measured according to standard protocols as previously described (15). Trained medical interviewers collected information on medical history, physical activity, smoking behavior, and alcohol consumption. Furthermore, participants with known diabetes were asked the question, "When has a physician examined your feet lately?" which could be answered with *1*) within the past 12 months, *2*) >12 months ago, *3*) not ever, and *4*) I don't know. As an indication for ever having had one's feet examined, answers 1 and 2 were considered confirmative of a foot examination and answer 3 was considered nonconfirmative.

Patients with known diabetes completed an additional self-administered questionnaire on diabetes care, which inquired about the presence of complications, the course of treatment, and whether the subject had been enrolled in a type 2 diabetes disease-management program (DDMP). Since DDMP names vary considerably between the supplying social health insurance companies and might not reveal the disease-management aspect, the family physician of each participant with known diabetes was contacted to validate DDMP participation.

Assessment of glucose metabolism

Cases of self-reported diabetes, as well as the date of diagnosis, were validated through contacting the participants' general practitioners. All other participants underwent an OGTT (World Health Organization criteria). After an overnight fasting period of at least 10 h, fasting blood samples were taken and participants were given an oral dose of 75 g anhydrous glucose (Dextro OGT; Boehringer Mannheim, Mannheim, Germany). Another blood sample was collected 2 h after the glucose load. Blood samples were collected without stasis. After withdrawal, the samples were centrifuged and refrigerated at 4°C until analysis in the central laboratory of the Augsburg Central Hospital at maximum 4 h after withdrawal. Blood glucose levels were assessed using the hexokinase method (Glu-Flex; Dade Behring, Marburg, Germany). Glucose tolerance categories were defined according to the 1999 World Health Organization diagnostic criteria (16). We considered participants with isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), or combined IFG-IGT as subjects with prediabetes. Furthermore, overall diabetes was defined as the combined group of subjects with known and newly diagnosed diabetes. It can be assumed that the great majority of case subjects with newly diagnosed diabetes in this age-group had type 2 diabetes.

Neurologic assessment

The neurologic examination of the F4 survey consisted of two parts. The first involved a detailed interview addressing the presence of (current) pain in the feet and other parts of the body, the presence of neurologic diseases, and the participant's history of foot ulcers and amputations. The second part comprised a foot inspection and a series of neurologic tests involving sensation to touch, vibration, and temperature and testing of ankle reflexes and sudomotor function.

We defined the presence of clinical DSPN as bilateral impairment of foot-vibration perception and/or bilateral impairment of foot-pressure sensation. Vibration perception was assessed at the dorsal side of the left and right big toe, using a calibrated 64-Hz Rydel Seiffer tuning fork. Increased thresholds were calculated according to the study of Martina et al. (17). Pressure sensation was measured at the dorsal side of the left and right big toe in between the nail fold and the metatarsophalangeal joint, using a 10-g monofilament (Twin-Tip, Heinsberg, Germany). Participants were asked to close their eyes during the test and to respond with "yes" each time the monofilament was sensed. No negative stimuli were tested. At least 8 of 10 correct responses were considered to indicate normal sensibility (18). Less than eight perceived applications indicated reduced sensibility, and when none of the applications were perceived, sensibility to touch was considered absent. Measurements of vibration perception and pressure sensation were performed by trained investigators under supervision of an experienced diabetologist (19) and according to the practical guidelines for the diabetic foot from the American Diabetes Association and the International Diabetic Foot Working Group (5,20). Our choice for these two specific tests lies in their quantitative nature to detect the insensate foot and the fact that both tests are predictors of future foot ulceration (21). Also, the two tests have previously been studied as being the most accurate tools for diagnosing large-fiber polyneuropathy in patients with diabetes. We have validated our clinical DSPN definition against nerve conduction studies as previously described (19).

During the interview on possible neurologic complaints, before undergoing the foot inspection and the neurologic testing, participants were asked whether a physician had ever told them that they were suffering from nerve damage, neuropathy, polyneuropathy, or diabetic foot. We defined subjects with clinical DSPN as being unaware of their disorder if they had answered this question with "no."

Statistical analysis

Follow-up characteristics are presented as means ± SD for normally distributed variables and as median (interquartile range) for variables without a normal distribution. Age- and sex-adjusted differences in characteristics were evaluated for participants with clinical DSPN who were either aware or unaware of their disorder using ANOVA. For log-normal variables, ANOVA was performed on a log scale. *P* values <0.05 were considered to indicate statistical significance. Analyses were performed with the STATA statistical software package (version 11; Stata).

RESULTS—The KORA F4 Survey comprised a total of 1,100 participants with complete information on the presence of clinical DSPN, glucose tolerance status, and other covariables. According

to our definition, clinical DSPN was present in 154 (14%) subjects, only 14 (9%) of whom were classified as being aware of their disorder and as many as 140 (91%) as being unaware. The prevalence of clinical DSPN and subsequent unawareness of having the disorder is presented in Table 1 according to glucose tolerance status. Participants with IFG-IGT and with known diabetes had the highest prevalence of clinical DSPN [23.9% (95% CI 12.6–38.8) and 22.0% (16.2–28.9), respectively]. Among those with IFG-IGT, 10 of 11 (91%) case subjects with clinical DSPN were unaware of having the disorder. This proportion was only slightly lower among those with known diabetes, among whom 30 of 39 (77%) case subjects with clinical DSPN were unaware of having the disorder.

In Table 2, differences in characteristics are presented between participants who were aware of having clinical DSPN and those who were unaware. Compared with the latter, subjects who were aware of their disorder had on average a higher systolic blood pressure and were more likely to have known diabetes. No differences between the two groups were observed for the prevalence of neurologic diseases, the prevalence of prediabetes, foot examinations, and DDMP participation (the latter two variables were only available for participants with known diabetes). With regard to neurologic characteristics, participants aware of having clinical DSPN more often had complaints of pain, paresthesias, and numbness in the feet over the last 24 h; foot ulcers; and absent ankle reflexes. The continuous monofilament test scores showed that clinical DSPN was more severe in subjects aware of having clinical DSPN as indicated by lower test scores compared with those who were unaware of having the disorder. The continuous tuning fork test scores indicated this as well; yet, only borderline statistical significance was reached.

Information on the performance of a foot examination by a physician was assessed for participants with known diabetes only (n = 177). Excluding those with missing data (n = 10), 113 of 167 (68%) subjects with known diabetes reported to have ever had their feet examined by a physician (Table 3). Of these foot examinations, 88 of 113 (78%) had taken place within the last 12 months and 25 of 113 (22%) had been performed >12 months ago. Approximately one-quarter of the subjects with known diabetes had never undergone a foot examination, and 13 (8%) could not remember. In total, 38 patients with known diabetes had clinical DSNP according to our definition, 29 (76%) of whom were unaware of having the disorder. Eighteen of these 29 (62%) subjects indicated having ever undergone a foot examination by a physician, whereas 8 stated to have never had their feet examined. Thirteen of the 18 (72%) foot examinations had taken place within the last 12 months and 5 (18%) >12 months ago. Of the nine case subjects aware of having clinical DSPN, a foot examination had been performed in seven.

According to the German National Disease Management Guidelines for neuropathy in adults with diabetes, individuals with diabetes should be screened for DSPN at diagnosis and yearly thereafter (7). Of the participants with available information on diabetes duration (n = 154), only 11 of 24 (46%) with a duration ≤1 year reported having ever undergone a foot examination by a physician. Of the 49 participants with a diabetes duration of ≤5 years, 30 (61%) indicated having ever had their feet examined, and this was also true for 75 of 105 (71%) subjects diagnosed with diabetes >5 years ago.

Table 1—*Prevalence of clinical DSPN according to glucose tolerance status: KORA F4 (2006–2008)*

		Clinical DSPN*	
	n	Prevalence of clinical DSPN (95% CI)*	Unawareness of clinical DSPN (%)†
Total study population (n = 1,100)	154	14.0 (12.0–16.2)	91
Normal glucose tolerance (n = 577)	64	11.1 (8.6–13.9)	98
Isolated IFG (n = 55)	3	5.5 (1.1–15.1)	100
Isolated IGT (n = 183)	27	14.8 (10.0–20.7)	89
IFG-IGT (n = 46)	11	23.9 (12.6–38.8)	91
Newly diagnosed diabetes (n = 62)	10	16.1 (8.0–27.7)	100
Known diabetes (n = 177)	39	22.0 (16.2–28.9)	77

*Defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation. †Defined by a nonaffirmative answer to the question, "Has a physician ever told you that you have nerve damage, neuropathy, polyneuropathy, or diabetic foot?" in combination with the presence of clinical DSPN.

CONCLUSIONS—The results of this cross-sectional population-based study demonstrated that a large proportion of subjects with prediabetes and diabetes were unaware of having clinical DSPN. While 113 of 167 (68%) participants with known diabetes had ever undergone a foot examination by a physician, only 7 of the 25 (28%) with clinical DSPN were aware of having clinical DSPN, whereas 18 of these 25 (72%) were unaware of having the disorder. Overall, the majority of the reported foot examinations had been carried out within the preceding 12 months.

The prevalence of unawareness of having clinical DSPN in participants with newly diagnosed diabetes was high. Yet, since these subjects were not receiving regular professional diabetes care, a high proportion of unaware DSPN cases was to be expected. Unexpected, though, was the high prevalence of unawareness of having DSPN among participants with known diabetes. Since these subjects are receiving regular diabetes care, the large proportion of unaware case subjects suggests that the current diabetes care practice may have serious shortcomings concerning appropriate attention to foot care. Next to subjects with diabetes, participants with IFG-IGT showed a strikingly high prevalence of unawareness of having clinical DSPN. In a previous report, we showed that IFG-IGT represents a high-risk group for developing DSPN (19). And since clinical DSPN is a strong risk predictor for the subsequent development of diabetic foot ulcers (21), these prediabetic individuals may also benefit from receiving preventive foot care.

To date, there are only two publications on the prevalence of undiagnosed DSPN in patients with known type 2 diabetes (13,14). Although a direct comparison of results is hampered by differences in study design, sample size, and assessment of undiagnosed DSPN, the main finding of the two is concordant:

Table 2—*Characteristics of KORA F4 participants according to awareness and unawareness of having clinical DSPN: KORA F4 (2006–2008)*

	Clinical DSPN*		
	Aware†	Unaware†	*P*
General characteristics			
N	14	140	
Male sex	17 (86)	84 (60)	0.058
Age (years)	71.8 ± 4.4	71.9 ± 5.8	0.929
Height (cm)	170 ± 8.4	168 ± 9.0	0.459
BMI (kg/m^2)	29.9 ± 4.5	29.1 ± 4.6	0.512
Waist circumference (cm)	106 ± 12.5	101 ± 12.6	0.394
Systolic blood pressure (mmHg)	138 ± 22.4	127 ± 19.4	0.015
Diastolic blood pressure (mmHg)	74.8 ± 11.6	71.6 ± 11.1	0.193
Hypertension‡	12 (86)	90 (64)	0.106
Current smoking	1 (7)	9 (6)	0.965
High alcohol consumption§	4 (29)	19 (14)	0.811
Low physical activity‖	8 (57)	85 (61)	0.735
Presence of neurologic disease¶	3 (21)	44 (31)	0.612
Prediabetes	4 (29)	37 (26)	0.103
Newly diagnosed diabetes	0	10 (7)	0.343
Known diabetes	9 (64)	30 (21)	0.001
Foot examination by physician#	7 (78)	18 (62)	0.736
Participation in DDMP**	3 (43)	13 (72)	0.162
Neurologic characteristics			
Pain (feet) in previous 24 h	6 (43)	23 (16)	0.005
Paresthesias (feet) in previous 24 h	8 (57)	29 (21)	0.002
Numbness (feet) in previous 24 h	11 (79)	40 (29)	<0.001
Dry skin of both feet	10 (71)	73 (52)	0.269
Callus formation on both feet	4 (29)	69 (49)	0.255
Fissures on both feet	3 (21)	12 (9)	0.297
Hallux valgus on both feet	3 (21)	24 (17)	0.595
Charcot foot	0	0	—
Absent ankle reflexes	10 (71)	30 (21)	0.001
Foot ulcer present	2 (14)	1 (1)	0.026
Severity of clinical DSPN††			
Monofilament test score	4.8 (1.5–8.5)	7.0 (5.0–10.0)	0.004
Tuning fork test score	0 (0–3.8)	2.5 (2.3–4.5)	0.069

Data are means ± SD, median (interquartile range), or *n* (%) unless otherwise indicated. *Defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation. †Awareness and unawareness of having clinical DSPN was defined as giving either a confirmative or negative answer to the question, "Has a physician ever told you that you have nerve damage, neuropathy, polyneuropathy or diabetic foot?" in combination with the presence of DSPN. ‡Defined as a blood pressure of ≥140/90 mmHg and/or the use of antihypertensive medication in subjects who reported to have been previously diagnosed with hypertension. §For women, ≥20 g/day and for men ≥40 g/day. ‖Performing <1 h of physical activity per week during leisure time in either winter or summer. ¶Neurologic diseases comprised conditions that might cause nerve damage, including cancer, stroke, dementia, and hernias. #Data on having one's feet examined by a physician were assessed in patients with known diabetes only. Because of missing data, percentages were based on 9 participants with known diabetes being aware of having clinical DSPN and 29 participants with known diabetes being unaware of having clinical DSPN. **Participation in a type 2 diabetes disease-management program was assessed in participants with known diabetes only. Because of missing data, percentages were based on 7 participants with known diabetes being aware of having clinical DSPN and 18 participants with known diabetes being unaware of having clinical DSPN. ††Severity of clinical DSPN was represented by the continuous scores of the monofilament test and tuning fork test. The average score of the left- and right-sided test was calculated, with lower test scores indicating a higher severity of clinical DSPN.

DSPN was underdiagnosed in over one-half of the diabetic patients. Wang et al. (14) have speculated that the underdiagnosis in their population sample might be the result of the low number of foot examinations performed by a health professional, since only 16.2% of their study sample had received preventive foot care. Herman and Kennedy did not have data on foot examinations (13). It is known that a large proportion of diabetic foot complications are preventable and that regular foot examinations by a general practitioner, a physician, or other health care providers play an important role in prevention (5). As such, a number of studies have reported on (frequency of) preventive foot care in individuals with diabetes (8,11,14,22–25). An Australian population-based cohort study on diabetes care practice reported that only 50% of the 396 participants with known type 2 diabetes had received a foot examination by a health professional within the last 12 months (11). Of those who were classified as being at risk for a future foot ulcer, only 46 of 81 (57%) reported to have had a foot examination. Another large cohort study of 3,564 patients with type 2 diabetes randomly selected from outpatient clinics and general practitioners found similar results (8). As many as 50% of these patients reported not to have had their feet examined in the last 12 months. And among the patients with symptomatic neuropathy or peripheral vascular disease—both risk factors of foot complications—over one-third had not undergone a foot examination. In summary, the general picture sketched by the previous literature on diabetes care is that attention to foot complications was poor and that a large proportion of patients were not offered regular foot examinations—not even those at high risk for developing foot complications. Whereas our data on preventive foot care are less elaborate, our findings fit this picture of insufficient and inadequate practice of preventive foot care. In addition, case subjects aware of having clinical DSPN showed a significantly higher proportion of absent ankle reflexes and foot ulcers compared with case subjects who were unaware of having DSPN (Table 2). Whereas there were no differences between the two groups concerning abnormal test scores on monofilament and tuning fork tests (data not shown), we can only speculate that overall, ankle reflex testing and the presence of ulcers have been the only criteria used to diagnose DSPN and that foot examinations were thus not performed according to clinical guidelines (7).

Some limitations and strengths of our study need to be discussed. First, the data on previous foot examinations being performed are self-reported and may suffer from recall bias. Also, the question of whether a physician has ever told the participant that he/she was suffering from nerve damage, neuropathy, polyneuropathy, or diabetic foot may also be subject to recall bias. Yet, the latter data were

Table 3—*Performance of a foot examination by a physician on participants with known diabetes: KORA F4 (2006–2008)*

Foot examination by a physician*	All subjects with known diabetes	Subjects with known diabetes		
		Subjects without clinical DSPN†	Subjects with clinical DSPN†	
			Aware of having clinical DSPN‡	Unaware of having clinical DSPN§
N	167	129	9	29
Yes	113 (68)	88 (68)	7 (78)	18 (62)
Within last 12 months	88 (78)	71 (81)	4 (57)	13 (72)
>12 months ago	25 (22)	17 (19)	3 (43)	5 (28)
No	41 (24)	32 (25)	1 (11)	8 (28)
Unknown	13 (8)	9 (7)	1 (11)	3 (10)

Data are *n* (%) unless otherwise indicated. *Participants were asked, "When has a physician examined your feet lately?" Answer options A (within the past 12 months) and B (>12 months ago) were combined to indicate that a foot examination had ever taken place. Answering option C (not ever) indicated that a foot examination had never taken place, and option D (I don't know) indicated an unknown status regarding the performance of a foot examination. †DSPN was defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation. ‡As defined by a confirmative answer to the question, "Has a physician ever told you that you have nerve damage, neuropathy, polyneuropathy, or diabetic foot?" in combination with the presence of DSPN. §As defined by a nonaffirmative answer to the question, "Has a physician ever told you that you have nerve damage, neuropathy, polyneuropathy, or diabetic foot?" in combination with the presence of DSPN.

collected by a trained interviewer (aware of the importance of this specific information) before the actual neurologic examination of the participant took place. It is unlikely that false memory may have had a substantial effect on our results and conclusion. Second, there is no uniform consensus on a definition of diagnosing DSPN for use in epidemiological studies. Also, we cannot rule out that our definition of clinical DSPN allowed for the inclusion of some case subjects that had developed DSPN due to a different cause rather than to chronic hyperglycemia. Subsequently, we performed a validation study to strengthen the validity of the present findings, and we observed that our clinical DSPN definition had an excellent diagnostic performance (19). A further strength of the current study includes the use of different bedside tests of peripheral sensory function, facilitating the construction of a relatively accurate definition of clinical DSPN.

In conclusion, our findings show a high prevalence of unawareness of having clinical DSPN among subjects with prediabetes and with diabetes. The high frequency of unawareness among the latter group is of particular concern, given that subjects with diabetes receive regular diabetes care. Despite the performance of foot examinations by a physician, the proportion of subjects with known diabetes unaware of having DSPN is high. Overall, these results suggest inadequate attention to diabetic foot prevention practice and insufficient adherence to the clinical guidelines for diabetes care necessary to prevent further development of severe diabetic foot complications.

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B.W.C.B. performed data analyses and wrote the manuscript. W.R. planned the study, contributed to data analyses, and wrote the manuscript. M.H., B.K., C.H., D.S., and C.M. reviewed and edited the manuscript. D.Z. planned the study, contributed to data analyses and discussion, and reviewed and edited the manuscript. W.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Dispensation Patterns of Glucose-Lowering Drugs in Newly Diagnosed Type 2 Diabetes: Routine Data Analysis of Insurance Claims in Germany

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ABSTRACT

Aims To describe dispensation patterns of glucose-lowering drugs in newly diagnosed type 2 diabetes in Germany.

Materials and methods Based on claims data from four statutory health insurances (German Pharmacoepidemiological Research Database, > 25 million insurants), all individuals with newly diagnosed type 2 diabetes were identified. Eligible patients had a first diagnosis for type 2 diabetes between January 2012 and December 2016. We analyzed the dispensation patterns of first-line glucose-lowering therapies initiated in the year after diabetes diagnosis and patterns of second-line therapies dispensed one year after first-line treatment.

Results A total of 356,647 individuals with newly diagnosed type 2 diabetes were included (average age [SD]: 63.5 [13.4] years; 49.3 % males). Of the 31.6 % of individuals who were pharmacologically treated in the year after diagnosis, metformin monotherapy was most frequently dispensed (73.1 %), followed by dual therapy of metformin and dipeptidyl peptidase-4 inhibitors (DPP-4is) (6.4 %), and monotherapy with DPP-4is (2.9 %). From 2012 through 2016, sulfonylurea dispensations were reduced by more than 50 %. Dispensations for combination therapies with DPP-4is increased up to 10.6 %. Glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors contributed to 2 % of all treatments. After a median of 5 months, 20.0 % of individuals on pharmacological therapy initiated second-line glucose-lowering treatment.

Conclusions Data from German statutory health insurances (2012 to 2016) showed that most individuals with newly diagnosed type 2 diabetes were dispensed metformin monotherapy in line with diabetes care guidelines. A substantial decrease in the use of sulfonylureas was observed after the introduction of DPP-4i and GLP-1 receptor agonists.

Introduction

Hyperglycemia in newly diagnosed type 2 diabetes is a strong predictor of the need for early intensification of glucose-lowering therapy [1]. Studies have shown that among newly diagnosed patients who failed to control glycemia with metformin monotherapy, treatment intensification within six months was related to a shorter time to achieve good HbA1c [2, 3]. Indeed, intensive glycemic control has been shown to put people´s health on a long-term trajectory. Well-controlled blood glucose levels following a diagnosis of diabetes reduce the risk of associated complications later in life [4], whereas neglected HbA1c levels put the individual at much higher risk of complications [5, 6].

National and international clinical guidelines for the treatment of type 2 diabetes recommend the use of metformin combined with lifestyle changes as a first-line glucose-lowering strategy [7]. When good glycemic control is not achieved within three months of therapy, guidelines recommend the addition of a second glucose-lowering drug and, if necessary, a third drug [7]. There is no international consensus on the optimal second and third-line regimen, and this has resulted in the prescription of various second and third-line treatment strategies in clinical practice.

In Germany, there are no data on glucose-lowering prescription patterns that are representative of the nation´s diabetes population. Studies on treatment patterns have previously been published using the IMS Disease Analyser database, which includes data from a sample of general and internal medicine practices in Germany [8]. A drawback of these data is that they do not provide the full treatment history of an individual since German citizens are free to change their treating physician at any time; consequently, only cases with known diabetes can be analyzed [8]. Glucose-lowering prescription patterns in Germany have further been analyzed using data from two diabetes registries, which comprise data from outpatient clinics throughout Germany [9]. Yet, these hospital-based data too, include individuals with known diabetes only. Data from Germany´s statutory health insurance companies could allow for a more comprehensive and nationwide overview of diabetes treatment in outpatients, including information on the diagnosis of type 2 diabetes and on the prescription and dispensation of drugs. Therefore, the current study aimed to describe dispensation patterns of glucose-lowering drugs in patients with newly diagnosed type 2 diabetes from January 2012 until December 2016 in Germany.

Materials and methods

Study design and data source

This study is a retrospective analysis of data from the German Pharmacoepidemiological Research Database (GePaRD) [10–12]. In brief, the database is based on pseudonymized claims data from four statutory health insurance providers in Germany. GePaRD currently possesses information of about 25 million people from all over Germany who have been insured with one of the participating insurance providers since 2004 or later, including three nationwide (DAK-Gesundheit, Handelskrankenkasse, Die Techniker) and one regional health insurance(s) (AOK Bremen/Bremerhaven). Besides its core data on the start and end of the insurance period and the reasons for the end of insurance coverage (e.g., death), the database contains information on demographic characteristics, outpatient and inpatient services, and diagnoses. GePaRD also contains information on drug dispensations, including Anatomical and Therapeutic Codes, defined daily dose, packaging size, generic, and brand name. Drugs purchased over the counter and in-hospital medications are not included [12]. In- and outpatient diagnoses are coded according to the German modification of the International Classification of Diseases, 10th Revision, (ICD-10-GM). Per data year, there is information on approximately 20 % of the general population of Germany, representing all geographical regions. GePaRD data are representative of the German general population with respect to age, sex, region of residence, and medication dispensations [12, 13]. The suitability of GePaRD data for pharmacoepidemiological research has been assessed methodologically and by validation studies [12, 14, 15]. GePaRD has been used for various types of pharmacoepidemiological studies including drug utilization studies in the elderly [16, 17] and studies investigating the risk associated with taking antidepressants [14, 18–20].

Study population

To be eligible for inclusion in the current study, people aged 18 years and older had to be newly diagnosed with type 2 diabetes between 1 January 2012 and 31 December 2016. Type 2 diagnosis was defined as (i) having at least one inpatient diagnosis (ICD-10-GM codes E11 and E14), (ii) having at least two outpatient diagnoses coded in different quarters yet less than 365 days apart, or (iii) having at least one outpatient diagnosis and a dispensation of an oral glucose-lowering agent or insulin less than 365 days apart. Patients with a diagnosis of polycystic ovary syndrome (ICD-10-GM code E28.2) who were dispensed metformin by their gynecologist were excluded. To make sure that only newly diagnosed individuals were selected we excluded individuals who, in the three years preceding the diagnosis of type 2 diabetes, did not have continuous insurance, had a diagnosis of any other type of diabetes (ICD-10-GM codes E10, E12, and E13), or had a dispensation for a glucose-lowering drug. Included individuals had to have at least one year of continuous insurance after their diabetes diagnosis to ensure sufficient follow-up data.

Definitions

Dispensations for the following glucose-lowering drug classes were assessed: biguanides, sulfonylureas, dipeptidyl peptidase-4 inhibitors (DPP-4is), glucose-like peptide-1 receptor agonists (GLP-1RAs), sodium-glucose co-transporter-2 inhibitors (SGLT-2is), alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, and insulins (ATX codes A10BA through A10BX). First-line treatment was defined as the first-ever glucose-lowering therapy an individual received, which could involve either monotherapy or combination therapy of two, three, or even more glucose-lowering drugs. Second-line and subsequent-line treatment were defined as a change in therapy by either switching to another drug (class), the discontinuation of one or more drugs, or the addition of one or more drugs to the previous-line regimen. Individuals who did not have a glucose-lowering drug dispensation in the first year after diagnosis were assumed to be treated with non-pharmacological therapy (e.g., lifestyle changes) only.

The presence of various comorbidities, diabetes complications, and dispensations for concomitant medication was assessed for the three years preceding the diagnosis of type 2 diabetes.

Statistical analyses

Baseline variables and clinical characteristics of the study population were reported as mean (standard deviation [SD]) or median (interquartile range [IQR]). The numbers of patients in different categories for a variable were reported as number (percentage). All statistical analyses were performed with SAS (version 9.4).

Results

Patient characteristics

A total of 16,386,288 adult people were insured in GePaRD between January 1, 2012, and December 31, 2016. After excluding those without a sufficiently long insurance period and a valid diagnosis of incident type 2 diabetes, 356,647 people (2.2 %) were included in this study (▶ **Fig. 1**). The average age (SD) was 63.5 (13.4) years and 49.3 % of the study population were male. Baseline demographic and clinical characteristics of the study population according to first-line glucose-lowering treatment are presented in ▶ **Table 1**. Individuals dispensed GLP-1RAs represented the youngest group (49.7 ± 11.4 years) while individuals treated with non-pharmacological therapy were on average the oldest (65.2 ± 13.2 years). The percentage participating in a diabetes management program also differed between the groups, with the lowest percentage amongst those dispensed insulins only (42.6 %) and the highest percentage among those dispensed treatment containing GLP-1RAs (77.3 %). Hypertension represented the most frequent comorbidity with percentages ranging from 40.3 % in the insulin-only group to as much as 61.0 % in individuals treated non-pharmacologically. The highest prevalences, however, were observed in both individuals with non-pharmacological therapy (61.0 %) and those dispensed oral drugs only (56.3 %). This was also observed for hyperlipidemia (44.3 and 33.6 %, respectively). The frequency of obesity was remarkably high among individuals dispensed GLP-1RA therapy (71.1 %) and lowest among those dispensed insulin only (27.1 %). Individuals who were not treated pharmacologically had the highest absolute prevalence of concomitant medication.

Dispensation frequencies of first-line glucose-lowering therapies

From 2012 through 2016, 31.6 % of the study population were treated with glucose-lowering drugs in the first year after diagnosis. The median time between diagnosis and first-line pharmacological therapy was less than a month (interquartile range: 0–2 months). ▶ **Table 2** presents the dispensation frequencies of the individual glucose-lowering strategies. Of all newly diagnosed patients who received pharmacological diabetes treatment, 73.1 % were dispensed metformin monotherapy and an additional 9.6 % were dispensed metformin in combination with other glucose-lowering agents. DPP-4is (35.5 %), insulin (10.5 %), and sulfonylureas (7.9 %) represented the most frequent combinations with metformin. About 5.6 % of the study population were exclusively dispensed insulin, a total of 5.4 % were dispensed a combination of insulin with one or more other glucose-lowering drugs. Overall, metformin monotherapy was by far the most often dispensed treatment (73.1 %), followed by dual therapy with metformin and DPP-4is (6.4 %), and monotherapy with DPP-4is (2.9 %). Across all possible forms of first-line therapies, GLP-1RAs and SGLT-2is contributed to only 2 % of treatment regimens.

Overall, there were no striking differences in treatment dispensations between men and women or between individuals living in West- versus East Germany. Furthermore, dispensed treatment frequencies did not significantly differ between individuals with and without baseline macrovascular disease or between those with and without a diagnosis of depression.

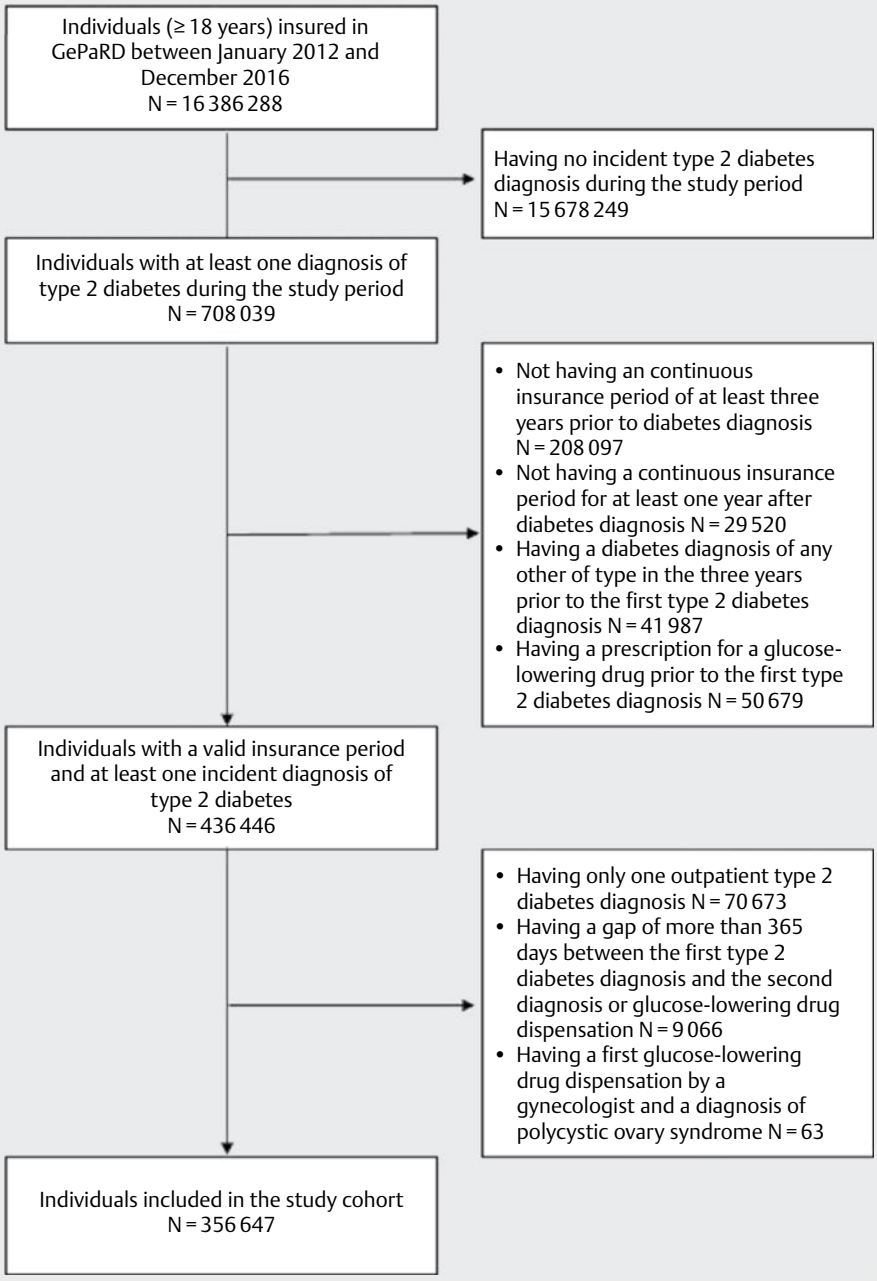
Trends in dispensation patterns of first-line glucose-lowering therapies

Within the groups of mono-, dual-, and triple therapies, changes in dispensation frequencies of certain treatment regimens were observed during the study period. First, dispensation frequencies of sulfonylureas and combination therapies with sulfonylureas decreased by more than 50 % over the study period. Sulfonylurea monotherapy decreased from 2.4 % in 2012 to 1.0 % in 2016; metformin and sulfonylurea dual therapy decreased from 15.9 % in 2012 to 6.0 % in 2016; metformin, sulfonylurea, and DPP-4i triple therapy decreased from 14.0 % in 2012 to 6.3 % in 2016; metformin, sulfonylureas and insulin triple therapy decreased from 5.8 % in 2012 to 1.1 % in 2016. Second, whereas dispensations with DPP-4is were already amongst the most frequent ones, an increase in dispensations of certain combined treatment strategies with DPP-4is could nevertheless be observed. Dispensations for combined therapy with DPP-4is and insulin increased from 0.9 % in 2012 to 2.5 % in 2016, and those for DPP-4is with metformin and SGLT-2is increased from 1.0 % in 2012 to 10.6 % in 2016.

The frequency of dispensations for insulin monotherapies and for insulin-based combination therapies, other than those that also comprised sulfonylureas or DPP-4is, showed only very minor changes from 2012 to 2016. The same was true for treatments with GLP-1RAs and with SGLT-2is. The only exception was dual therapy of metformin with SGLT-2is, for which a relative increase of more than 10 % was observed during the study period.

Dispensation patterns of second-line glucose-lowering treatment

A total of 22,579 people (20.0 % of glucose-lowering drug users) initiated second-line glucose-lowering therapy within the first year after the start of first-line pharmacological treatment. We did not observe any apparent baseline differences in demographic and clinical characteristics between those who, relatively early after the diagnosis of diabetes, initiated second-line therapy and those who did not (results not shown). Overall, second-line treatment was started after a median of five (IQR: 3–8) months. The percentage that initiated second-line treatment was highest among (first-line) monotherapy users (51.2 %) and lowest among those who had been treated with a combination of more than three glucose-lowering drugs (3.6 %). Overall, the most frequently dispensed second-line therapy was the combined treatment with metformin and DPP-4is (21.4 %), followed by metformin monotherapy (16.7 %) and monotherapy with either insulin or DPP-4is (both 12.0 %).



▶ **Fig. 1** A flow chart for the inclusion of participants in this study. Individuals may have been excluded from the study cohort for more than one reason.

The total percentage of individuals who merely switched to other drugs within their mono, dual or triple therapy regimen amounted to 16.5 % (▶ **Fig. 2**). For these treatment classes, the most commonly dispensed regimens were DPP-4i monotherapy (48.6 %), metformin and DPP-4i dual therapy (28.7 %), and metformin, DPP-4is and insulin triple therapy (40.0 %), respectively.

Amongst individuals initially dispensed monotherapy, second-line therapy involved a switch to dual therapy in 60.3 % of cases (▶ **Fig. 2**). For those on first-line dual or triple-drug therapy, a downgrade of treatment to mono or dual therapy was the commonest strategy followed. This was also true for people who were treated with more than three glucose-lowering drugs.

Finally, while treatment with DPP-4is was the most frequently dispensed second-line monotherapy for individuals whose first-line strategy comprised monotherapy (48.6 %), metformin monotherapy was this for initial users of dual and triple therapy who downgraded their treatment (45.2 and 53.8 %, respectively) (▶ **Fig. 2**). The combined treatment with metformin and DPP-4is was most frequently dispensed of all second-line dual treatments (52.1 %), irrespective of the type of first-line therapy. Besides, among the triple

▶ **Table 1** Baseline demographic and clinical characteristics of 356,647 individuals with newly diagnosed type 2 diabetes between January 2012 and December 2016 starting first-line glucose-lowering therapy within 12 months after diagnosis.

	Glucose-lowering therapy[a]				
Baseline characteristics	**Non-pharmacological[b]**	**Oral drugs only[c]**	**Oral drugs and insulin[d]**	**Insulin only[e]**	**GLP-1RA[f]**
N	243,909	98,135	7,158	6,327	1,118
Age (SD), years	65.2 (13.2)	60.2 (12.6)	57.8 (13.4)	57.3 (17.6)	49.7 (11.4)
Male sex (%)	113,684 (46.6)	53,953 (55.0)	4,471 (62.5)	3,124 (49.4)	619 (55.4)
Participation in a diabetes management program (%)	131,131 (53.8)	60,789 (61.9)	4,920 (68.7)	2,695 (42.6)	864 (77.3)
Months between diagnosis and pharmacological therapy, median (IQR)	–	1 (0–2)	0 (0–1)	1 (0–2)	0 (0–1)
Initiation of second-line pharmacological therapy within 12 months after first-line therapy (%)	–	14,643 (14.9)	4,826 (67.4)	2,639 (41.7)	471 (42.1)
Microvascular complications[g] (%)					
Retinopathy	3,762 (1.5)	608 (0.6)	80 (1.1)	63 (1.0)	8 (0.7)
Nephropathy	3,707 (1.5)	1,301 (1.3)	164 (2.3)	139 (2.2)	21 (1.9)
Neuropathy	7,069 (2.9)	2,473 (2.5)	294 (4.1)	208 (3.3)	35 (3.1)
Comorbidities[g] (%)					
Coronary heart disease	46,369 (19.0)	11,913 (12.1)	784 (11.0)	774 (12.2)	90 (8.1)
Heart failure	19,539 (8.0)	5,443 (5.5)	485 (6.8)	585 (9.2)	53 (4.7)
Myocardial infarction	4,601 (1.9)	1,614 (1.6)	151 (2.1)	127 (2.0)	13 (1.2)
Peripheral vascular disease	39,936 (16.4)	10,555 (10.8)	683 (9.5)	757 (12.0)	84 (7.5)
Hypertension	148,738 (61.0)	55,275 (56.3)	3,094 (43.2)	2,549 (40.3)	551 (49.3)
Hyperlipidemia	108,121 (44.3)	32,940 (33.6)	1,547 (21.6)	1,402 (22.2)	267 (23.9)
Obesity	77,175 (31.6)	40,971 (41.5)	2,539 (35.5)	1,714 (27.1)	795 (71.1)
Chronic liver disease	35,617 (14.6)	13,375 (13.6)	790 (11.0)	892 (14.1)	120 (10.7)
Chronic kidney disease	21,562 (8.8)	4,615 (4.7)	385 (5.4)	706 (11.2)	52 (4.7)
Cancer	26,632 (10.9)	7,259 (7.4)	481 (6.7)	899 (14.2)	44 (3.9)
Depression	85,770 (35.2)	30,603 (31.2)	2,018 (28.2)	2,055 (32.5)	403 (36.0)
Concomitant medication[h] (%)					
Statins	69,732 (28.6)	21,258 (21.7)	1,126 (15.7)	1,108 (17.5)	135 (12.1)
Angiotensin-converting enzyme inhibitors/Angiotensin-II receptor blockers	137,725 (56.5)	51,709 (52.7)	2,964 (41.4)	2,428 (38.4)	529 (47.3)
Beta-blockers	111,135 (45.6)	39,976 (40.7)	2,409 (33.7)	2,192 (34.6)	396 (35.4)
Calcium channel blockers	56,912 (23.3)	19,956 (20.3)	1,149 (16.1)	1,109 (17.5)	196 (17.5)
Diuretics	61,735 (25.3)	21,822 (22.2)	1,611 (22.5)	1,809 (28.6)	229 (20.5)

Values are presented as numbers and percentages unless otherwise indicated. GLP-1RA: glucose-like peptide-1 receptor agonist; IQR: interquartile range; SD: standard deviation; [a] dispensed within 12 months after the diagnosis of type 2 diabetes; [b] defined as not having been dispensed with a glucose-lowering drug in the first year after the diagnosis of type 2 diabetes; [c] includes any type of oral glucose-lowering drug dispensed as monotherapy or as combination therapy with other oral glucose-lowering drugs; [d] includes one or more oral glucose-lowering drugs in combination with one or more types of insulin; [e] includes any type of insulin dispensed as monotherapy or in combination with other types of insulin; [f] includes any type of glucose-like peptide-1 receptor agonist dispensed as monotherapy or as combination therapy with one or more oral glucose-lowering drugs and/or one or more types of insulin; [g] diagnosed up to three years preceding the diagnosis of type 2 diabetes; [h] dispensed up to three years preceding the diagnosis of type 2 diabetes.

therapies, the combination of metformin, DPP-4is and insulin represented the most frequently dispensed second-line regimen (32.5 %), again, regardless of the type of first-line therapy.

Discussion and Conclusions

Based on data from statutory health insurances in Germany (2012–2016), 31.6 % of all individuals with newly diagnosed type 2 diabetes received some form of pharmacological therapy in the first year after diagnosis. In line with national and international diabetes care guidelines, 73.1 % of these individuals were dispensed with metformin monotherapy. During the study period, certain combination therapies including DPP-4is were dispensed more often, while frequencies of combination therapies that included sulfonylureas substantially decreased. Overall, no differences in dispensation patterns were observed between men and women or between individuals living in West- and East Germany. In addition, comparisons of dispensation patterns did not suggest that the general practitioners tailored first-line glucose-lowering therapy to whether or not an individual had a diagnosis of macrovascular disease or de-

▶ **Table 2** First-line glucose-lowering therapy of 112,738 individuals in the first year after being newly diagnosed with type 2 diabetes between January 2012 and December 2016.

	N	%
Monotherapy	**90,899**	**80.6**
Metformin	82,450	73.1
Sulfonylureas	1,527	1.4
DPP-4 inhibitors	3,290	2.9
GLP-1 receptor agonists	145	0.1
SGLT-2 inhibitors	271	0.2
Insulin	3,091	2.7
Other	125	0.1
Dual therapy	**15,795**	**14.0**
Metformin and sulfonylureas	1,599	1.4
Metformin and DPP-4 inhibitors	7,218	6.4
Metformin and GLP-1 receptor agonists	393	0.4
Metformin and SGLT-2 inhibitors	681	0.6
Metformin and insulin	2,134	1.9
Sulfonylureas and DPP-4 inhibitors	84	0.1
Sulfonylureas and GLP-1 receptor agonists	5	0.0
Sulfonylureas and SGLT-2 inhibitors	7	0.0
Sulfonylureas and insulin	89	0.1
DPP-4 inhibitors and SGLT-2 inhibitors	24	0.0
DPP-4 inhibitors and insulin	297	0.3
GLP-1 receptor agonists and SGLT-2 inhibitors	6	0.0
Insulins	3,176	2.8
Other	82	0.1
Triple therapy	**4,545**	**4.0**
Metformin, sulfonylureas and DPP-4 inhibitors	446	0.4
Metformin, sulfonylureas and GLP-1 receptor agonists	18	0.0
Metformin, sulfonylureas and SGLT-2 inhibitors	26	0.0
Metformin, sulfonylureas and insulin	140	0.1
Metformin, DPP-4 inhibitors and GLP-1 receptor agonists	62	0.1
Metformin, DPP-4 inhibitors and SGLT-2 inhibitors	266	0.2
Metformin, DPP-4 inhibitors and insulin	1,111	1.0
Metformin and insulins	1,806	1.6
Other	670	0.6
More than three drugs	**1,499**	**1.4**

DPP4: dipeptidyl peptidase-4, GLP1: glucose-like peptide-1, SGLT-2: sodium-glucose co-transporter-2.

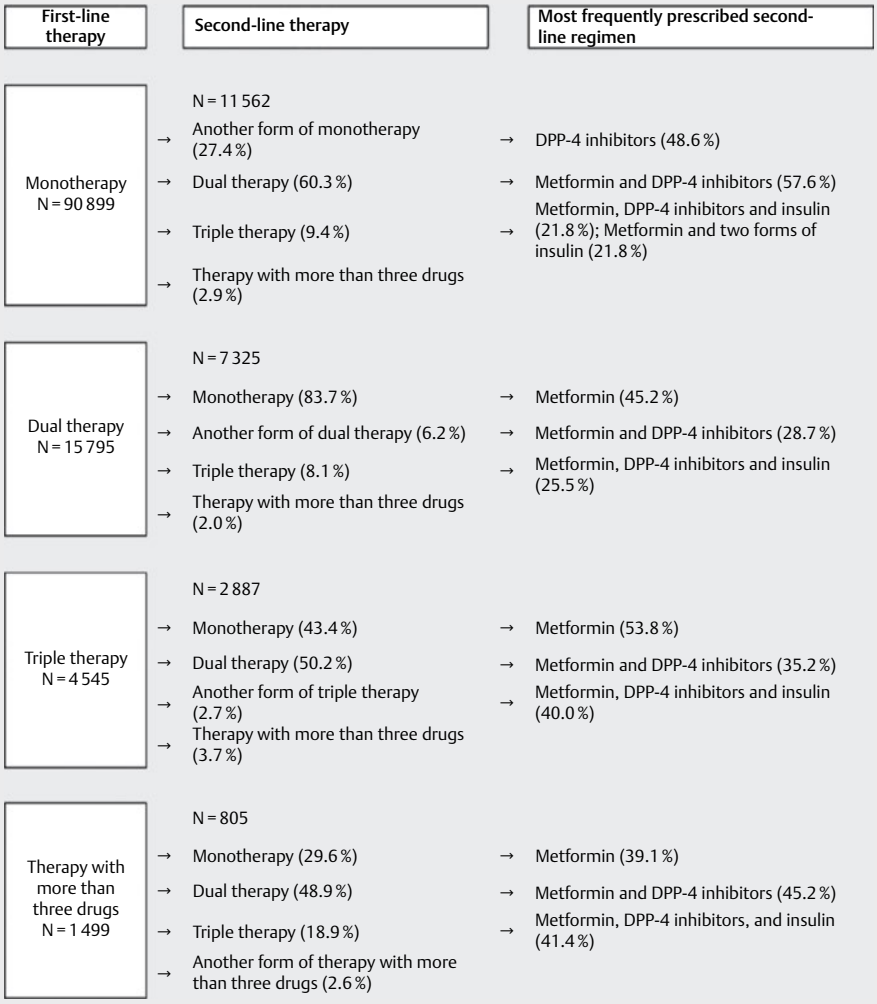
pression. As many as 20.0 % of the study population initiated second-line treatment within one year after starting first-line therapy. The most frequently dispensed second-line treatment was dual therapy with metformin and DPP-4is (21.4 %).

Our data suggested that treatment strategies with DPP-4is were increasingly preferred for newly diagnosed diabetes over strategies with sulfonylureas, confirming previous reports on populations of known diabetes cases in general practices (2008–2016) [8] and in outpatient clinics in Germany (2014–2016) [9]. Also, the observed downward trends in dispensation frequencies of both monotherapy and combination therapy with sulfonylureas had been previously observed in general practice [8]. In that study, the authors reported that the prescription frequency of sulfonylureas declined substantially from the start of the study period in January 2008 (12.5 %) until the end of September 2016 (3.5 %). At the same time, therapies with DPP-4is were prescribed more often, from 0.3 % in 2008 until 4.9 % in 2016 [8]. Since this study only reported how frequently a certain drug had been prescribed in total, without distinguishing between specific mono- and combination therapies, a further comparison of distinct treatment strategies was not possible. The study that reported on glucose-lowering therapy in German outpatient clinics had not analyzed treatment patterns at multiple time points [9].

The decreasing use of sulfonylureas is most likely due to the existing (cardiovascular) safety concerns and potential side effects, such as hypoglycemia and weight gain, which can be avoided by the use of other, novel glucose-lowering drugs including DPP-4is [7, 21]. In our study, DPP-4is and combinations with DPP-4is were dispensed substantially more often than sulfonylureas and its combination regimens.

The dispensation frequencies of therapy regimens containing GLP-1RAs or SGLT-2is were low throughout the study period. This is not surprising given that these cost-intensive drugs were only available in Germany since 2007 and 2012, respectively. The fact that many of the cardiovascular safety trials and real-world data reporting on cardiovascular benefits of SGLT-2is and GLP-1RAs were published after 2015 [22–25] may further explain why we did not find any differences between individuals with and without baseline macrovascular disease.

The proportion of individuals in our population who did not receive pharmacological therapy in the first year after a diabetes diagnosis was rather high (68.4 %). Previous studies have reported lower frequencies, ranging from 22–59 % in general practice and outpatient populations, respectively [8, 9], and from 14–25 % in various German population-based cohort studies, respectively [26]. A comparison of these studies with the current study, however, may not be entirely justified for two reasons. First, in line with diabetes care guidelines, we only analyzed glucose-lowering drug dispensations for individuals who started pharmacological treatment within the first year after a diabetes diagnosis. Those who started pharmacological therapy more than one year after diagnosis (12.8 %) were assumed to have initiated glucose-lowering treatment with diet and lifestyle changes instead of medication. Second, previous studies on drug prescription patterns in Germany have all analyzed populations of persons with known diabetes. The current study sample, however, comprises newly diagnosed patients only. In newly diagnosed diabetes, a first strategy may well be to first assess whether diet and lifestyle changes are sufficient to control blood glucose before taking the step to start pharmacological therapy. According to diabetes care guidelines, patient preferences, needs, and values should be central when deciding on an appropriate treatment [21]. To gather potential clues which might explain the relatively high percentage of non-pharmacologically treated individuals, we compared baseline characteristics between indi-



▶ **Fig. 2** Second-line glucose-lowering therapy within 12 months after the initiation of first-line therapy in individuals with newly diagnosed type 2 diabetes. DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1.

viduals with and without pharmacological therapy in the first year after diagnosis. The data showed that individuals with non-pharmacological therapy were on average five years older, diagnosed more often with dyslipidemia, yet less often with obesity, and were taking statins more often. There were no differences concerning other concomitant medication, frequency of microvascular complications, or other comorbidities. Individuals without pharmacological treatment also somewhat less often had German nationality. No further clues for the high proportion of non-pharmacological therapy were thus found.

We did not find significant differences in treatment patterns between individuals living in West- and East Germany. Previously published data from six different German cohort studies performed throughout the country indicated regional differences in self-reported treatment of type 2 diabetes, and a more frequent use of both oral glucose-lowering drugs and insulin in the east than in the west [26]. The authors speculated that the regional patterns might be explained by differences in health care existing between the Federal States in Germany at that time, and at the different times of data collection of the included studies, which was between 1997 and 2006. The fact that we could not reproduce treatment differences between East- and West Germany likely underlies the timing of data collection, which for our study was from 2012 to the end of 2016. Similar to our findings, analyses of general practice data [8] with data collection spanning from 2008 to 2016, have not either found a difference in treatment patterns between East and West Germany. Indeed, over the last decades, the living and working conditions, as well as health care systems, have become more uniform in the country [27].

A strength of the current study is the large database representative for Germany, providing data on glucose-lowering dispensation patterns in a real-life setting and on a population level [28]. The large size of the GePaRD enabled the analysis of specific glucose-lowering treatments, rather than merely counting single drugs. Recall bias is avoided by using the pharmacy dispensing data, and since the exact dates of drug dispenses are available, the risk

of exposure misclassification is low [29]. It has also been shown previously that drug dispensation data provide valid information on drug use in Germany [28]. Our study also has some limitations. The GePaRD does not contain information on inpatient drug dispensations. But because the analyzed glucose-lowering drugs are available by prescription only, the database should have valid and relatively complete information on the use in outpatient diabetes treatment. Our analyses were based on dispensation data and there is no information available on whether the patients actually took the medication and were adherent to therapy. Finally, making statements on non-pharmacological therapy using claims data requires caution, as therapy in form of diet and lifestyle changes is not reimbursed and therefore not documented in the database.

In conclusion, data from statutory health insurance companies in Germany covering 2012 until 2016, showed that a relatively large proportion of individuals with newly diagnosed type 2 diabetes did not receive pharmacological therapy in the first year after diagnosis. Of the 31.6 % of individuals that did, a total of 73.1 % were dispensed metformin monotherapy in line with national and international diabetes care guidelines.

One sentence summary Data from German statutory health insurances (2012 to 2016) showed that most people with newly diagnosed type 2 diabetes were dispensed metformin monotherapy in line with diabetes care guidelines and that there was a substantial decrease in dispensation of therapies including sulfonylureas.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Inappropriate intensification of glucose-lowering treatment in older patients with type 2 diabetes: the global DISCOVER study

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ABSTRACT

Introduction Although individualized target glycated hemoglobin (HbA_{1c}) levels are recommended in older people with type 2 diabetes, studies report high levels of potential overtreatment. We aimed to investigate the proportion of older patients (aged ≥65 years) who potentially received an inappropriately intensive treatment (HbA_{1c} level <7.0% (53.0 mmol/mol)) in a global study. Factors associated with intensive glycemic management and using glucose-lowering medications associated with a high risk of hypoglycemia (high-risk medications (insulin, sulfonylureas, and meglitinides)) were also assessed.

Research design and methods DISCOVER is a 3-year observational study program of 15 992 people with type 2 diabetes initiating second-line glucose-lowering therapy in 38 countries. Data were collected at baseline (initiation of second-line therapy) and at 6, 12, and 24 months. Factors associated with an inappropriately intensive treatment or using high-risk medications were assessed using a hierarchical regression model.

Results Of the 3344 older patients with baseline HbA_{1c} data in our analytic cohort, 23.5% received inappropriate treatment intensification. Among those who had follow-up HbA_{1c} data, 55.2%, 54.2%, and 53.5% were inappropriately tightly controlled at 6, 12, and 24 months, respectively, with higher proportions in high-income than in middle-income countries. The proportion of patients receiving high-risk medications was higher in middle-income countries than in high-income countries. Gross national income (per US$5000 increment) was associated with increased odds of inappropriately intensive treatment but with decreased odds of receiving high-risk medications.

Conclusions A large proportion of older DISCOVER patients received an inappropriately intensive glucose-lowering treatment across the 2 years of follow-up, with substantial regional variation. The use of high-risk medications in these patients is particularly concerning.

Significance of this study

What is already known about this subject?

- Studies from high-income countries, such as the USA and the UK, show that a high proportion of older patients (aged ≥65 years) with type 2 diabetes are potentially overtreated (glycated hemoglobin (HbA_{1c}) level <7.0% (53.0 mmol/mol)) in routine clinical practice.

What are the new findings?

- We found that although gross national income (per US$5000 increment) was associated with greater odds of an inappropriately intensive treatment, participants from lower-middle-income and upper-middle-income countries had greater odds of receiving high-risk glucose-lowering medication than those from high-income countries.
- Almost a quarter of older DISCOVER patients (aged ≥65 years) received inappropriate treatment intensification (HbA_{1c} level <7.0% (53.0 mmol/mol)) at baseline (initiation of second-line glucose-lowering treatment); for approximately half of the patients, treatment was inappropriately intensified during follow-up.

How might these results change the focus of research or clinical practice?

- Our findings demonstrate the need for a more personalized approach to treatment of type 2 diabetes, particularly among older patients from lower-middle-income and upper-middle-income countries.

INTRODUCTION

Guidelines generally recommend a glycated hemoglobin (HbA_{1c}) target level of ≤7.5% (53.0 mmol/mol) in otherwise healthy older (aged ≥65 years) people with type 2 diabetes[1–3] and an HbA_{1c} level of ≤8.5% in older individuals with complex comorbidities. An HbA_{1c} level target of >7.5% may therefore be more appropriate in some older patients[1–7] because they are at an increased risk of hypoglycemic events[8] and related complications, including falls,[9] fractures,[9] cognitive impairment,[10] vascular complications,[11] and increased

mortality.[12] Stringent HbA_{1c} targets to control type 2 diabetes and diabetes-related complications in older individuals often result in complex treatment regimens, leading to an increased risk of polypharmacy (most commonly described as concomitant use of five or more medications), which has been linked to adverse drug events, drug–drug interactions, prescribing cascades, and in some cases poor treatment adherence.[13] With this in mind, guidelines suggest an individualized treatment approach in older patients, with a focus on simple treatment regimens and glucose-lowering drugs that have a low risk of hypoglycemia, such as metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium glucose cotransporter 2 (SGLT-2) inhibitors.[1 7 8 14]

Studies from Europe and the USA suggest that these guidelines are not always followed in clinical practice, with high proportions of older patients potentially being overtreated (patients aged ≥65 years with an HbA_{1c} level of <7.0% (53.0 mmol/mol)).[14–18] This may partially explain the high number of hospitalizations for hypoglycemia among older patients from high-income countries.[19] There is currently lack of available data on the inappropriate intensification of treatment of patients with type 2 diabetes from low-income and middle-income countries.

In order to fill this knowledge gap, we used data from the DISCOVER study program—a 3-year global prospective, observational study program investigating clinical outcomes, health-related quality of life, and treatment patterns in individuals with type 2 diabetes initiating second-line glucose-lowering therapy in 38 countries across 6 continents[20 21]—to assess the prevalence of, and factors associated with, an inappropriately intensive treatment of older patients during the first 24 months of the study.

METHODS

Research design

The methods of the DISCOVER study program have been described in detail elsewhere.[20 21] In brief, the DISCOVER study program comprises two similar 3-year non-interventional, prospective, observational studies of 15 992 patients with type 2 diabetes initiating second-line glucose-lowering therapy across 38 countries (DISCOVER (NCT02322762) in 37 countries and J-DISCOVER (NCT02226822) in Japan).[20 21] Countries participating in the DISCOVER study are as follows: Algeria, Argentina, Australia, Austria, Bahrain, Brazil, Canada, China, Colombia, Costa Rica, Czech Republic, Denmark, Egypt, France, India, Indonesia, Italy, Japan, Jordan, Kuwait, Lebanon, Malaysia, Mexico, the Netherlands, Norway, Oman, Panama, Poland, Russia, Saudi Arabia, South Africa, South Korea, Spain, Sweden, Taiwan, Tunisia, Turkey, and the United Arab Emirates. In line with the non-interventional nature of the study, the protocol did not mandate the use of specific drugs. Treatment decisions were made by physicians, as they would be in routine clinical practice.

Patient enrollment

Patients were enrolled in DISCOVER from December 2014 to June 2016 and in J-DISCOVER from September 2014 to December 2015. To ensure that data were as reflective of routine clinical practice as possible, inclusion and exclusion criteria were kept to a minimum. Briefly, patients aged ≥18 years who were initiating second-line glucose-lowering therapy (defined as adding a glucose-lowering drug or switching between therapies) were eligible for inclusion, provided that they were not pregnant, were not undergoing dialysis, and had no history of renal transplant, and if their first-line therapy was not an injectable agent, or a herbal remedy or natural medicine alone. Whereas J-DISCOVER enrolled only patients who were receiving oral monotherapy as first-line treatment, DISCOVER enrolled patients who were receiving any type of oral therapy (one or more oral agents, or a fixed-dose combination). Full inclusion and exclusion criteria are shown in online supplemental table 1. All eligible patients were invited to participate in the study by their physician and provided written informed consent. A list of participating investigators can be found in online supplemental appendix list 1.

Data collection

Data from China (n=1293) were not included because they were not available at the time of publication owing to governance reasons. Data were collected at baseline (initiation of second-line glucose-lowering therapy) and at 6, 12, and 24 months within a 4-month window (±2 months) to reflect patient visits in routine clinical practice. Data were captured by the treating physician using a standardized electronic case report form (eCRF). Some data were extracted from existing electronic health records in Canada, Denmark, France, Norway, and Sweden. In these countries, data not routinely captured in electronic medical records, such as the reason(s) for treatment change, were obtained by the investigators using a questionnaire that was linked back to patients' medical records. Data collected at baseline and during follow-up included the following: patient demographics (such as sex, age, body mass index (BMI), and duration of type 2 diabetes); clinical variables (such as HbA_{1c} levels); and first-line and second-line glucose-lowering treatments. First-line and second-line therapy refers to a patient's first ever treatment regimen for type 2 diabetes (before study entry) and second treatment regimen (at study baseline), respectively. Treatment at each follow-up visit was recorded because participants may have changed treatment at other routine clinical visits not recorded as part of DISCOVER. Clinical variables were measured in accordance with routine clinical practice, and data collection for these variables was not mandatory.

Gross national income (GNI) per capita in the DISCOVER countries in 2015 was sourced from the

World Bank using the *Atlas* method (online supplemental figure 1).[6] The *Atlas* conversion factor uses a country's exchange rate for the current and preceding 2 years, adjusted for the difference between the rate of inflation in that country and international inflation.

Statistical analyses

Our analytic cohort comprised older participants (aged ≥65 years) with an available baseline HbA_{1c} measurement (N=3344).[22] Inappropriately intensive glucose-lowering treatment was defined (cross-sectionally) as participants having an HbA_{1c} level of <7.0% (53.0 mmol/mol) at the time of data collection at baseline, and at 6, 12, and 24 months after baseline. Insulin, sulfonylureas, and meglitinides were considered medications associated with a high risk of hypoglycemia (high-risk glucose-lowering medications). It is important to note that, while there is no formal definition of inappropriate tight glycemic management in older individuals with type 2 diabetes, our definition is in line with other published studies and is in agreement with the current American Diabetes Association (ADA) guidelines.[1 18 23]

Exploratory variables are presented as numbers (percentages), mean (SD), and median (IQR), as appropriate. P values were calculated, as a measure of statistical significance, using Student's t-test (continuous variables), χ^2 test (categorical variables), or Fisher's exact test (categorical variables). P values <0.05 were considered statistically significant.

Factors associated with having an HbA_{1c} level of <7.0% (53.0 mmol/mol) at 12 months were assessed using a hierarchical regression model with country as a random effect, and with baseline covariates (sex, age, BMI, time since diabetes diagnosis, GNI, and medical history (microvascular complications, macrovascular complications, and chronic kidney disease)) as well as treatment with high-risk glucose-lowering medications at 12 months as fixed effects. A similar model was used to assess the factors associated with use of high-risk glucose-lowering medications at 12 months, with country as a random effect and with the aforementioned baseline covariates and HbA_{1c} level at 12 months as fixed effects. Multiple imputation was used to account for unreported data, which used iterative sequential regression to sample missing values from the predictive distribution of each variable, conditional to all other variables. Variables included in the imputation model were the dependent variables (HbA_{1c} level or use of high-risk medication); all the independent variables (patient demographics (such as sex, age, BMI, and duration of type 2 diabetes), clinical variables (such as HbA_{1c} levels), and first-line and second-line glucose-lowering treatments); and country. Ten randomly imputed data sets were generated in this way. Analyses were replicated on each imputed data set and the model estimates were pooled across imputations using Rubin's rules. All statistical analyses were performed using the SAS V.9.4 statistical software system.

RESULTS

Among the 14 699 DISCOVER participants, 11 891 (80.9%) had an HbA_{1c} measurement at baseline. Our analytic cohort comprised 3344 patients (28.1%) aged ≥65 years. At baseline, when initiating second-line glucose-lowering therapy, 785 (23.5%) patients aged ≥65 years had an HbA_{1c} level of <7.0% (53.0 mmol/mol; figure 1). Of these potentially inappropriately intensified patients, 252 (32.1%) received second-line treatment with high-risk glucose-lowering medications (figure 1A). Baseline characteristics were similar between patients with HbA_{1c} levels of <7.0% or ≥7.0% (53.0 mmol/mol) at 12 months (table 1).

Follow-up data at 6, 12, and 24 months were available for 2431 (72.7%), 2578 (77.1%), and 2465 (73.7%) older patients, respectively. An HbA_{1c} level of <7.0% (53.0 mmol/mol) was noted in 1343 (55.2%), 1398 (54.2%), and 1320 (53.5%) patients at 6, 12, and 24 months, respectively (figure 1A). Among patients with HbA_{1c} levels of <7.0% (53.0 mmol/mol), high-risk glucose-lowering medications were prescribed in 474 (35.4%), 495 (36.0%), and 462 (36.1%) patients at 6, 12, and 24 months, respectively (figure 1A).

The proportion of patients with an HbA_{1c} level of <7.0% (53.0 mmol/mol) varied between lower-middle-income, upper-middle-income, and high-income countries (figure 1B–D). Whereas the proportion of patients with an HbA_{1c} level of <7.0% (53.0 mmol/mol) was highest in high-income countries, the proportion of patients receiving treatment with high-risk glucose-lowering medications was highest in middle-income countries at all time points.

In the hierarchical regression model, patients with a longer duration of diabetes and those who were prescribed treatment with high-risk glucose-lowering medications, at the time of their 12-month visit, had decreased odds of having an HbA_{1c} level of <7.0% (53.0 mmol/mol) (figure 2). Country income (GNI per US$5000 increment) was associated with increased odds of a patient having an HbA_{1c} level of <7.0% (53.0 mmol/mol) at 12 months.

The proportion of patients receiving treatment with sulfonylureas at 12 months was significantly lower in patients with an HbA_{1c} level of <7.0% (53.0 mmol/mol; 29.5%) than in those with an HbA_{1c} level of ≥7.0% (53.0 mmol/mol; 42.4%) (table 1). Similarly, the proportion of patients receiving treatment with insulin at 12 months was also significantly lower in patients with an HbA_{1c} level of <7.0% (53.0 mmol/mol; 2.3%) than in those with an HbA_{1c} level of ≥7.0% (53.0mmol/mol; 10.9%) (table 1).

In the multivariable model, high BMI at baseline (per 5 kg/m^2 increment), 12-month HbA_{1c} level of <7.0% (53.0 mmol/mol, vs ≥7.0%), and shorter duration of type 2 diabetes were associated with decreased odds of being treated with high-risk glucose-lowering medication (figure 3). Country income (GNI per US$5000 increment) was also associated with decreased odds of being

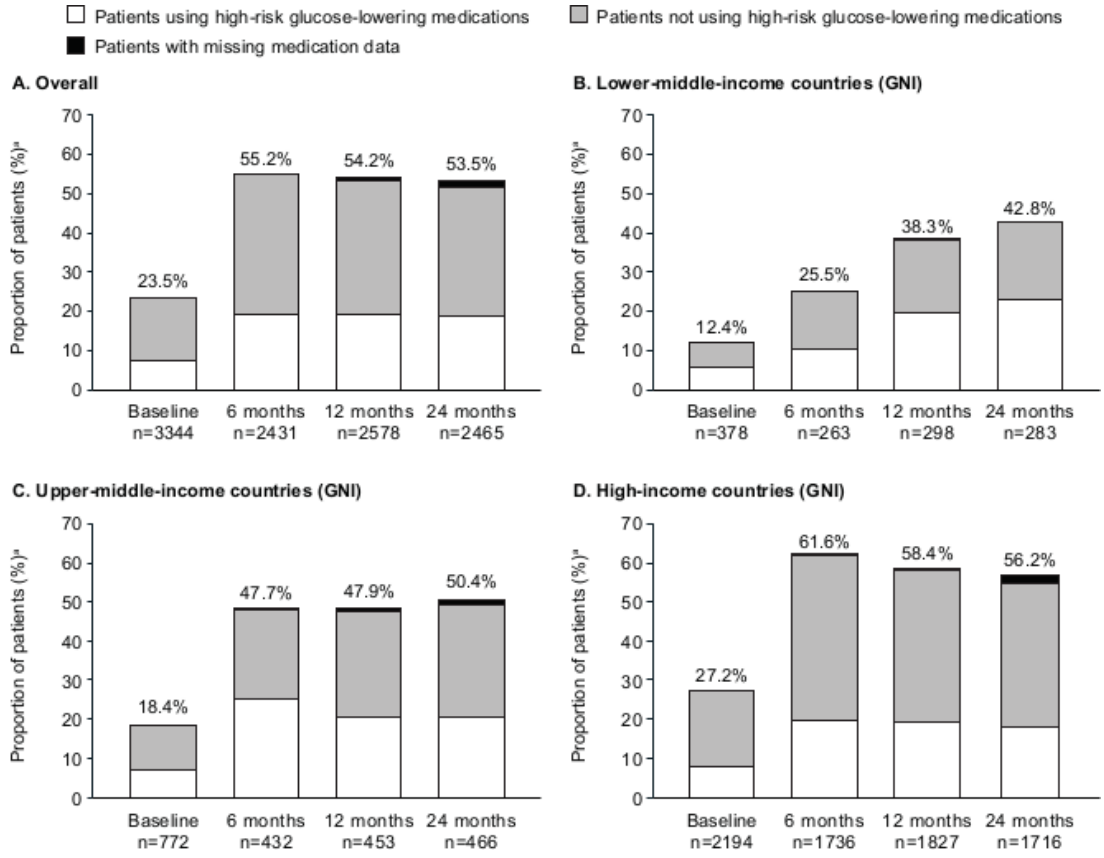

Figure 1 Proportion of older patients (aged ≥65 years) with HbA_{1c} level of <7.0% treated with or without high-risk glucose-lowering medications (insulin, sulfonylureas, and/or meglitinides): (A) overall, (B) lower-middle-income countries (GNI: US$1005–US$3955), (C) upper-middle-income countries (GNI: US$3956–US$12 235), and (D) high-income countries (GNI: ≥US$12 236). This analysis included older patients with treatment information available at baseline and at 6, 12, and 24 months. [a]Patients aged ≥65 years and had an HbA_{1c} level of <7.0%. GNI, gross national income; HbA_{1c}, glycated hemoglobin.

treated with high-risk glucose-lowering medications at 12 months.

CONCLUSIONS

In an observational analysis of a large global cohort of patients with type 2 diabetes, we found that a quarter of older participants had an HbA_{1c} level of <7.0% (53.0 mmol/mol) at baseline and approximately half of participants had an HbA_{1c} level of <7.0% (53.0 mmol/mol) during follow-up. The overall increase in the proportion of patients receiving inappropriately intensive treatment could be explained, in part, by the fact that all DISCOVER participants were initiating second-line glucose-lowering therapy (defined as add-on or switching), which may result in a decrease in the overall mean HbA_{1c} level between baseline and 6 months. Thereafter, the proportion of participants for whom therapy was inappropriately tight remained high, possibly because some physicians failed to recognize inappropriate intensification and adapt treatment accordingly.

The proportion of patients who were overly intensively treated varied across countries in all income brackets. A novel finding was that patients in high-income countries were more likely to have intensive glycemic control, potentially reflecting stricter treatment regimens, with a greater emphasis placed on glucose monitoring and achieving glycemic targets, and better access to healthcare. The increased prevalence of baseline vascular complications in patients from high-income countries, compared with patients from lower-middle-income countries seen in a previous analysis of DISCOVER data,[11] may also play a part in driving the high rate of inappropriately intensively treated diabetes, with a focus on ensuring that these patients achieve good glycemic control to minimize their risk of diabetes-related vascular complications. Intensive glycemic control and the presence of comorbidities that require medical treatment may place some patients at an increased risk of polypharmacy, with low HbA_{1c} levels only achieved, in some cases, through the use of multiple glucose-lowering medications. In the USA, 57% of women and 59% of men reported using more than five different medications on a weekly basis, with older adults with type 2 diabetes at high risk of polypharmacy.[13] Similarly, in Italy, 51.7% of older individuals (aged ≥65 years) with type 2 diabetes were reported to have polypharmacy, with comorbidities and diabetes-related complications shown to be associated with increased risk of polypharmacy.[24]

At each time point, approximately one-third of overly intensively controlled patients received a

Table 1 Characteristics of DISCOVER study patients aged ≥65 years, according to HbA_{1c} level after 12 months of follow-up

	Overall n=2578	HbA_{1c} level after 12 months of follow-up		
		HbA_{1c} <7.0% n=1398	HbA_{1c} ≥7.0% n=1180	P value*
Sex, male, n (%)	1422 (55.2)	788 (56.4)	634 (53.8)	0.188
Missing, n	3	1	2	
Age, years, mean (SD)	72.2 (5.5)	72.4 (5.5)	71.9 (5.5)	0.042
HbA_{1c} level at baseline, %, mean (SD)	7.8 (1.3)	7.4 (1.2)	8.3 (1.3)	<0.001
BMI, kg/m^2, mean (SD)	24.6 (4.3)	24.4 (4.3)	25.1 (4.2)	0.018
Missing, n	1777	884	893	
Country GNI, n				
Lower-middle	298	114	184	<0.001
Upper-middle	453	217	236	<0.001
High	1827	1067	760	<0.001
Time since diagnosis, years, mean (SD)	7.8 (6.4)	7.4 (6.2)	8.3 (6.4)	<0.001
Missing, n	109	66	43	
Medical history, n (%)				
Macrovascular complications	676 (26.3)	370 (26.6)	306 (26.0)	0.712
Missing, n	10	8	2	
Microvascular complications	759 (29.5)	406 (29.1)	353 (29.9)	0.661
Missing, n	4	4		
Chronic kidney disease	323 (12.5)	192 (13.8)	131 (11.1)	0.041
Missing, n	4	4	0	
First-line treatment†, n (%)				
Metformin	1699 (65.9)	872 (62.4)	827 (70.1)	<0.001
DPP-4 inhibitors	559 (21.7)	309 (22.1)	250 (21.2)	0.573
Sulfonylureas	488 (18.9)	204 (14.6)	284 (24.1)	<0.001
α-glucosidase inhibitors	85 (3.3)	58 (4.1)	27 (2.3)	0.008
Meglitinides	62 (2.4)	31 (2.2)	31 (2.6)	0.498
SGLT-2 inhibitors	26 (1.0)	13 (0.9)	13 (1.1)	0.663
Thiazolidinediones	60 (2.3)	35 (2.5)	25 (2.1)	0.518
Treatment at 12 months†, n (%)				
Metformin	1680 (66.7)	866 (63.0)	814 (71.3)	<0.001
DPP-4 inhibitors	1514 (60.2)	861 (62.6)	653 (57.2)	0.005
Sulfonylureas	889 (35.3)	405 (29.5)	484 (42.4)	<0.001
α-glucosidase inhibitors	145 (5.8)	89 (6.5)	56 (4.9)	0.092
GLP-1 receptor agonists	68 (2.7)	41 (3.0)	27 (2.4)	0.341
Meglitinides	143 (5.7)	73 (5.3)	70 (6.1)	0.375
SGLT-2 inhibitors	259 (10.3)	134 (9.7)	125 (10.9)	0.323
Thiazolidinediones	242 (9.6)	134 (9.7)	108 (9.5)	0.806
Insulin	157 (6.2)	32 (2.3)	125 (10.9)	<0.001
Missing	61	23	38	

Percentages were calculated for all patients with data available; patients with missing data were excluded.
*P value was calculated using Student's t-test.
†Treatment categories are not mutually exclusive, and each category includes monotherapies and combination therapies.
BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GNI, gross national income; HbA_{1c}, glycated hemoglobin; SGLT-2, sodium glucose cotransporter 2.

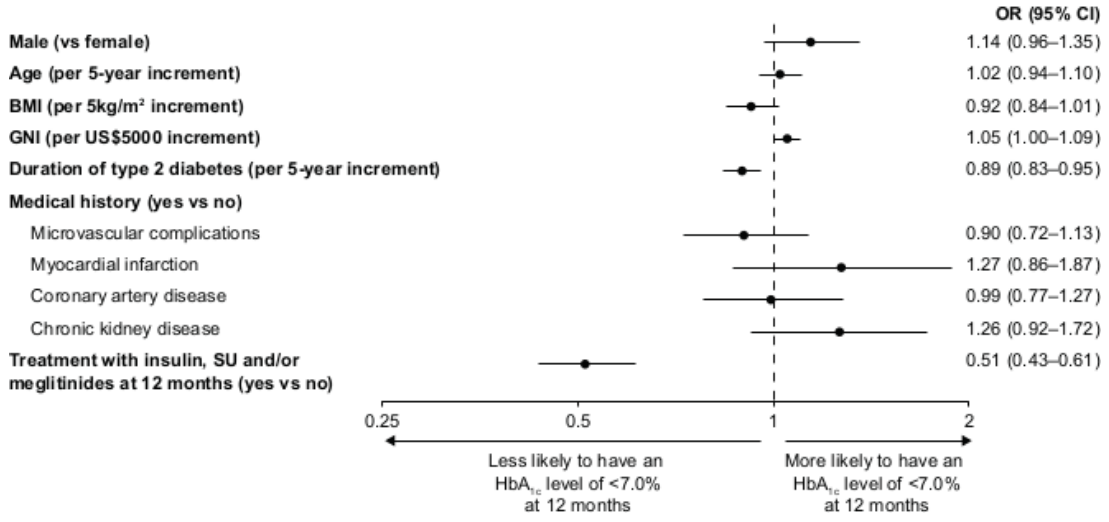

Figure 2 Baseline factors associated with odds of having HbA_{1c} level of <7.0% at 12 months of follow-up. OR was calculated using hierarchical logistic model, adjusted for baseline covariates and treatment at 12 months of follow-up, with country as a random effect. BMI, body mass index; GNI, gross national income; HbA_{1c}, glycated hemoglobin; SU, sulfonylurea.

glucose-lowering treatment associated with a high risk of hypoglycemia. However, patients in lower-middle-income and upper-middle-income countries were more likely to use medications with a high risk of hypoglycemia. This may be indicative of the limited availability and affordability of alternative glucose-lowering therapies, such as DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors, in middle-income countries.[25–27] As such, there seems to be a substantial global opportunity for quality improvement by adopting a personalized treatment approach to decrease the risk of hypoglycemia in older patients with type 2 diabetes.

Our findings are in line with a previous study in the USA in which half of the participants with type 2 diabetes who were aged ≥75 years were prescribed therapies associated with a high risk of hypoglycemia, despite having an HbA_{1c} level of <7.0% (53.0 mmol/mol).[15 18] A similar study in the UK found that 35.7% of people with type 2 diabetes aged ≥70 years were prescribed either insulin or a sulfonylurea; of these individuals, one-third had an HbA_{1c} level of <7.0% (53.0 mmol/mol).[16] Finally, the Guideline Adherence to Enhance Care (GUIDANCE) study of people aged >65 years with type 2 diabetes in eight European countries found that 44.7% of patients were prescribed either insulin or a sulfonylurea despite having an HbA_{1c} level of <7.0% (53.0 mmol/mol).[17] In addition, these studies were all conducted in either Europe or the USA and are therefore not representative of a global population. Our study extends these previous findings to a global cohort of patients from countries with varied income levels.

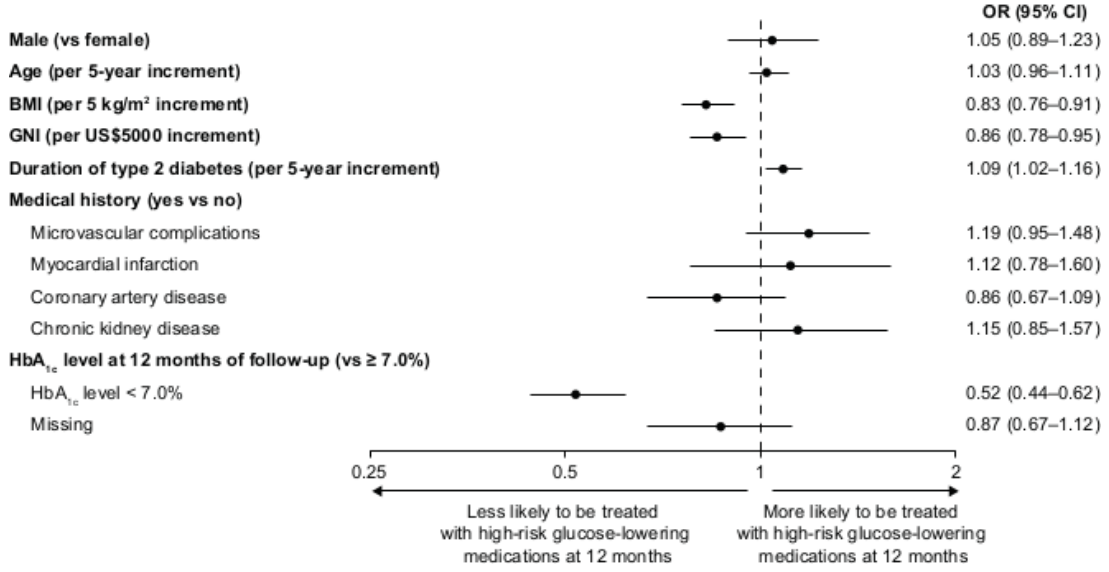

Figure 3 Baseline factors associated with odds of being treated with insulin, sulfonylureas, and/or meglitinides at 12 months. Data on treatment regimen at 12 months were available for 2980 patients. OR was calculated using hierarchical logistic model, adjusted for baseline covariates and HbA_{1c} level at 12 months of follow-up, with country as a random effect. BMI, body mass index; GNI, gross national income; HbA_{1c}, glycated hemoglobin.

Our results, in combination with those of previous studies, indicate that many older patients are still potentially being inappropriately tightly controlled.[15–17] These individuals may thus be at an increased risk of polypharmacy, with adherence to stringent glycemic targets requiring treatment with multiple glucose-lowering medications.[13] The addition of multiple glucose-lowering medications to the treatment regimen of older individuals is associated with an increased risk of drug–drug interactions and other adverse events.[28] The use of glucose-lowering medications that are associated with hypoglycemia in a substantial proportion of these patients is of particular concern. Data from previous studies have shown severe hypoglycemia to be a common cause of hospitalization among older individuals with type 2 diabetes, with the proportion of individuals hospitalized for hypoglycemia exceeding that of hyperglycemia.[29 30] Given the association between inappropriately intensive treatment and risk of hypoglycemia, there may be a need for some physicians to consider treatment regimen simplification (discontinuation of at least one glucose-lowering agent or a reduction in dosage) in some older patients, as per the current ADA guidelines.[1] The benefits and risks of different combinations of glucose-lowering therapies, in combination with medications for associated comorbidities, must be weighed and discussed with the individual and/or caregiver.[13] Primary healthcare practitioners may also benefit from education on how to recognize and manage potentially inappropriate treatment intensifications in older patients. Too tightly controlled glycemia may also result from, at least in part, variables we were unable to measure, such as physician preference and experience, medication costs and availability, and number of physician visits. However, without studying the long-term effects of inappropriate treatment intensification on patient outcomes, our data do not support treatment de-intensification in these patients.

The primary strengths of the DISCOVER study program are both the large number of patients enrolled and the range of treatment sites and countries included, some of which have rarely been studied before. Data collection with a standardized eCRF allowed for the comparison of results between countries and regions. The observational nature of DISCOVER provided an ideal setting to investigate global treatment patterns, with minimal external influence and all treatment decisions made by the physician, as in routine clinical practice. However, our results must be interpreted with several limitations in mind. Although DISCOVER sites were selected to optimize diversity in each country, it is unclear if our findings truly reflect the quality of care within each country or can be generalized outside of the countries and regions included in the study. Participation in DISCOVER may have caused some healthcare practitioners to make different treatment decisions than they would if the data were not being recorded. Given that participants enrolled in DISCOVER were all initiating second-line glucose-lowering therapy, our findings may also not be representative of the entire type 2 diabetes population and may overestimate the proportion of older individuals who are inappropriately strictly managed. Given their involvement in DISCOVER, participating physicians and sites may also be more focused on quality of care than others. This may have resulted in an over-representation of more advanced treatment centers. In line with the observational nature of the study, there was no requirement to record all study variables and a complete data set was not available for all patients. Although these analyses highlight a subset of patients whose treatments are inappropriately intensive, associations between intensive glycemic control and potential adverse effects related to severe hypoglycemia could not be assessed due to the limited follow-up time. Of note, only a small number of participants experienced major hypoglycemic events during the first 12 months after baseline (no participants among those receiving inappropriate treatment intensification at baseline but no high-risk medication and three participants among those receiving inappropriate treatment intensification at baseline and high-risk medications; data not shown). Finally, our definition of an inappropriately intensive glucose-lowering treatment in this older population was based on an HbA_{1c} level of <7.0%, in line with ADA guidelines, which recommend an HbA_{1c} level of <7.5% in older patients. However, lower HbA_{1c} targets may be appropriate for some of these patients. For example, patients early in the disease process, who are otherwise healthy without comorbidities, may benefit from initial tight glycemic control to reduce the risk of microvascular complications and may have been misclassified as being inappropriately tightly controlled.[1]

To conclude, in a global cohort of patients with type 2 diabetes initiating second-line glucose-lowering therapy, we found that 23.5% of older patients treated in routine clinical practice are potentially receiving an inappropriately intensive treatment, leaving them at an increased risk of polypharmacy and possible downstream complications, such as severe hypoglycemia. This proportion of patients increased to more than 50% during follow-up, with substantial variation between regions. Overall, up to one-third of these patients, or more in lower-middle-income and upper-middle-income countries, received treatment with high-risk glucose-lowering medication, potentially leaving them at an even greater risk of hypoglycemia. This highlights the inequality of type 2 diabetes care across the globe and also the need for a more personalized approach to treatment of type 2 diabetes in older patients, with a greater consideration of the benefit to risk ratio of intensive glycemic control. Future analyses could provide information on outcomes associated with inappropriate treatment intensifications and the possible benefits and harms of complex treatment regimens and treatment with high-risk medications and could complement results from interventional studies.

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Contributors BB, SVA, BHC, HC, AC, PF, MG, LJ, KK, MK, JM, AN, MS, IS, FT, HW, and WR agreed on the general content of the manuscript. BB, WR, HC, and FT developed the statistical analysis plan, which was conducted by HC and FT. The first draft of the manuscript was developed by BB, and WR, SVA, BHC, HC, AC, PF, MG, LJ, KK, MK, JM, AN, MS, IS, FT, and HW contributed to its development. BB, SVA, BHC, HC, AC, PF, MG, LJ, KK, MK, JM, AN, MS, IS, FT, HW, and WR approved the final version of the manuscript before its submission. An AstraZeneca team reviewed the manuscript during its development and was given the opportunity to make suggestions. However, the final content was determined by BB, SVA, BHC, HC, AC, PF, MG, LJ, KK, MK, JM, AN, MS, IS, FT, HW, and WR. BB and WR are the guarantors of this work.

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Competing interests BHC, MG, LJ, KK, MK, AN, MS, IS, HW, and WR are members of the DISCOVER Scientific Committee and received financial support from AstraZeneca to attend DISCOVER planning and update meetings. BB and SVA have no competing interests to disclose. HC, AC, PF, and JM are employees of AstraZeneca. In addition, BHC has received payment from AstraZeneca, Boehringer Ingelheim, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, and Takeda. MG has received honoraria from Merck Serono. LJ has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Takeda, Sanofi, and Roche; and research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Roche, and Sanofi. KK has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, Takeda, Servier, and Pfizer; research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, and Pfizer; and also acknowledges support from the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care-East Midlands (NIHR CLAHRC-EM) and the NIHR Applied Research Collaboration and the Leicester Biomedical Research Centre. MK has received honoraria from Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eisai, GlaxoSmithKline, Glytec Systems, Intarcia, Janssen, Merck (Diabetes), Novartis, Novo Nordisk, and Sanofi; and research support from AstraZeneca and Boehringer Ingelheim. AN has received honoraria from AstraZeneca, Eli Lilly, Medtronic, and Novo Nordisk; and research support from Artsana, Dexcom, Novo Nordisk, and Sanofi. MS has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Servier; and research support from Novo Nordisk and Sanofi. IS has received honoraria from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Kowa Pharmaceuticals America, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novo Nordisk, Ono Pharmaceutical, Sanwa Kagaku Kenkyusho, and Takeda; and research support from Astellas Pharma, AstraZeneca, Daiichi Sankyo, Eli Lilly, Japan Foundation for Applied Enzymology, Japan Science and Technology Agency, Kowa Pharmaceuticals America, Kyowa Hakko Kirin, Midori Health Management Center, Mitsubishi Tanabe Pharma, Novo Nordisk, Ono Pharmaceutical, Sanofi, Suzuken Memorial Foundation, and Takeda. HW has received honoraria from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Sumitomo Dainippon Pharma, Eli Lilly, Kissei Pharmaceutical, Kowa Pharmaceuticals America, Kyowa Hakko Kirin, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novartis, Novo Nordisk, Ono Pharmaceutical, Sanofi, Sanwa Kagaku Kenkyusho, and Takeda; and research support from Abbott, Astellas Pharma, AstraZeneca, Bayer, Benefit One Health Care, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Dainippon Sumitomo Pharma, Eli Lilly, Johnson & Johnson, Kissei Pharmaceutical, Kowa Pharmaceuticals America, Kyowa Hakko Kirin, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Nitto Boseki, Novartis, Novo Nordisk, Ono Pharmaceutical, Pfizer, Sanofi, Sanwa Kagaku Kenkyusho, Taisho Toyama Pharmaceutical, Takeda, and Terumo. FT is an employee of the Mid America Heart Institute and has received research support from AstraZeneca. WR has received research support from Novo Nordisk.

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Data availability statement Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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ORIGINAL ARTICLE

WILEY

HbA1c trajectories over 3 years in people with type 2 diabetes starting second-line glucose-lowering therapy: The prospective global DISCOVER study

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Abstract

Aim: To identify distinct HbA1c trajectories in people with type 2 diabetes (T2D) starting second-line glucose-lowering therapy.

Materials and Methods: DISCOVER was a 3-year observational study of individuals with T2D beginning second-line glucose-lowering therapy. Data were collected at initiation of second-line treatment (baseline) and at 6, 12, 24 and 36 months. Latent class growth modelling was used to identify groups with distinct HbA1c trajectories.

Results: After exclusions, 9295 participants were assessed. Four distinct HbA1c trajectories were identified. Mean HbA1c levels decreased between baseline and 6 months in all groups; 72.4% of participants showed stable good levels of glycaemic control over the remainder of follow-up, 18.0% showed stable moderate levels of glycaemic control and 2.9% showed stable poor levels of glycaemic control. Only 6.7% of participants showed highly improved glycaemic control at month 6 and stable control over the rest of follow-up. For all groups, dual oral therapy use decreased over time, compensated for by the increasing use of other treatment regimens. Use of injectable agents increased over time in groups with moderate and poor glycaemic control. Logistic regression models suggested that participants from high-income countries were more probable to be in the stable good trajectory group.

Conclusions: Most people receiving second-line glucose-lowering treatment in this global cohort achieved stable good or highly improved long-term glycaemic control. One-fifth of participants showed moderate or poor glycaemic control during follow-up. Further large-scale studies are required to characterize possible factors associated with patterns of glycaemic control to inform personalized diabetes treatment.

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glucose-lowering drug, glycaemic control, observational study, type 2 diabetes

1 | INTRODUCTION

A variety of classes of glucose-lowering therapies are available for the treatment of type 2 diabetes (T2D), allowing physicians to follow individualized approaches to disease management in their patients.[1-4] Evidence-based, individualized treatment regimens require information about how people will probably respond to treatment, and can thus be supported by the identification of groups of patients who may experience favourable patterns of glycaemic changes over time with certain therapies.[5,6] Using latent class growth modelling, previous studies identified a large group of individuals with T2D who have stable levels of good glycaemic control after treatment. However, there are substantial differences in the HbA1c trajectories of groups exhibiting poor glycaemic control between studies.[7-10] For example, a longitudinal study of 1091 patients with T2D found that 52.8% had either moderate or poor glycaemic control after 2 years of follow-up,[7] whereas a separate longitudinal study of 20 816 patients newly diagnosed with T2D found that just 17.5% had either moderate or poor glycaemic control after 10 years of follow-up.[8] Such heterogeneity may potentially be attributable to differences in study populations and treatment regimens. Currently, no study has exclusively investigated HbA1c trajectories in people with T2D after initiation of second-line glucose-lowering therapy.

DISCOVER was a global observational study of more than 15 000 people with T2D starting second-line glucose-lowering therapy.[11] Participants were recruited from 2014 to 2016 from 38 countries across six regions (Africa, the Americas, South-East Asia, the Eastern Mediterranean, Europe and the Western Pacific) and were followed up for 3 years.[11] Using data from DISCOVER, we aim to identify HbA1c trajectory groups in individuals at an early stage of T2D progression. This is the first study on HbA1c trajectories in people with T2D starting second-line therapy, and the first study on HbA1c trajectories on a global level, including low- and middle-income countries rarely or never having been previously studied.[11,12] We also assess demographic, clinical and treatment characteristics associated with different trajectories.

2 | METHODS

2.1 | Research design

DISCOVER was a 3-year prospective observational study programme of 15 983 people with T2D beginning second-line glucose-lowering therapy in 38 countries (DISCOVER [ClinicalTrials.gov identifier: NCT02322762] in 37 countries and J-DISCOVER [NCT02226822] in Japan).[11,12] Study methods have been described in detail previously.[11,12] Countries were grouped into regions according to World Health Organization categories[13] (Data S1, Table S1), and were categorized by gross national income using 2016 data from the World Bank.[14]

Participants were enrolled in DISCOVER from December 2014 to June 2016, and in J-DISCOVER from September 2014 to December 2015. To ensure that data were as reflective of routine clinical practice as possible, inclusion and exclusion criteria were kept to a minimum. Individuals with T2D were eligible for inclusion if they were starting second-line glucose-lowering therapy, provided that their first-line therapy was not an injectable agent or an herbal remedy/natural medicine alone. Second-line therapy was defined as the addition of one or more drugs, or a switch of drug to another class of hyperglycaemic drug, if first-line therapy was an oral form of monotherapy. Second-line therapy was defined as the discontinuation of a drug, a switch of at least one drug to another class of drug, or a third drug added, if first-line therapy was dual therapy. Similarly, so for first-line therapy being triple or quadruple drug therapy. Full inclusion and exclusion criteria are shown in Data S1, Table S2. Eligible individuals were invited to participate in the study by their physician and provided written informed consent. A list of participating investigators can be found in Data S2.

The study protocol was approved by the clinical research ethics committee in each participating country, along with the appropriate institutional review board at individual study sites. The protocol complied with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guideline and local regulations for clinical research.

2.2 | Data collection

Data were collected at baseline (the date of second-line therapy initiation) and during follow-up at 6, 12, 24 and 36 months using a standardized electronic case report form, and were transferred to a central database via a web-based data capture system. Data collected at baseline and during follow-up included participant demographics (such as sex, age, body mass index [BMI] and duration of diabetes), clinical variables (such as HbA1c levels) and first- and second-line glucose-lowering therapies. In line with the observational nature of the study, variables were measured by participating physicians in accordance with routine clinical practice and data collection for these variables was not mandatory.

2.3 | Statistical analysis

Participants in the DISCOVER study were included in the present HbA1c trajectory analysis if they had at least two HbA1c measurements during follow-up in addition to a baseline measurement. Data from China were excluded because of changes in regulatory requirements during the study (n = 1292). Data are presented as numbers (percentages), means (standard deviations [SDs]) and medians (interquartile ranges [IQRs]), as appropriate.

Latent class growth modelling was used to model HbA1c patterns and identify groups of participants with similar HbA1c trajectories over time (baseline to 36 months).[6] The maximum likelihood method was used to estimate model parameters, with polynomial functions fitted using quadratic and cubic orders. The Bayes Information Criterion (BIC) was used to help assess the optimal number of trajectory groups, with higher BIC values indicating a better model fit than lower values.[15,16] In addition, each HbA1c trajectory group had to contain at least 2.0% of our analytical cohort to avoid identification of groups containing only a small number of participants.[15,16] Very small groups increase statistical uncertainty and numerically destabilize models. The clinical interpretation of each trajectory model was also considered.

Logistic regression models were used to investigate the odds of participants being assigned to different HbA1c trajectory groups, with baseline covariates (sex, age, BMI, country income and second-line therapy [oral monotherapy, dual oral therapy, three or more oral therapies or an injectable agent]) as fixed effects. Our analyses were standard logistic models and hypothesis generating. Multiple imputation was used to impute any unreported data for the independent variables included in the logistic regression model. Iterative sequential regression was employed to sample missing values from the predictive distribution of each variable, conditional on all other variables included in the model. Variables included in the imputation model were the dependent variable (HbA1c trajectory groups) and independent variables (patient demographics [such as sex, age, BMI and country income] and first- and second-line glucose-lowering treatments). Ten randomly imputed datasets were generated in this way. Analyses were repeated on each imputed dataset and model estimates were pooled across imputations using Rubin's rule. Statistical analyses were performed using the SAS 9.4 statistical software system (SAS Institute Inc., Cary, NC).

3 | RESULTS

3.1 | HbA1c trajectory groups and baseline patient characteristics

Of the 14 691 eligible DISCOVER participants, 9295 (63%) had three or more HbA1c measurements, including a baseline measurement, and were included in the analysis (Figure 1).

Latent class growth modelling identified rising BIC values with increasing numbers of patient groups. Based on the criteria of plausible clinical interpretation and a minimum group size of 2.0% of participants, a four-group model (BIC: −60 535) was chosen.

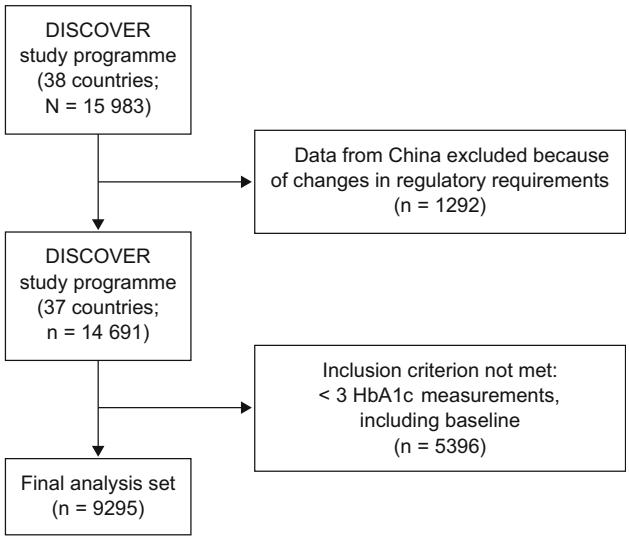

FIGURE 1 Number of participants eligible for analysis

HbA1c trajectories of the resulting four groups are shown in Figure 2. A total of 72.4% of the study population were defined as having 'stable good' levels of glycaemic control, characterized by baseline mean HbA1c levels of 7.6% (59.6 mmol/mol) followed by a decrease in HbA1c level to 6.8% (50.8 mmol/mol) at 6 months and HbA1c levels remaining stable at less than 7.0% (< 53.0 mmol/mol) over the rest of the follow-up period. A total of 18.0% of participants were defined as having 'stable moderate' levels of glycaemic control. In these patients, after an initial fall in HbA1c levels from 8.9% (73.8 mmol/mol) at baseline to 8.3% (67.2 mmol/mol) at 6 months, concentrations remained well above international recommendations for target HbA1c levels of less than 7.0% (< 53.0 mmol/mol).[17] A third trajectory group, comprising 6.7% of the population, was defined as having 'highly improved' levels of glycaemic control. These participants had a high baseline HbA1c level of 11.7% (104.4 mmol/mol), which decreased to 7.8% (61.7 mmol/mol) by 6 months and further decreased to 7.3% (56.3 mmol/mol) by 12 months, remaining stable thereafter. The fourth trajectory group, comprising 2.9% of the study population, was defined as having 'stable poor' levels of glycaemic control. These participants had a high baseline HbA1c level of 11.6% (103.3 mmol/mol), which decreased to 10.9% (95.6 mmol/mol) after 6 months, followed by a small gradual decrease to 10.4% (90.2 mmol/mol) by 36 months.

Baseline characteristics of the analytical cohort overall and by HbA1c trajectory group are shown in Table 1. At baseline, the mean age of participants ranged from 52.3 (SD: 11.2) years in the stable poor group to 59.3 (SD: 12.0) years in the stable good group. The proportion of female participants ranged from 41.3% in the highly improved group to 51.9% in the stable poor group. The mean baseline BMI was similar across the four trajectory groups, while the median duration of T2D ranged from 3.2 (IQR: 1.1-7.3) years in the highly improved group to 4.8 (IQR: 2.3-8.8) years in the stable moderate

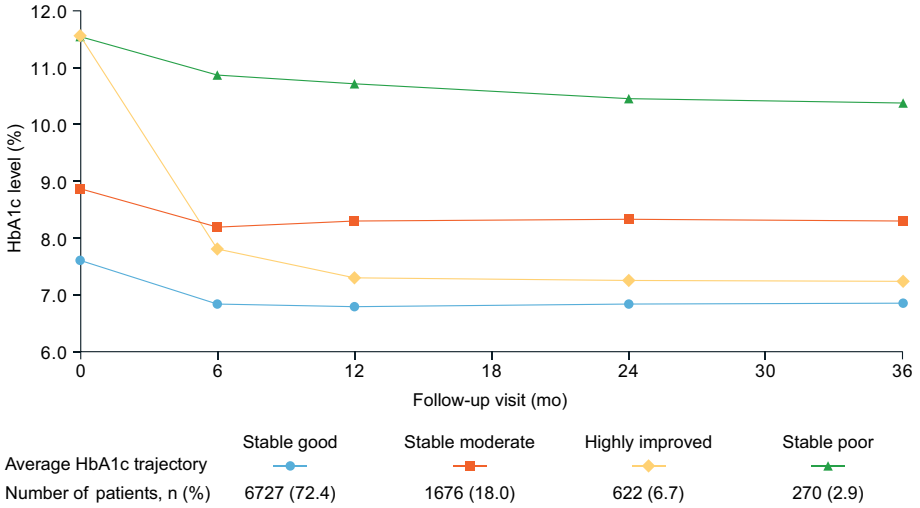

FIGURE 2 Mean HbA1c trajectories of participants assigned to each trajectory group. [a]Stable good group (72.4% of the cohort): a decrease in HbA1c level over the first 6 months followed by stable average HbA1c levels < 7.0% (< 53.0 mmol/mol) for the remainder of follow-up. Stable moderate group (18.0% of the cohort): a decrease in HbA1c level over the first 6 months followed by stable levels for the remainder of follow-up; however, the mean HbA1c level at 36 months remained on average > 7.0% (> 53.0 mmol/mol). Highly improved group (6.7% of the cohort): a steep decrease in HbA1c level between baseline and 6 months before remaining stable for the remainder of follow-up. Stable poor group (2.9% of the cohort): a high baseline HbA1c with a small decrease in HbA1c level over time; however, the mean HbA1c level at 36 months remained high

group. The rate of microvascular co-morbidities at baseline was 21.4% in the stable good group, 22.3% in the stable moderate group, 25.4% in the highly improved group and 25.6% in the stable poor group.

Among the different forms of second-line glucose-lowering therapies at baseline, use of injectable agents was observed most frequently in the stable poor group, whereas oral monotherapy and dual oral therapies were most frequently used in the stable good group. The proportion of participants in each HbA1c trajectory group varied substantially across regions.

3.2 | Logistic regression of factors associated with glycaemic control

Logistic regression models assessing factors associated with different HbA1c trajectories showed that older participants (aged 65-74 and ≥ 75 years) and those treated in a high-income country were more probable to be in the stable good group than in the other trajectory groups (Figure 3). Participants who received three or more oral therapies or an injectable agent were more probable to be in the stable moderate, highly improved or stable poor groups than in the stable good group (relative to those receiving oral monotherapy).

3.3 | Treatment regimens during follow-up

The proportion of participants in each HbA1c trajectory group who received oral monotherapy, dual oral therapy, three or more oral therapies or an injectable agent (glucagon-like peptide-1 receptor agonist or insulin, with or without one or more oral therapies) at each time point is detailed in Figure 4.

In the stable good group (baseline HbA1c level of 7.6% [59.6 mmol/mol]), dual oral therapy was the most common second-line regimen initiated at baseline (69.7% of participants in this group). The slight decrease in use of dual oral therapy during follow-up was matched by an increase in the use of three or more oral therapies, although dual oral therapy accounted for 56.1% of treatment at 36 months. Proportions of oral monotherapy and injectable therapy users were low and remained stable throughout follow-up (Figure 4A). At baseline and 36 months, respectively, in the stable good group, the most commonly used drugs were metformin (75.7% and 76.1%), dipeptidyl peptidase-4 inhibitors (57.3% and 58.5%) and sulphonylureas (34.1% and 35.6%) (Data S1, Figure S1).

In the stable moderate group (baseline HbA1c level of 8.9% [73.8 mmol/mol]), dual oral therapy was the most common second-line regimen at baseline (53.9%), but its use decreased rapidly over time, reaching 28.9% at 36 months of follow-up. The use of three or more oral therapies and injectable agents increased, with three or more oral therapies becoming the most common regimen by the end of follow-up (36.6%) (Figure 4B). Metformin was the most commonly used drug from baseline to 36 months, with the proportions of users being 81.2% and 80.4%, respectively (Data S1, Figure S1).

In the highly improved group (baseline HbA1c level of 11.7% [104.4 mmol/mol]), there was a steady decrease in the use of dual oral therapy from baseline (55.5%) to 36 months of follow-up (37.9%). This was met by an increase in the use of three or more oral therapies from

TABLE 1 Baseline characteristics of participants in the entire cohort and by HbA1c trajectory group

	Overall	Trajectory group[a]			
		Stable good	Stable moderate	Highly improved	Stable poor
Participants, n (%)[b]	9295 (100.0)	6727 (72.4)	1676 (18.0)	622 (6.7)	270 (2.9)
Female, n (%)[b]	4003 (43.1)	2879 (42.8)	727 (43.4)	257 (41.3)	140 (51.9)
Age, y, mean (SD)[b]	58.1 (12.0)	59.3 (12.0)	55.8 (11.9)	54.1 (10.7)	52.3 (11.2)
BMI, kg/m^2, mean (SD)[b]	29.3 (5.8)	29.2 (5.8)	29.9 (5.6)	29.1 (5.8)	30.5 (7.0)
HbA1c level, %, mean (SD)[b]	8.2 (1.6)	7.6 (0.9)	8.9 (1.0)	11.7 (1.3)	11.6 (1.8)
Duration of type 2 diabetes, y, median (IQR)[b]	4.2 (2.1-8.0)	4.2 (2.0-7.9)	4.8 (2.3-8.8)	3.2 (1.1-7.3)	4.1 (2.2-7.9)
First-line therapy, n (%)[b]					
Metformin monotherapy	5417 (58.3)	4034 (60.0)	892 (53.2)	345 (55.5)	146 (54.1)
Other monotherapies	2002 (21.5)	1626 (24.2)	252 (15.0)	92 (14.8)	32 (11.9)
Metformin + SU	1129 (12.1)	600 (8.9)	332 (19.8)	132 (21.2)	65 (24.1%)
Metformin + DPP-4i	311 (3.3)	206 (3.1)	69 (4.1)	28 (4.5)	8 (3.0)
Other combinations[c]	436 (4.7)	261 (3.9)	131 (7.8)	25 (4.0)	19 (7.0)
Second-line therapy, n (%)[b]					
Oral monotherapy	1048 (11.3)	859 (12.8)	142 (8.5)	29 (4.7)	18 (6.7)
Dual oral therapy	6065 (65.3)	4691 (69.7)	903 (53.9)	345 (55.5)	126 (46.7)
Three or more oral therapies	1445 (15.5)	820 (12.2)	427 (25.5)	131 (21.1)	67 (24.8)
Injectable agent[d]	737 (7.9)	357 (5.3)	204 (12.2)	117 (18.8)	59 (21.9)
Region, n (%)[b]					
Africa	344 (3.7)	215 (3.2)	81 (4.8)	30 (4.8)	18 (6.7)
Americas	852 (9.2)	580 (8.6)	168 (10.0)	76 (12.2)	28 (10.4)
South-East Asia	1534 (16.5)	997 (14.8)	356 (21.2)	116 (18.6)	65 (24.1)
Europe	2472 (26.6)	1860 (27.6)	427 (25.5)	141 (22.7)	44 (16.3)
Eastern Mediterranean	1735 (18.7)	1128 (16.8)	385 (23.0)	156 (25.1)	66 (24.4)
Western Pacific	2358 (25.4)	1947 (28.9)	259 (15.5)	103 (16.6)	49 (18.1)
Country income, n (%)[b,e]					
Lower middle	2430 (26.1)	1630 (24.2)	515 (30.7)	202 (32.5)	83 (30.7)
Upper middle	2099 (22.6)	1375 (20.4)	446 (26.6)	188 (30.2)	90 (33.3)
High	4766 (51.3)	3722 (55.3)	715 (42.7)	232 (37.3)	97 (35.9)
Medical history, n (%)[f]					
Macrovascular complications[g]	1158 (12.5)	898 (13.4)	180 (10.7)	56 (9.0)	24 (8.9)
Missing	31	28	0	3	0
Microvascular complications[h]	2038 (21.9)	1438 (21.4)	373 (22.3)	158 (25.4)	69 (25.6)
Missing	10	9	0	1	0
Major hypoglycaemic event[j]	72 (0.8)	48 (0.8)	18 (1.1)	4 (0.7)	2 (0.8)
Missing	548	398	90	46	14
Minor hypoglycaemic event[j]	271 (3.1)	196 (3.1)	55 (3.5)	13 (2.2)	7 (2.7)
Missing	516	373	88	41	14
Chronic kidney disease	567 (6.1)	431 (6.4)	88 (5.3)	36 (5.8)	12 (4.4)
Missing	10	9	0	1	0

Note: Data are reported as n (%) unless otherwise stated.

Abbreviations: BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitors; IQR, interquartile range; SD, standard deviation; SU, sulphonylureas.

[a]Stable good group (72.4% of the cohort): a decrease in HbA1c level over the first 6 months followed by stable average HbA1c levels < 7.0% (< 53.0 mmol/mol) for the remainder of follow-up. Stable moderate group (18.0% of the cohort): a decrease in HbA1c level over the first 6 months followed by stable levels for the remainder of follow-up; however, the mean HbA1c level at 36 months remained on average > 7.0% (> 53.0 mmol/mol). Highly improved group (6.7% of the cohort): a steep decrease in HbA1c level between baseline and 6 months before remaining stable for the remainder of follow-up. Stable poor group (2.9% of the cohort): a high baseline HbA1c with a small decrease in HbA1c level over time; however, the mean HbA1c level at 36 months remained high.

[b]100% of data available.

[c]Two or more agents.

[d]Glucagon-like peptide-1 receptor agonist or insulin.

[e]Categorized using the 2016 World Bank classification.

[f]Percentages were calculated for all participants with data available; participants with missing data were excluded.

[g]Macrovascular complications include coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure and implantable cardioverter defibrillator use.

[h]Microvascular complications include nephropathy, retinopathy and neuropathy.

[i]Major hypoglycaemic events are those that required an emergency room visit, a hospital admission, a visit to a physician or other healthcare professional, or third-party assistance in the year before baseline.

[j]Minor hypoglycaemic events did not require third-party assistance and occurred in the 4 weeks before baseline.[14]

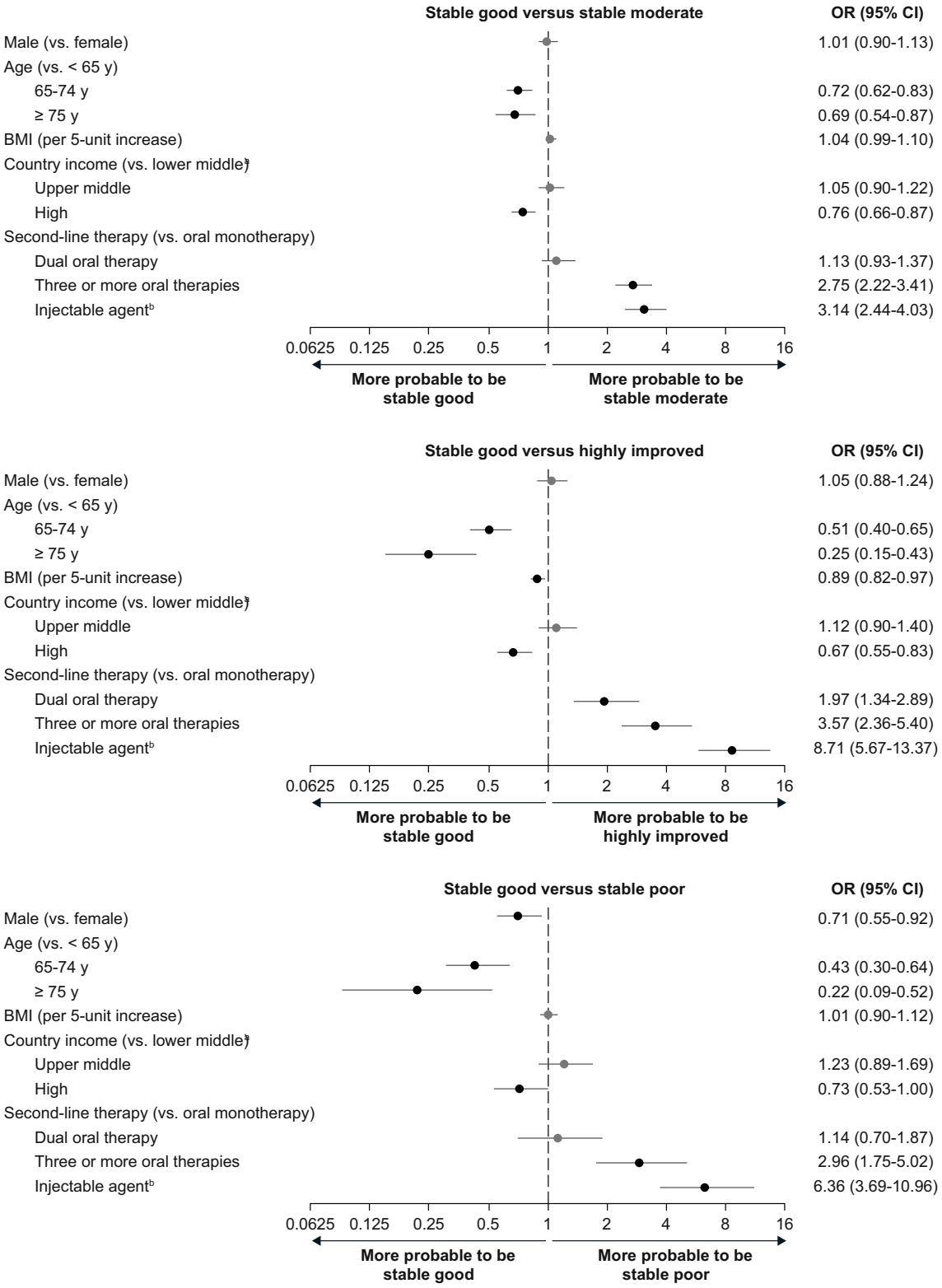

FIGURE 3 Multivariate logistic regression analysis of factors associated with the odds of a participant belonging to an HbA1c trajectory group. ORs were calculated using a logistic regression model adjusted for all variables in the figure. Statistically significant factors are coloured in black. BMI, body mass index; CI, confidence interval; OR, odds ratio. [a]Country income categorized using the 2016 World Bank classification.[14] [b]Injectable agents include glucagon-like peptide-1 receptor agonists and insulin

21.1% to 29.8% (Figure 4C). Again, the most commonly used glucose-lowering drug was metformin (84.6% at baseline and 83.2% at 36 months) (Data S1, Figure S1). In the stable poor group (baseline HbA1c level of 11.6% [103.3 mmol/mol]), where mean HbA1c levels remained high, there was a large decrease in the use of dual oral therapy from 46.7% at baseline to 12.8% at 36 months. This was largely

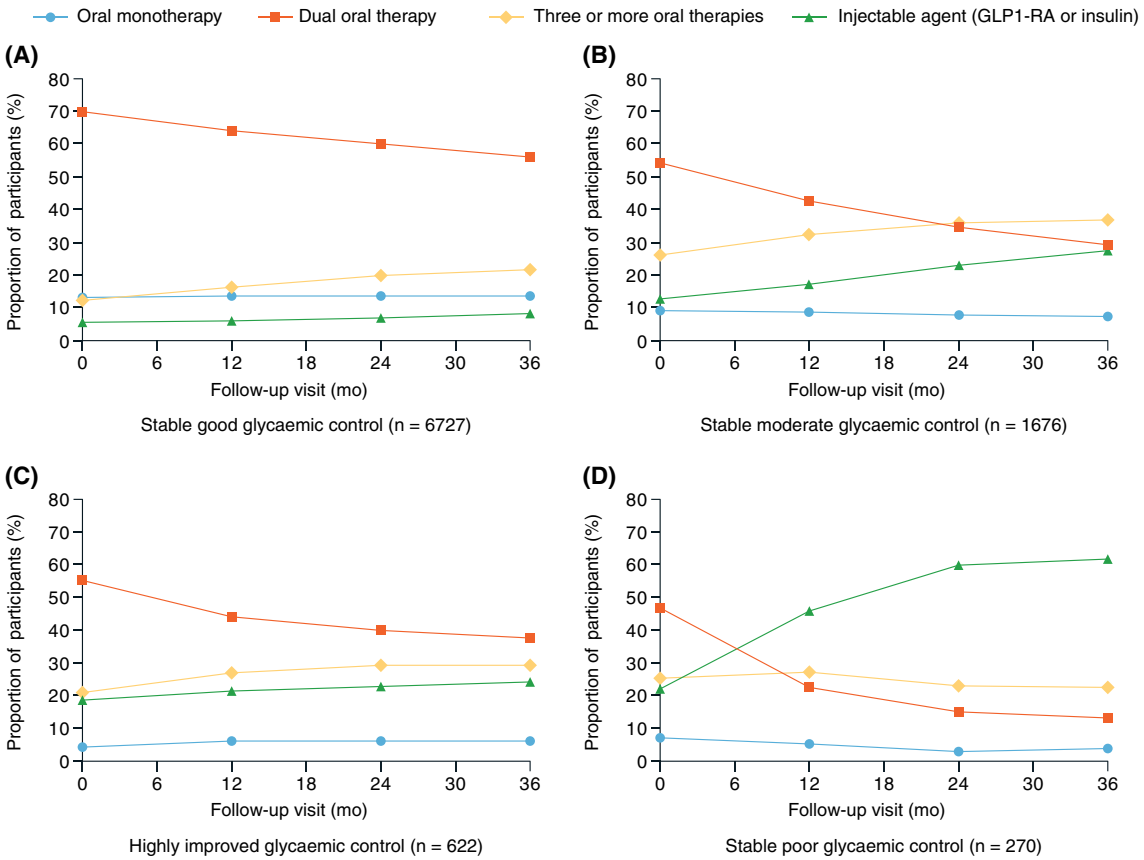

FIGURE 4 Second-line glucose-lowering therapy regimens from baseline to 36 months in the A, Stable good, B, Stable moderate, C, Highly improved, and D, Stable poor glycaemic control groups. GLP1-RA, glucagon-like peptide-1 receptor agonist

compensated for by an increase in the use of injectable agents, from 21.9% at baseline to 61.5% at 36 months (Figure 4D). The large increase in the use of injectable agents largely corresponded to an increase in the use of insulin, from 18.5% at baseline to 58.7% at 36 months (Data S1, Figure S1).

4 | DISCUSSION

This analysis from the DISCOVER global observational study of people with T2D starting second-line glucose-lowering therapy identified four distinct HbA1c trajectories, all of which showed a clear decrease in mean HbA1c level between baseline and 6 months. In all groups after 6 months, either the decrease in HbA1c levels slowed down or the HbA1c levels stabilized. Although there was a continued modest decrease in HbA1c levels in the stable poor group by 12 months, the levels remained very high during the 3-year follow-up, reflected in a shift from mainly dual oral therapy to injectable agents. By contrast, the highly improved group, which had a similar mean HbA1c level to the stable poor group at baseline, showed highly improved glycaemic control during the remainder of follow-up, with treatment with injectable agents remaining comparatively stable and few participants switching from dual oral therapy to three or more oral therapies.

The identification of a large cohort of participants with good glycaemic control (72.4%) is consistent with findings from previous studies in individuals with newly diagnosed diabetes.[8,9] A systematic review of nine studies investigating HbA1c trajectories in individuals with T2D between 2 and 13.6 years of follow-up revealed that up to 89% of participants formed a large group with stable mean HbA1c levels just above 7.0% (53.0 mmol/mol).[5] The review found a wide range in the proportion of participants belonging to a group with a stable HbA1c level (15%-89%); this may be partly explained by differences in study populations such as duration of T2D, prevalence of obesity, use of different glucose-lowering medications and local differences in quality of care. Furthermore, different definitions of glycaemic control make it challenging to compare studies directly.

Treatment regimen at baseline and during follow-up varied between the four HbA1c trajectory groups. Dual oral therapy use was highest in the stable good group at all time points, probably because this group had good glycaemic control at baseline and throughout follow-up, with no need to intensify treatment. The proportion of participants who received an injectable agent almost tripled during follow-up in the stable poor group, probably because of high HbA1c levels at baseline and throughout follow-up. This observation is in line with the results of a large longitudinal study in the United States and five European countries, which indicated that initiation of basal insulin

treatment, with or without oral glucose-lowering drugs, was related to a failure to achieve an HbA1c target of 7.0% or less after 3 and 24 months of treatment.[18]

In all four trajectory groups metformin remained the most commonly used drug at all time points, showing that its use was a stable factor in treatment, regardless of the regimen. Apart from metformin, the most frequently used therapies were sulphonylureas and dipeptidyl peptidase-4 inhibitors in all groups. In line with the published literature, there was a modest yet steady increase in the use of sodium-glucose co-transporter-2 inhibitors in all groups over the entire follow-up period.[19]

The likelihood of being in the stable moderate, highly improved and stable poor groups (compared with the stable good group) was significantly higher in participants receiving second-line therapy regimens including three or more oral therapies or an injectable agent than in those receiving second-line monotherapy. Indeed, more intensive treatments, such as multiple therapies and injectable agents, are more probable to be prescribed to patients with less well-controlled T2D. In the stable poor group, with both high baseline HbA1c levels and the comparatively frequent use of injectables, participants were comparatively young (52.3 vs. 58.1 years in the population overall), with a comparatively high rate of microvascular co-morbidity at baseline (25.6% vs. 21.9% in the overall population). Baseline characteristics and suboptimal glycaemic control during follow-up in the stable poor group may be indicative of a more severe metabolic phenotype, or may have been associated with factors such as poor adherence to injectable therapy. Regarding the effect of age on outcomes among people with T2D, previous studies have shown a more severe metabolic phenotype in younger individuals than in their older counterparts,[20] as well as lower levels of treatment adherence.[21] Furthermore, data from Project Dulce in the United States revealed that people with T2D aged younger than 50 years had higher, less stable HbA1c levels than those aged 50 years or older.[22] Of note, in our study, participants aged 65 years or older, particularly those aged 75 years or older, were more probable to be in the stable good group than those aged younger than 65 years.

Participants from high-income countries were more probable to be in the stable good group than in the other three trajectory groups. This may, at least in part, reflect a higher quality of diabetes care or greater availability of novel glucose-lowering therapies in these countries than in lower-income countries. Countries with a lower socioeconomic status have also been shown to be associated with unstable and poor glycaemic control, with a sharp increase in HbA1c levels seen in the first 5 years following T2D diagnosis in this group of patients.[23]

The large number of participants and the range of treatment sites and countries, some of which have rarely been studied before, are some of the primary strengths of the DISCOVER study. Use of a standardized electronic case report form allowed comparison of results between countries and regions. Although DISCOVER sites were selected to optimize diversity in each country, it is unclear whether our findings truly reflect the quality of care within each country or can be generalized outside the countries and regions included in the study. The proportion of patients in each HbA1c trajectory group varied across regions, suggesting that different diabetes phenotypes may be more prevalent in some regions than in others, although BMI and duration of T2D were similar across HbA1c trajectories.

As participants enrolled in DISCOVER were all beginning second-line glucose-lowering therapy, our findings are not representative of the entire T2D population. Given the observational nature of the study, there was no requirement to record all study variables, and a complete dataset was not available for all participants. Indeed, the entire DISCOVER cohort could not be included in this analysis as only those with three or more HbA1c level measurements, including a baseline measurement, were eligible. This criterion meant that a large proportion of participants was excluded from the analysis (n = 5396). This has the potential to introduce selection bias, as those participants with a greater number of HbA1c measurements may have been better monitored, better managed or may have had characteristics related to more favourable diabetes management. However, in order to adequately assess a trajectory, at least three HbA1c measurements are required. Additionally, the observational nature of this study prevents the control of regression to the mean; however, the trajectories of groups with similar baselines differed remarkably.

In conclusion, our findings support current diabetes care guidelines in advocating a personalized treatment strategy. As the aim of this study was to identify distinct HbA1c trajectories, future studies will be key in further investigations of underlying behavioural, genetic, phenotypical and regional and socioeconomic factors associated with different patterns of glycaemic control, further helping to guide healthcare practitioners treating patients on an individual basis.

AUTHOR CONTRIBUTIONS

All authors contributed to the development of the manuscript and approved the final version before submission. B.B., W.R. and O.K. developed the statistical analysis plan, which was conducted by H.C. An AstraZeneca team reviewed the manuscript during its development and was given the opportunity to make suggestions. However, the final content was determined by the authors. B.B. and W.R. are the guarantors of this work.

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CONFLICT OF INTEREST

B.B. and O.K. have no competing interests to disclose. W.R., F.B., M. B.G., L.J., K.K., A.N., M.V.S. and H.W. are members of the DISCOVER Scientific Committee and received financial support from AstraZeneca to attend DISCOVER planning and update meetings. H.C., A.C., P.F. and J.M. are employees of AstraZeneca. N.H. is a former employee of AstraZeneca. In addition, W.R. has received research support from Novo Nordisk; F.B. has received honoraria from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novartis, Novo Nordisk, Sanofi and Takeda; M.B.G. has received honoraria from Merck Serono; L.J. has received honoraria from AstraZeneca, Bayer, Boehringer

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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REVIEW

Pharmacogenetics of novel glucose-lowering drugs

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Abstract

The aim of this work was to review studies in which genetic variants were assessed with respect to metabolic response to treatment with novel glucose-lowering drugs: dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i). In total, 22 studies were retrieved from the literature (MEDLINE). Variants of the GLP-1 receptor gene (*GLP1R*) were associated with a smaller reduction in HbA_{1c} in response to DPP-4i. Variants of a number of other genes (*KCNQ1*, *KCNJ11*, *CTRB1/2*, *PRKD1*, *CDKAL1*, *IL6* promoter region, *TCF7L2*, *DPP4*, *PNPLA3*) have also been related to DPP-4i response, although replication studies are lacking. The *GLP1R* gene was also reported to play a role in the response to GLP-1 RA, with larger weight reductions being reported in carriers of *GLP1R* variant alleles. There were variants of a few other genes (*CNR1*, *TCF7L2*, *SORCS1*) described to be related to GLP-1 RA. For SGLT2i, studies have focused on genes affecting renal glucose reabsorption (e.g. *SLC5A2*) but no relationship between *SLC5A2* variants and response to empagliflozin has been found. The relevance of the included studies is limited due to small genetic effects, low sample sizes, limited statistical power, inadequate statistics (lack of gene–drug interactions), inadequate accounting for confounders and effects modifiers, and a lack of replication studies. Most studies have been based on candidate genes. Genome-wide association studies, in that respect, may be a more promising approach to providing novel insights. However, the identification of distinct subgroups of type 2 diabetes might also be necessary before pharmacogenetic studies can be successfully used for a stratified prescription of novel glucose-lowering drugs.

Keywords Dipeptidyl peptidase-4 inhibitors · Glucagon-like peptide-1 receptor agonists · Pharmacogenetics · Precision medicine · Review · Sodium–glucose cotransporter 2 inhibitors · Type 2 diabetes

Abbreviations

CDKAL1	Cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1
DPP-4	Dipeptidyl peptidase-4
DPP-4i	DPP-4 inhibitors
EMPHASIS-HF	Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms
GLP-1	Glucagon-like peptide-1
GLP-1 RA	GLP-1 receptor agonists
GWAS	Genome-wide association study
NAFLD	Non-alcoholic fatty liver disease
PDFF	Proton density fat fraction
PIR	Proinsulin/insulin ratio
PNPLA3	Patatin-like phospholipase 3
SGLT2	Sodium–glucose cotransporter 2
SGLT2i	SGLT2 inhibitors
SORCS1	Sortilin related VPS10 domain containing receptor 1
UGT	Uridine diphosphate-glucuronosyltransferase

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Introduction

There is a considerable variation of the interindividual response to glucose-lowering drugs in people with type 2 diabetes [1]. The hope is that genetic variants can be used to explain these therapeutic differences and can be used to stratify subgroups that respond particularly well to specific drug therapies for type 2 diabetes [1]. For example, pharmacogenetic studies have

Summary

Heterogeneity of diabetes

Subgroups of diabetes, based on clinical variables, disease progression or genetic makeup, determine response to treatment with novel glucose-lowering drugs, along with lifestyle factors

Pharmacogenetic studies

Pharmacogenetics reveals that certain genes are associated with therapeutic responses: e.g. variants of *GLP1R*, *KCNQ1*, *KCNJ11*, *CTRB1/2*, *PRKD1*, *CDKAL1*, *IL6* promoter region, *TCF7L2*, *DPP4* and *PNPLA3* have been associated with DPP-4i response; *GLP1R*, *CNR1*, *TCF7L2* and *SORCS1* variants are also reported to play a role in the response to GLP-1 RA; *SLC5A2* has been studied in relation to response to SGLT2i

Limitations of studies

Only a small number of studies have been undertaken, meaning that few data are available. Better-designed studies are needed that are sufficiently large and sufficiently powered; results of existing studies should be replicated; meta-analyses across studies and GWAS are needed

Outlook

The identification of distinct subtypes of type 2 diabetes will be necessary before pharmacogenetic insights can be successfully used for providing stratified prescriptions of novel glucose-lowering drugs. Other areas of focus include studies on microbiome composition and its effect on drug metabolism; application of lessons from monogenic diabetes to the field of pharmacogenetics

reported clinically relevant effects for a genetic variant of GLUT2 in response to treatment with metformin [2, 3]. The C allele of the SNP rs8192675 of the *SLC2A2* gene that encodes GLUT2 was related to a 3.6 mmol/mol (0.33%) greater reduction in HbA_{1c} (CC vs TT alleles) in users of metformin monotherapy (equivalent to a metformin dose difference of 550 mg) [2]. In addition, in individuals with newly diagnosed type 2 diabetes being treated with metformin monotherapy, having at least one C allele was associated with a greater reduction in multivariable-adjusted fasting blood glucose in the first year after diabetes diagnosis compared with individuals without a C allele (6.3 vs 3.9 mmol/l; genotype difference 2.4 mmol/l) [3]. Moreover, the difference between genotypes in individuals treated with metformin was statistically significantly larger than that in people not treated with glucose-lowering drugs (p value for interaction <0.01) [3]. Similar reports exist of genetic variants interfering with metabolic responses to treatment with sulfonylureas and meglitinides [4].

The field of pharmacogenetics is still emerging and there remains a lack of studies on the role of gene variants in treatment effects of novel glucose-lowering drugs, including dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i) [5]. The present review will focus on gene variants related to metabolic responses to these novel agents, including glycaemic effects, diabetes-related metabolic traits and body-weight changes. Mainly, studies in people with type 2 diabetes will be reviewed, although important studies in people without diabetes will also be considered. We carried out a narrative (not a systematic) review because a first investigation of the current literature showed only a few eligible studies with largely different populations and few replications of study findings. Therefore, a meta-analysis would not be possible.

The pathophysiological basis for the therapeutic action of these novel agents has been extensively covered in previous reviews [6, 7] and will not be described here. Although of importance, adverse drug reactions will not be a topic of discussion either, because this requires an in-depth overview of pharmacokinetics and pharmacodynamics, which is beyond the scope of the current work [8].

Heterogeneity of type 2 diabetes

The heterogeneity of type 2 diabetes is a major challenge throughout the entire field of diabetes research. Recently, there have been attempts to categorise different phenotypes of type 2 diabetes [9–11]. First, the so-called ‘palette model’ attempted to explain the heterogeneity of people with diabetes by using a spectrum of factors that contribute to the individual

risk of type 2 diabetes, including pancreatic islet development, number of islets and beta cells, islet function and autoimmunity, and incretin activity, as well as obesity, body fat distribution and insulin resistance [9]. Phenotypes were then categorised by individual (genetic) variations of these traits in a person and their associations with risk factors [9].

Another approach involved a data-driven cluster analysis to classify five diabetes subgroups with differing disease progression and risk of complications [10, 11]. Moreover, genetic differences between these diabetes clusters have been described. The severe autoimmune diabetes cluster was strongly associated with variants of the HLA locus, similar to type 1 diabetes [10]. The non-autoimmune severe insulin-deficient diabetes cluster showed an association with a variant of the *TCF7L2* gene, a locus which shows one of the strongest genetic associations with type 2 diabetes risk [10]. The severe insulin-resistant diabetes cluster was not associated with any of these genetic features [10]. So far, none of the above approaches to distinguish different diabetes phenotypes have been used in pharmacogenetic studies.

The statistical method of latent class analysis has been used in an attempt to identify different subgroups of diabetes [10, 11]. This methodology may benefit pharmacogenetic studies as was shown previously for heart failure [12]. In the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF) trial, 2279 people with heart failure were randomised to receive either eplerenone (an aldosterone receptor blocker) or placebo [12]. Based on a latent class analysis using routinely available clinical variables, four subgroups with a different response to eplerenone treatment were identified. Two of the subgroups derived a larger benefit from eplerenone in the EMPHASIS-HF trial, whereas the other two groups demonstrated a higher rate of eplerenone side effects (hyperkalaemia) and drug discontinuation [12]. These findings may not only help to generate hypotheses on why some individuals respond differently to treatment but also can be a starting point to analyse potential genetic associations with treatment efficacy in distinct subgroups.

Still, it remains important to realise that type 2 diabetes is a heterogenous polygenic disease [1] with many different interacting patient characteristics influencing disease progression and treatment success. Thus, although a study may report for example an improved glycaemic response to a specific drug in a subgroup of individuals that carry a particular SNP, most likely in clinical practice various patient characteristics, including obesity, metabolic risk factors and lifestyle, may dilute the observed effect of the particular SNP. Hence, the integration of pharmacogenetic principles into precision diabetology will likely be highly complex [1]. Predictions of drug efficacy will therefore have a given degree of uncertainty and will need to take into account various metabolic and behavioural factors.

Pharmacogenetic studies of novel glucose-lowering drugs

A MEDLINE literature search for pharmacogenetic studies was conducted independently by the two authors from database inception up to 12 August 2020, by using a predefined search algorithm (see electronic supplementary material [ESM] Methods: Search strategy). We did not apply any restrictions or filters. Out of the 2663 identified articles, 37 duplicates were removed and titles and abstracts of the remaining 2626 publications were scanned. To identify further relevant articles, we also screened the reference lists of included articles. Finally, 12 published studies on DPP-4i, six on GLP-1 RA and four on SGLT2i were included. The characteristics and main results of these pharmacogenetic studies are summarised in Tables 1, 2 and 3.

In the following text, we, describe which genes have been associated with therapeutic responses to each of the three newest glucose-lowering drugs. Then, after summarising the main findings we highlight important limitations of the currently available studies.

DPP-4i

GLP1R The *GLP1R* gene encodes the receptor for glucagon-like peptide-1 (GLP-1), a peptide hormone expressed in pancreatic beta cells [13]. Activation of the GLP-1 receptor facilitates a glucose-stimulated insulin secretion [13]. It has been hypothesised that genetic alterations of the GLP-1 receptor may change the therapeutic response to DPP-4i. In fact, a variant in the *GLP1R* gene (rs6923761; p.Gly168Ser) was found to be associated with a smaller reduction in HbA_{1c} (by 3.0 mmol/mol [0.27%] per A allele) in individuals with type 2 diabetes treated with sitagliptin, vildagliptin or linagliptin for 6 months [14]. This study confirmed an earlier report that this particular gene variant was related to a smaller HbA_{1c} reduction during 6 months of gliptin treatment [15]. Another variant in the *GLP1R* gene (rs3765467; p.Arg131Gln) was reported to be linked to an insulinotropic effect [16]. People with type 2 diabetes with the A allele (GA/AA vs GG) responded better to therapy with DPP-4i (>10% relative HbA_{1c} reduction) and showed a greater HbA_{1c} decrease after 24 weeks of therapy (1.3 ± 1.1 vs $0.9 \pm 1.2\%$; $p = 0.02$) [16].

Potassium channel gene family Potassium voltage-gated KQT-like (KCNQ1) channels play a role in the intestinal secretion of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), and polymorphisms in the gene coding for these channels have been linked to type 2 diabetes through a role in insulin release [17]. A variant in *KCNQ1* (rs163184) was found to be associated with a smaller reduction in HbA_{1c} after 6 months of newly onset DPP-4i therapy in type 2 diabetes patients (0.3% reduction in response per each G allele)

Table 1 Genotypes associated with response to treatment of type 2 diabetes with DPP-4i

Gene	Genetic variant	Study population (*n*)	Glucose-lowering treatment	Clinical outcome	Reference
GLP1R	rs6923761 (G>A, C)	206 with T2D	Sitagliptin 100 mg/day, vildagliptin 100 mg/day, or linagliptin 5 mg/day added to metformin or to metformin and sulfonylurea for 6 months	Smaller reduction in HbA_{1c} (by 4.4 mmol/mol; p=0.016) for AA vs AG and GG genotypes	[14]
GLP1R	rs6923761 (G>A, C)	140 with T2D	Sitagliptin 100 mg/day or vildagliptin 100 mg/day added to metformin or to metformin and sulfonylurea for 6 months	The A allele was associated with HbA_{1c} reduction (β=−3.6 mmol/mol, p=0.011) Smaller reduction in HbA_{1c} for AA vs AG and GG genotypes (change: −1.3 mmol/mol vs −8.7 mmol/mol; p=0.008)	[15]
GLP1R	rs3765467 (G>A, C, T)	246 with T2D	Vildagliptin, sitagliptin, linagliptin, saxagliptin, gemigliptin for 24 weeks	Greater reduction in HbA_{1c} for AA and GA vs GG genotypes (14.2 mmol/mol vs 9.8 mmol/mol; p=0.022); OR for ≥10% HbA_{1c} reduction 2.00 (95% CI 1.03, 3.89) in multivariable logistic regression analysis	[16]
KCNQ1	rs163184 (T>C, G)	137 with T2D	Sitagliptin 100 mg/day or vildagliptin 100 mg/day added to metformin or to metformin and sulfonylurea for 6 months	Smaller reduction in HbA_{1c} for GG and GT vs TT genotypes (β= −3.3 mmol/mol) in multivariate general linear models	[18]
KCNJ11	rs2285676 (T>C)	331 with T2D, 331 control individuals	Sitagliptin 100 mg/day, vildagliptin 50–200 mg/day, linagliptin 5 mg/day for ≥3 months	CC genotype (vs CT and TT genotypes) had a twofold higher chance of attaining HbA_{1c} ≤53 mmol/mol (OR 2.00 [95% CI 1.03, 3.77]) in logistic regression analysis	[20]
CTRB1/CTRB2	rs7202877 (T>C, G)	49 with T2D (Netherlands), 305 with T2D (UK)	Vildagliptin, sitagliptin for ≥3 months	G allele carriers showed a 5.6 mmol/mol smaller HbA_{1c} response compared with the TT genotype (p=0.0015)	[21]
PRKD1	rs57803087 (A>G)	171 with T2D	Sitagliptin, saxagliptin, vildagliptin or linagliptin	Mean HbA_{1c} change after 3 months was −10.4 mmol/mol; in GWAS rs57803087 was associated with response to DPP-4i ($p=3.2\times10^{-6}$)	[23]
CDKAL1	rs7754840 (G>C) rs7756992 (A>G)	798 with T2D	DPP-4i (n=512)	HbA_{1c} reduction after 3 months was −1.1 mmol/mol per rs7754840 C risk allele (p=0.02), maintained after 12 months For rs7756992, HbA_{1c} reduction per risk allele was also significant over 12 months (G risk allele: HbA_{1c} −0.9 to 1.9 mmol/mol)	[24]
IL-6	rs1800796 (G>A, C) rs2097677 (G>A)	331 with T2D	DPP-4i in combination with other glucose-lowering drugs	No relationship between two *IL6* SNPs and non-response to DPP-4i (≥2.2 mmol/mol HbA_{1c} decrease at 3 months); OR for both SNPs combined was 0.45, (p=0.07) Lower odds (OR 0.15) for non-response in moderate/high physical activity group (for both SNPs combined)	[27]
TCF7L2	rs7903146 (C>G, T)	961 with T2D	Linagliptin (5 mg/day) plus metformin or pioglitazone (placebo controlled)	Linagliptin lowered HbA_{1c} in all variant carriers (CC −9.0 mmol/mol, CT −8.4 mmol/mol, TT −6.2 mmol/mol) HbA_{1c} response was reduced in TT compared with CC carriers (2.8 mmol/mol; p=0.02)	[30]
DPP4	rs2909451 (C>A, T) rs759717 (G>C)	27 with T2D and hypertension and 38 healthy control individuals	Sitagliptin 100 or 200 mg/day or matching placebo (RCT)	Genotypes associated with higher DPP4 activity during sitagliptin (rs2909451 TT and rs759717 CC) Predictors of DPP4 activity (multivariable analysis): sitagliptin dose, history of type 2 diabetes or hypertension, age, baseline systolic BP, rs2909451 genotype (β=0.19, p=0.04)	[32]
PNPLA3	rs738409 (C>G, T)	41 with T2D and NAFLD	Alogliptin 25 mg/day	G allele carriers showed a stronger positive correlation between change in HbA_{1c} and changes in liver aminotransferases In the weight-loss group, improvements in total cholesterol and triacylglycerols were greater in CG and GG carriers than in CC carriers	[34]

T2D, type 2 diabetes

Table 2 Genotypes associated with response to treatment of type 2 diabetes with GLP-1-RA

Gene	Genetic variant	Study population (*n*)	Glucose-lowering treatment	Clinical outcome	Reference
GLP1R	rs3765467 (G>A, C, T) rs761386 (C>G, T)	36 with T2D	CSII for 6 days followed by combination with exenatide (5 μg twice daily) for 3 days	rs761386 CT/TT genotypes: higher glucose levels at 120 min (75 g OGTT; p=0.032) Insulin and C-peptide (OGTT) were not significantly different between the genotypes after exenatide treatment	[35]
GLP1R	rs6923761 (G>A, C)	90 with T2D and obesity	Liraglutide (1.8 mg/day s.c.) added to metformin for 14 weeks	Variant A allele carriers showed greater decreases in BMI (−0.59 vs −1.69 kg/m^2) and fat mass (−0.59 vs −1.69 kg) Weight reduction after liraglutide was greater in A allele carriers by 2.9 kg (95%CI 0.27, 5.64) in multiple regression analysis	[36]
GLP1R	rs10305420 (C>T) rs3765467 (G>A, C, T)	289 with T2D and obesity	Exenatide 5 μg twice daily for 6 months	T allele (rs10305420) was associated with smaller reductions in HbA_{1c} (−4.4 mmol/mol) and body weight (−1.27 kg) after exenatide (6 months)	[37]
CNR1	rs1049353 (G>A)	86 with T2D and obesity	Liraglutide (1.8 mg/day s.c.) added to metformin or sulfonylurea for 14 weeks	Before and after treatment, BMI, body weight, fat mass and waist circumference were higher in G vs A allele carriers The decrease in basal glucose and HbA_{1c} was similar in both genotypes. In A allele carriers, HOMA-IR decreased (7.6±8.8 at baseline; 5.8±7.4 at 14 weeks)	[39]
TCF7L2	rs7903146 (C>G, T)	162 with T2D	Exenatide for 8 weeks (n=56)	Plasma glucose values were similar in CC and CT/TT genotypes (meal tests) before and after exenatide treatment After exenatide, CT and TT (vs CC) carriers demonstrated insulin reduction at 30–180 min during meal test (p<0.05)	[40]
SORCS1	rs1416406 (A>G, T)	101 with newly diagnosed T2D	Exenatide 5 μg twice daily (weeks 1–4) then 10 μg twice daily (weeks 5–48)	rs1416406 was significantly associated with PIR change (p<0.05) after adjustment for age, sex and baseline BMI HbA_{1c} and PIR in linear regression: greater reduction in PIR in GG genotype	[43]

CSII, continuous subcutaneous insulin infusion; T2D, type 2 diabetes

[18]. This study indicated a clinically relevant pharmacogenetic effect, although persistence of the effect was not assessed due to lack of a longer follow-up of HbA_{1c} values.

The *KCNJ11* gene regulates one of the pancreatic beta cell ATP-sensitive potassium channels, that play a role in insulin secretion [19]. After sitagliptin, vildagliptin or linagliptin therapy (≥3 months), individuals with type 2 diabetes and who carried the *KCNJ11* rs2285676 CC alleles had a twofold higher odds of responding to DPP-4i, defined as HbA_{1c} ≤53.0 mmol/mol (7.0%), than other individuals [20].

CTRB1/CTRB2 A SNP (rs7202877) that is located near genes that encode chymotrypsinogen B1 and B2 (*CTRB1/CTRB2*), with no known functional effect, is related to GLP-1-stimulated insulin secretion [21]. The rs7202877 GG and GT genotypes were associated with a 5.5 mmol/mol (0.5%) smaller reduction in HbA_{1c} compared with the TT genotype after 3 months of gliptin therapy [21]. The genetic variant was shown to be associated with GLP-1-induced insulin secretion. *CTRB1*/2 encodes chymotrypsin, and the G allele was also associated with increased chymotrypsin levels in the pancreas and faeces [21]. Thus, chymotrypsin may be important for the response to DPP-4i treatment.

PRKD1 The serine/threonine protein kinase D1 enzyme, encoded by *PRKD1*, plays a role in various processes such as the regulation of cell proliferation, differentiation and apoptosis, immune reactions, cardiac contraction, angiogenesis and cancer development. Furthermore, the enzyme has been shown to contribute to insulin secretion [22]. A genome-wide association study (GWAS) found that in people with type 2 diabetes treated with sitagliptin, saxagliptin, vildagliptin or linagliptin, a polymorphism in *PRKD1* (rs57803087; intron variant) was associated with a greater response to the DPP-4i [23]. In a replication cohort, rs57803087 remained significantly associated with a better DPP-4i response after controlling for BMI [23]. However, the results of this small GWAS (n = 171) need to be replicated in a larger sample and the lacking information on the association of specific risk alleles should be provided.

CDKAL1 GWAS revealed relationships between several SNPs in *CDKAL1*, encoding cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1 (CDKAL1), and type 2 diabetes risk [24]. Cyclin-dependent kinase 5, which shares similarities with CDKAL1, is a serine/threonine protein kinase, which contributes to the glucose-dependent regulation

Table 3 Genotypes associated with response to treatment of type 2 diabetes with SGLT2i

Gene	Genetic variant	Study population (*n*)	Glucose-lowering treatment	Clinical outcome	Reference
SLC5A2	rs3116149 (G>A) rs9934336 (G>A) rs3813008 (G>A) rs11646054 (G>A) rs3116650 (G>A)	908 with T2D	Empagliflozin 10 mg (*n*=603) vs placebo (*n*=305)	No association between SNPs and response to treatment with empagliflozin (HbA_{1c}, fasting glucose, body weight, systolic BP)	[44]
PNPLA3	rs738409 (C>G, T)	80 with T2D and NAFLD	Dapagliflozin 10 mg, *n*-3 carboxylic acid 4 g, combination of both, or placebo (RCT)	Combination treatment: reduction in liver fat (PDFF) was greater for CG and GG genotypes (relative change −25.4%) than for the CC genotype (−16.1%)	[46]
UGT1A9	rs72551330 (T>A, C)	764 with T2D, 397 healthy control individuals	Canagliflozin 25–400 mg/day (in T2D group)	Higher median dose-normalised canagliflozin AUC in *UGT1A9*3* allele carriers (ratio 1.26 [95% CI 1.08, 1.44])	[47]
UGT1A9	rs72551330 (T>A, C)	65 with T2D, 69 healthy control individuals	Canagliflozin 50–300 mg/day	Dose-normalised AUC for canagliflozin was higher (by 45%) in *UGT1A9**3 allele carriers (*n*=4)	[48]

T2D, type 2 diabetes

of insulin secretion [25]. In individuals with type 2 diabetes treated with DPP-4i, the HbA_{1c} reduction after 6 months varied according to two *CDKAL1* SNPs (rs7754840, G>C, intron variant; rs756992, A>G) [24]. The HbA_{1c} decrease was greater in people who carried at least one variant allele in comparison with two copies of the common allele (for rs7754840, GG 4.4 mmol/mol [0.4%], CG 5.5 mmol/mol [0.5%] and CC 8.7 mmol/mol [0.8%], $p = 0.02$; for rs7756992, AA 4.4 mmol/mol [0.4%], AG 5.5 mmol/mol [0.5%] and GG 8.7 mmol/mol [0.8%], $p = 0.01$) [24]. The differences persisted after adjusting for age, sex, BMI, diabetes duration, baseline HbA_{1c} and the number of concomitant glucose-lowering drugs in a linear regression analysis [24]. Thus, people with *CDKAL1* type 2 diabetes risk variants showed a better glycaemic response to DPP-4i.

***IL6* promoter region** IL-6, derived from muscle cells during exercise, was shown to enhance intestinal GLP-1 secretion in animal models [26]. It has been hypothesised that genetic variants that upregulate *IL6* transcription might also increase GLP-1 synthesis and secretion in humans [27]. In people with type 2 diabetes, DPP-4i treatment response (3 months) was defined as a ≥2.2 mmol/mol (0.2%) HbA_{1c} decrease (about 70% responders) [27]. Two *IL6* SNPs were then analysed (rs1800796, intron variant; rs2097677) and multivariate analysis showed that the adjusted OR for DPP-4i non-response of the two SNPs combined (rs1800796 G* and rs2097677 A* vs CC-GG) was 0.45 ($p = 0.07$). After stratifying the population into low ($n = 149$) and moderate/high ($n = 167$) levels of physical activity, the OR for each group was 1.58 ($p = 0.62$) and 0.15 ($p < 0.01$), respectively [27]. These data suggest that *IL6* variants might contribute to an improved DPP-4i response in people who are more physically active.

TCF7L2 Variation in the *TCF7L2* gene has been associated with an increased risk of type 2 diabetes [28]. There are several hypotheses as to how the *TCF7L2* gene product, transcription factor 7-like 2, exerts its effects on the gut, liver or pancreatic beta cells [28]. *TCF7L2* variant alleles impact GLP-1-induced insulin secretion, suggesting a functional defect in pancreatic GLP-1 signalling [29]. After genotyping *TCF7L2* variants in participants with type 2 diabetes undergoing phase 3 trials with 24 weeks of treatment with linagliptin, a smaller decrease in HbA_{1c} was observed in individuals with the rs7903146 TT genotype (6.2 mmol/mol [0.57%]) compared with other genotypes (9.0 mmol/mol [0.82%] for CC; 8.4 mmol/mol [0.77%] for CT; $p = 0.02$ for TT vs CC genotypes) [30]. Thus, the *TCF7L2* SNP rs7903146 may be associated with lower response to incretins.

DPP4 DPP-4i bind to the dipeptidyl peptidase-4 (DPP-4) enzyme to enhance GLP-1 activity [31]. The efficacy of DPP-4i could be affected by *DPP4* gene variants [31]. This hypothesis was investigated in a small study comparing people with type 2 diabetes receiving treatment with sitagliptin (100 mg/day or 200 mg/day) with healthy control individuals [32]. In regression analysis, *DPP4* genotype rs2909451 (intron variant) TT was associated with increased short-term DPP-4 enzyme activity during sitagliptin treatment in the whole sample (standardised regression coefficient, 0.19 nmol ml^{-1} min^{-1}; $p = 0.04$) [32].

PNPLA3 Variants in the *PNPLA3* gene, encoding patatin-like phospholipase 3 (PNPLA3), are related to increased plasma levels of hepatic NEFA and triacylglycerols [33, 34]. A genetic variant (rs738409) of *PNPLA3* was associated with non-alcoholic fatty liver disease (NAFLD) and its histological

severity in GWAS [33]. In a small study of people with biopsy-proven NAFLD and type 2 diabetes treated with alogliptin (25 mg/day; median follow-up 33 months), participants with the rs738409 G allele showed a positive correlation between temporal changes in HbA_{1c} and aminotransferase levels (CG/GG and alanine aminotransferase: $r = 0.52$; $p = 0.001$) [34]. In addition, in participants who lost weight, those with CG and GG genotypes showed greater improvements in total cholesterol and triacylglycerols, and similar improvement in HbA_{1c} [34]. Thus, the effects of alogliptin (and possibly other DPP4i) on liver function in type 2 diabetes and NAFLD may differ by *PNPLA3* genotypes.

GLP-1 RA

GLP1R SNPs around the exon region of the *GLP1R* gene were genotyped in a small sample of people with poorly controlled type 2 diabetes, who received exenatide for 3 days (5 μg twice daily) and were also treated with a continuous subcutaneous insulin infusion [35]. The CT/TT genotypes of rs761386 (intron variant) were related to higher glucose levels at 120 min of a 75 g OGTT ($p = 0.032$). Insulin and C-peptide throughout the OGTT were not significantly different between the genotypes. Unfortunately, data on the long-term effects, in particular on HbA_{1c}, are lacking.

Two further studies from Spain [36] and China [37] explored the relationship between *GLP1R* variants and weight loss in type 2 diabetes. The study from Spain included individuals with poorly controlled type 2 diabetes and who were overweight, who began liraglutide treatment up to 1.8 mg/day for 14 weeks [36]. The *GLP1R* rs6923761 (non-coding) A allele (GA/AA vs GG) was associated with a 2.9 kg larger weight reduction after liraglutide treatment in multivariable analysis [36]. The decreases in basal glucose levels, HOMA-IR and HbA_{1c} were similar in both groups. In a hospital-based Chinese study including obese individuals with poorly controlled type 2 diabetes, the variant T allele of *GLP1R* rs10305420 (amino acid change: Pro to Leu) was associated with a smaller reduction in HbA_{1c} (4.4 mmol/mol [0.4%]) and body weight (−1.3 kg) after 6 months of exenatide treatment [37]. It is unclear whether these genetic associations would be of the same magnitude in people with type 2 diabetes who were of normal body weight.

CNR1 The endocannabinoid system plays a role in appetite and body-weight regulation [38]. The cannabinoid type 1 receptor, encoded by the *CNR1* gene, is located in adipose tissue and in several brain areas [38]. In obese people with type 2 diabetes stratified by *CNR1* genotypes (GA and AA genotypes vs GG genotypes), glucose, HbA_{1c}, insulin sensitivity, BMI, body weight, waist circumference and fat mass were measured before and after 14 weeks of liraglutide treatment [39]. Among metabolic markers, insulin resistance was found to decrease in individuals carrying the variant *CNR1* A allele. However, liraglutide therapy resulted in comparable improvements of anthropometric measures and glycaemic markers in all *CNR1* genotypes [39].

TCF7L2 In a small pharmacogenetic study, individuals with type 2 diabetes and the *TCF7L2 rs*7903146 CC genotype were matched with individuals with CT and TT genotypes and similar diabetes duration and BMI [40]. Participants received a 500 kcal (2092 kJ) mixed-meal test and treatment with exenatide for 8 weeks [40]. The rs7903146 (intron variant) T allele was associated with higher secretion of insulin, proinsulin and C-peptide in response to the mixed meal [40]. After exenatide treatment, T allele carriers showed lower postprandial plasma insulin and C-peptide levels compared with non-carriers. The data suggest that use of GLP-1 RA could play a role in beta cell function in individuals with the rs7903146 CT and TT genotypes. However, no difference between genotype was observed for plasma glucose values during the meal tests after exenatide treatment; the same was true for HbA_{1c} and body-weight reduction [40].

SORCS1 Sortilin related VPS10 domain containing receptor 1 (SORCS1) is expressed in the brain, heart, kidney and pancreatic islets, and in beta cell lines [41]. SORCS1 belongs to the sortilin family of vacuolar protein sorting-10 domain-containing proteins and has been genetically linked to Alzheimer's disease [42]. *SORCS1* haplotypes were associated with higher fasting insulin levels and insulin secretion in non-diabetic obese women but not in men or lean individuals [41]. In persons with newly diagnosed type 2 diabetes treated with exenatide for 48 weeks, stratifying for *SORCS1* rs1416406 genotypes, revealed differences in HbA_{1c}, glucose values and beta cell function between the genotype groups (GG, GA, AA) following treatment [43]. However, only the proinsulin/insulin ratio (PIR) showed a greater reduction in people with the GG genotype vs other genotypes and this difference persisted after adjusting for age, sex and BMI in regression analysis [43]. The reduced PIR suggests that people with newly diagnosed type 2 diabetes and the rs1416406 GG genotype might benefit from exenatide treatment.

SGLT2i

SLC5A2 The sodium–glucose cotransporter 2 (SGLT2) protein, which contributes to renal glucose reabsorption, is encoded by the *SLC5A2* gene [44]. Several rare mutations of this gene result in familial renal glucosuria [44]. Therefore, variants in the *SLC5A2* pose a promising target for pharmacogenetic research. So far, only one study has investigated the association between *SLC5A2* gene variants (intron variants) and the glycaemic effects of SGLT2i therapy [44]. Between five common gene variants, no clinically relevant differences

in response to empagliflozin treatment after 24 weeks were observed in type 2 diabetes [44]. Moreover, these variants were not associated with diabetes-related metabolic traits in people at increased risk of type 2 diabetes [44].

PNPLA3 PNPLA3 is expressed in liver and adipose tissue and mediates triacylglycerol hydrolysis [45]. A *PNPLA3* variant has been identified as a risk factor for steatohepatitis [45]. A 12 week randomised clinical trial investigated the effects of a combination of dapagliflozin and *n*-3 carboxylic acids on the hepatic proton density fat fraction (PDFF) in people with type 2 diabetes and NAFLD [46]. Baseline liver PDFF was lower in individuals with the *PNPLA3* rs738409 (p.Ile148Met) CC genotype (median 17%) than in those with the CG and GG genotype (20%). In response to the combination therapy, the relative PDFF reduction was greater in individuals with the CG and GG genotypes (relative change, −25%) than in those with the CC genotype (−16%). The relative change in PDFF observed following dapagliflozin monotherapy differed from that seen with the combination therapy (CG and GG, +7%; CC, −22%) [46].

UGT1A9 Canagliflozin is mainly metabolised by uridine diphosphate-glucuronosyltransferase (UGT) 1A9 and UGT2B4 into inactive glucuronides [47]. In vitro studies suggested that *UGT1A9* gene variants result in an alteration of UGT enzymatic activity [47]. Therefore, variants in the *UGT* genes could potentially influence the pharmacokinetics of canagliflozin or other SGLT2i [47, 48]. A pharmacokinetic model of canagliflozin based on data from 14 clinical trials showed that carriers of the rare *UGT1A9*3* allele showed 26% higher median dose-normalised AUC values for canagliflozin, indicating a better drug availability [47]. A smaller study based on phase 1 clinical trials confirmed the role of UGT genes in canagliflozin metabolism, with higher plasma canagliflozin levels being observed in carriers of the *UGT2B4**2 genotype compared with non-carriers [48]. However, because of the small number of individuals with this gene variant in those with diabetes these findings may not be clinically relevant.

Summary of studies, and limitations

The small number of studies, thus far, that report associations between genetic variants and response to novel glucose-lowering drug treatment have focused on glycaemic response (e.g. HbA_{1c}) and changes in body weight. With respect to DPP-4i and GLP-1 RA, most studies of gene variants have focused on the drug's metabolic pathways (e.g. variants of *GLP1R*) and variants of genes involved in intestinal GLP-1 secretion (e.g. *KCNQ1*). The few studies on *GLP1R* variants indicated a reduced glycaemic response to treatment with both DPP-4i and GLP-1 RA. Conflicting results for *GLP1R* gene variants were found for body weight changes under GLP-1 RA therapy. Other studies have examined SNPs in genes that are implicated in the development of diabetes by affecting pathophysiological defects such as beta cell failure (e.g. *TCF7L2* and *CDKAL1*). For these genes, reductions in HbA_{1c} in response to DPP-4i therapy have been reported to be greater for *CDKAL1* variants and smaller for *TCF7L2* variants.

SGLT2i reduce blood glucose concentrations via inhibition of renal glucose reabsorption, a mechanism that is not related to type 2 diabetes aetiology. Therefore, genetic variants related to the development of diabetes are not likely to affect the response to SGLT2i therapy. Most studies have focused on examining genes affecting renal glucose reabsorption (e.g. *SLC5A2*). However, the few data available indicate no clinically relevant differences between *SLC5A2* variants in response to SGLT2i treatment. In addition, variants of genes potentially involved in the pharmacokinetics of SGLT2i were found to have no clinically relevant effects on therapeutic response.

The relevance of the currently available pharmacogenetic studies is largely hampered by small genetic effects, low sample sizes, limited statistical power, often inadequate statistics (e.g. lack of gene–drug interactions in models), inadequate account of confounders and effects modifiers (e.g. obesity, comorbidity), limited comparability due to different study designs, study populations and definitions of study outcomes, and a lack of replication studies. Therefore, more well-designed studies with a sufficiently large sample size and well-characterised diabetes phenotypes are required to investigate and replicate the effect of genetic variants on the metabolic response to novel glucose-lowering drugs. A major limitation of the current studies is that most findings have not been replicated. Currently, the replication of results for relevant gene variants is more important than producing new findings. When possible, meta-analysis across studies should be undertaken to provide robust evidence for associations.

This review also indicates that genetic studies on drug response to DPP-4i, GLP-1 RA and SGLT2i in type 2 diabetes have been mainly based on candidate genes, derived from aetiological processes or drug pathways. Overall, the degree of insight provided by these studies is rather limited. GWAS, on the other hand, have the potential to provide novel insights, as these studies make no assumptions about drug mechanisms or underlying disease processes [1]. Only GWAS of metformin have been reported to date [2, 49].

In conclusion, the amount and level of evidence of the current research results are not sufficient to guide stratified prescription use of novel glucose-lowering drugs in type 2 diabetes.

Outlook

We provide an outlook on future perspectives of pharmacogenetics in type 2 diabetes. First, we indicate which novel topics will likely turn out to be more important in pharmacogenetic studies of glucose-lowering drugs (e.g. the microbiome composition and its effect on drug metabolism) and then we elaborate on how the identification of distinct subgroups of diabetes could advance pharmacogenetic research. Finally, we add some lessons learnt from monogenic diabetes that can be applied to the field of pharmacogenetics and we conclude by highlighting various aspects that may advance the future of precision diabetology of type 2 diabetes.

Novel topics in pharmacogenetic studies

Genetic heterogeneity due to ethnic background may explain why the associations between polymorphisms and therapy response differ between populations. Furthermore, epigenetic modifications that regulate how genes involved in the metabolism of glucose-lowering drugs are expressed in different populations may also have contributed to heterogenous findings. It is also worth noting that heritable DNA variants are only one approach for identifying different responses to glucose-lowering drugs. This approach should be complemented by other analyses including targeted and non-targeted metabolomics and proteomics. Artificial intelligence and machine learning algorithms provide tools to analyse and gain insight into this vast amount of data (computational diabetology). Furthermore, the gut microbiome is known not only to play a role in metabolism but also to modify certain drug effects (e.g. by altering drug pharmacokinetics or even inactivating drugs) [50]. Thus, clinical studies to investigate the impact of different microbiome compositions on response to, and side effects of, glucose-lowering drugs are needed in order to advance personalised medicine. Finally, another limitation of current pharmacogenetic studies in diabetes is the implication of a single pathogenic gene, or a limited number of pathogenic genes. Thus, studies only identify small genomic regions that may contribute to the heterogeneity of drug response. Yet, in complex disorders such as type 2 diabetes, genetic heterogeneity of multiple different genomic regions is the likely scenario. Deep phenotyping and genotyping approaches are required to identify genetic networks involved in drug response. Thus, pharmacogenetics, the application of a single genetic variant to describe an alteration in drug effect, needs to be extended to pharmacogenomics, a broader application of the genome, to predict response to glucose-lowering medications.

Subgroups of diabetes

Untangling the heterogeneity of type 2 diabetes will most likely improve pharmacogenetic studies. For example, a data-driven cluster analysis was able to identify five diabetes subgroups with distinct phenotypes, risk of complications and genetic associations [10, 11]. These subgroups were comprised of individuals with predominately insulin deficiency or with insulin resistance [10]. In turn, low beta cell function has been shown to be associated with reduced glycaemic response to GLP-1 RA [51] and higher insulin resistance was associated with reduced glycaemic response to DPP-4i [52]. Thus, reducing phenotypic heterogeneity by characterisation of type 2 diabetes subgroups with predominately insulin deficiency or insulin secretion may be a good starting point to further study the associations between genetic markers and glycaemic response to novel glucose-lowering drugs.

Lessons from monogenic diabetes

A strategy to advance pharmacogenetic progress in diabetology is to reduce heterogeneity in patient populations with type 2 diabetes. This strategy has already been proven successful for studies on drug effects in monogenic diabetes, including MODY and neonatal diabetes [1]. The most common cause of MODY are mutations in the gene encoding hepatocyte nuclear factor 1α (*HNF1A*). A small, randomised crossover trial demonstrated that people with genetically defined *HNF1A* diabetes not only had a five-fold greater glycaemic response to gliclazide (a sulfonylurea) than to metformin therapy but also an almost four-fold greater response to gliclazide than people with type 2 diabetes [53]. This dramatic pharmacogenetic finding has resulted in a specific treatment algorithm for *HNF1A* MODY [1]. Rare neonatal forms of diabetes that develop within the first year of life are often caused by mutations in the *KCNJ11* gene, which encodes a subunit of the pancreatic potassium channel that tightly regulates insulin secretion by beta cells [54]. In individuals with diabetes caused by *KCNJ11* mutations the sensitivity of these potassium channels was decreased, thereby reducing insulin secretion in the presence of glucose. Sulfonylureas have been shown to promote insulin secretion in these individuals by closing the potassium channels and have been proposed as a safe and more effective replacement of insulin therapy [54].

Precision drug treatment

In the future, genetic information from individuals with type 2 diabetes may be usefully combined with other clinical markers to guide a stratified prescription of the most effective glucose-lowering therapy for a particular person [55]. Both single SNP and genetic scores may be useful in this respect, as are non-genetic traits. An example relevant to precision drug treatment is a recent study showing that non-genetic markers of insulin

resistance were related to glycaemic response to DPP-4i [52]. In this cohort study from the UK, a subgroup (22% of the study population) had type 2 diabetes and were obese and had high triacylglycerol levels [52]. This metabolic subgroup showed both a reduced short-term glycaemic response as well as a reduced long-term efficacy of DPP-4i treatment. Interestingly, with respect to GLP-1 RA there was no evidence of an association between clinical markers of insulin resistance and either 6 month glycaemic effects or durability of response for up to 3 years [52]. In the future, genetic information may be combined with such clinical markers to guide stratified drug prescription in type 2 diabetes.

Another important aspect of precision diabetology is that the costs of genotyping are currently high but this will most likely change in the future. Still, genotyping costs need to be weighed against the costs of suboptimal glucose-lowering treatment over several months or years. Therefore, there is a need to develop implementation and evaluation strategies to assess the cost-effectiveness of pharmacogenetic information in diabetes care compared with conventional treatment approaches.

The final question remains of how pharmacogenomic results can be applied to the complex heterogeneous disease that is type 2 diabetes. Most likely, the identification of distinct subtypes of type 2 diabetes will be necessary before pharmacogenetic insights can be successfully used for providing stratified prescriptions of novel glucose-lowering drugs.

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APPENDIX 2: Validation study for defining clinical sensorimotor polyneuropathy

We validated our definition of clinical distal sensorimotor polyneuropathy (DSPN) in an unselected population of 151 in- and out-patients with type 2 diabetes, referred by their general practitioner or diabetologist to the German Diabetes Center. The average age of the patients was 54 ± 11.2 years. Compared to the patients with known diabetes from KORA F4, patients from the validation dataset were younger and more often current smokers. Sex, body mass index, blood cholesterol, HbA1c and creatinine levels were comparable between the two study samples.

Patients from the validation dataset had undergone nerve conduction velocity measurements of the peroneal nerve and the sural nerve. Also, the neurology disability score (NDS) was assessed for which a score of three or more was considered indicative of peripheral polyneuropathy. Furthermore, data on several other neurological examinations were available, such as vibration perception measured with a 64-Hz tuning fork, sensibility to touch assessed with a 10-g monofilament, elaborate foot inspection and ankle reflexes measured with a reflex hammer. A final diagnosis of peripheral polyneuropathy was given if both nerve conduction velocity assessments and the NDS indicated the presence of the disorder (n=19).

In KORA F4, we defined the presence of clinical DSPN as an impaired bilateral vibration perception and/or an impaired bilateral foot-pressure sensation. When applying this definition to the validation dataset, 34 patients were diagnosed with clinical peripheral neuropathy. In table S2, both diagnostic definitions are shown in a 2x2 contingency table. The agreement of between the two definitions of peripheral polyneuropathy was 86.1% (95% confidence interval (CI): 78.8%-90.2%). Sensitivity was 84.2% (95% CI: 60.4%-96.6%), specificity was 86.4% (95% CI: 79.3%-91.7%), positive predictive value was 47.1% (95% CI: 29.8%-64.9%) and negative predictive value was 97.4% (95% CI: 92.7%-99.5%) (Table S2). Whereas all measures are relatively high, the positive predictive value of predicting clinical DSPN is low. Most likely this reflects the low prevalence of the disorder in the study sample, which is merely 13% (95% CI: 7.7-19).

Subsequently, we constructed a receiver operating characteristics (ROC) curve to determine the ability of the clinical DSPN definition to discriminate between patients with and without peripheral polyneuropathy (figure S1). The area under the ROC curve (AUC) was 0.91 (95% CI: 0.84-0.97), indicating excellent discriminative ability.

Table S1: Characteristics and blood concentration values of the KORA F4 participants according to the presence of clinical distal sensorimotor polyneuropathy* and adjusted for age and sex; KORA F4 (2006-2008)

	Clinical DSPN		
	No	**Yes**	***p*-value**
Characteristics			
N	946	154	
Sex (% men)	49.1	62.3	0.002
Age (years)	70.0 ± 5.4	71.9 ± 5.7	<0.001
Height (cm)	165 ± 9.0	168 ± 9.0	<0.001
Body mass index (kg/m²)	28.7 ± 4.5	29.2 ± 4.6	0.122
Waist circumference (cm)	97.7 ± 12.1	101 ± 12.6	0.015
Systolic blood pressure (mm Hg)	129 ± 19.9	128 ± 19.8	0.381
Diastolic blood pressure (mm Hg)	74.5 ± 9.9	71.9 ± 11.1	0.002
Hypertension (% yes)	62.2	66.2	0.332
Smoking (% yes)	7.7	6.5	0.840
High alcohol consumption (% yes) †	17.3	14.9	0.128
Low physical activity (% yes)	48.1	60.4	0.039
Previous AMI (% yes)	6.0	7.8	0.906
Previous stroke (% yes)	3.6	7.1	0.140
Absent ankle reflexes (% yes)	7.6	26.0	<0.001
Foot ulcer present (%yes)	0.1	2.0	0.023
Glucose tolerance status			
NGT (% yes)	54.2	41.6	0.040
i-IFG (% yes)	5.5	2.0	0.034
i-IGT (% yes)	16.5	17.5	0.971
IFG-IGT (% yes)	3.7	7.1	0.044
Undiagnosed diabetes (% yes)	5.5	6.5	0.962
Known diabetes (% yes)	14.6	25.3	0.004
Blood concentrations			
Fasting glucose (mg/dL)‡	97.5 ± 11.1	98.7 ± 12.3	0.794
2-h glucose (mg/dL)‡	118 (99-148)	130 (102-160)	0.069
Hb1Ac (%)	5.8 ± 0.6	6.0 ± 0.8	0.007
Total cholesterol (mg/dL)	223 ± 40.6	207 ± 38.0	<0.001
Creatinine (mg/dL)	0.9 (0.8-1.1)	1.0 (0.9-1.1)	0.112

DSPN: distal sensorimotor polyneuropathy, NGT: normal glucose tolerance, i-IFG: isolated impaired fasting glucose, i-IGT: isolated impaired glucose tolerance, AMI: acute myocardial infarction, Hb1Ac: glycated haemoglobin A, LDL: low-density lipoprotein, HDL: high-density lipoprotein

Data are presented as mean ± sd or as median (interquartile range).

* Defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation.

† For women >=20 g/day and for men >=40 g/day.

‡ Patients with known diabetes were excluded. Since they did not need to undergo an oral glucose tolerance test the fasting blood glucose levels were unreliable and the 2-h post-load glucose levels were not assessed. Data are based on 808 subjects without clinical peripheral neuropathy and 115 subjects with clinical peripheral neuropathy.

Table S2: Contingency table assessing the number of peripheral polyneuropathy diagnoses by the definition of clinical distal sensorimotor polyneuropathy

Confirmed clinical peripheral polyneuropathy*	**Clinical distal sensorimotor polyneuropathy†**		
	No	**Yes**	**Total**
No	114	18	132
Yes	3	16	19
Total	117	34	151

*Confirmed clinical peripheral polyneuropathy was defined as an impaired nerve conduction velocity measurement of both the peroneal nerve and the sural nerve and a score of 3 or higher on the neuropathy disability score.

†Clinical distal sensorimotor polyneuropathy was defined as an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation.

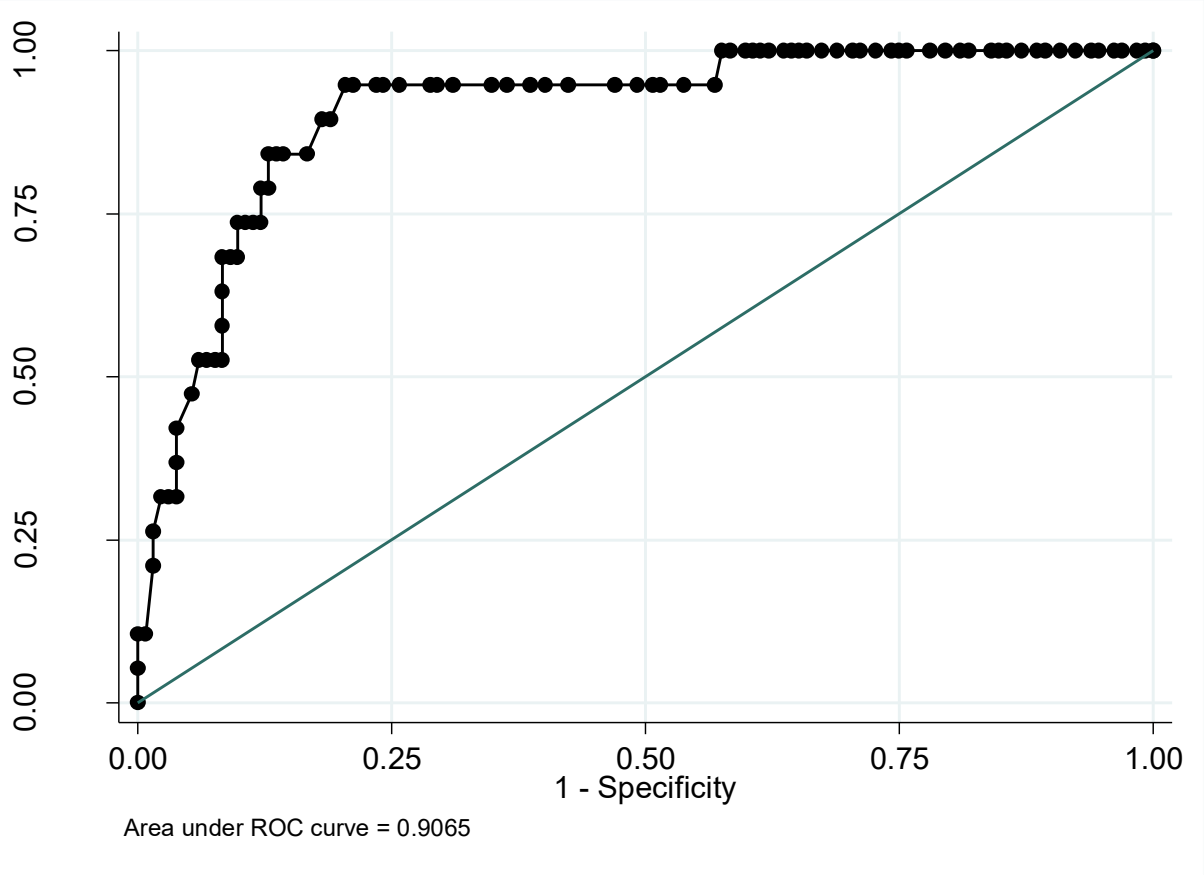

Figure S1: Receiver operating characteristics curve for diagnosing clinical distal sensorimotor polyneuropathy. The area under the curve is 0.91 (95% confidence interval: 0.84-0.97), indicating excellent discrimination.

APPENDIX 3: Systematic review protocol

Effectiveness of Chronic Care Models for the Management of Type 2 Diabetes Mellitus in Europe: a Systematic Review

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Background

A growing number of European citizens suffer from diabetes, constituting a growing health, social, and economic burden. The number of individuals with diabetes in Europe in 2013 was estimated by the International Diabetes Federation to be 56.3 million, or 8.5% of the adult population (20-79 years), and is expected to increase to 68.9 million people, or 10.3% by the year 2035 (1). It is generally believed that lifestyle, with diets high in saturated fat and decreased physical activity, together with an increased longevity, are the main factors in the current increase in T2DM. In individual, as well as in societal terms, the burden of T2DM is enormous, resulting in increased morbidity and mortality [1].

Historically, healthcare systems were developed to respond rapidly and efficiently to acute diseases. The focus was on the immediate problem, a rapid diagnosis, and the initiation of professional treatment; a process in which the patient's role was largely passive. However, with the rapid ageing of the population and the growing prevalence of chronic diseases, improvement in quality of chronic care requires more than evidence about effective diagnostic procedures and treatments. Despite much progress in clinical and behavioural interventions, it is suggested that many chronically-ill patients do not profit from these advances (2).

In the current healthcare systems in European countries, a shift from disease management to chronic care management may prevent costly complications and frailty in elderly with T2DM, enabling them to live independent, healthy and active lives as long as possible. With the aim of describing essential elements for improving outcomes in care of chronic diseases, the Chronic Care Model (CCM) was developed in the mid-1990s and was further refined in 1997 (3, 4). As such, CCM is a primary care-based comprehensive model, advocating evidence-based changes in healthcare of patients with chronic disease. The model is based on the assumption that improvements in care require an approach that incorporates patients, healthcare providers, and system level interventions. It can be applied to a

variety of chronic illnesses, healthcare settings and target populations, with the goal of healthier patients, more satisfied providers, and cost savings.

The CCM comprises six components deemed essential for providing high-quality care to patients with chronic disease:

1. Healthcare organisation (i.e., providing leadership for securing resources and removing barriers to care).
2. Self-management support (i.e., facilitating skills-based learning and patient empowerment).
3. Decision support (i.e., providing guidance for implementing evidence-based care).
4. Delivery system design (i.e., coordinating care processes).
5. Clinical information systems (i.e., tracking progress through reporting outcomes to patients and providers).
6. Community resources and policies (i.e., sustaining care by using community-based resources and public health policy).

Reports indicate a widespread application of CCM to multiple illnesses (5, 6), yet, to date, only one study has reviewed how CCM has been applied in diabetes care in primary care settings and what the outcomes were of this implementation (7). This systematic review showed that CCM approaches in the United States have indeed been effective in improving the health of individuals with diabetes who receive care in primary care settings. Regarding quality of diabetes care in Europe, observational studies have been performed in different European countries (8-11). The recently published GUIDANCE study (12) reported encouraging levels of adherence to the main recommended process measures in diabetes care, e.g., HbA1c levels <7%, blood pressure <130mmHg (systolic) and <80 mmHg (diastolic), and LDL cholesterol concentrations <2.6 mmol/L. The level of actual achievement of these target goals by the individual patients was, on the other hand, much lower. Findings from the GUIDANCE study supported previously made suggestions (13-15) that process adherence may only have a limited influence in terms of reaching target goals (risk factor control) or enhanced management, e.g., appropriate adjustments to medication. Also, the existence of substantial between-country variation in quality of diabetes care in Europe was confirmed by the GUIDANCE study (12).

Aims

This systematic review will focus on the scientific evidence regarding the specific treatment and care of elderly suffering from T2DM and associated comorbidities. Its aim is to summarize previous research on the effects of current European disease management models specifically related to the complex interaction between T2DM and comorbidities in the elderly, and on improving outcomes of interest.

Objectives (research question)

To assess the effects of chronic care models with a duration of at least 6 months on the following outcomes in older patients with T2DM and diabetes-related comorbidities:

- biophysical outcomes (e.g., serum HbA1c concentrations, and change in BMI),
- patient-reported outcomes (e.g., diabetes-related quality of life), and
- diabetes complications (e.g., micro- and macrovascular complications),

compared to routine diabetes care.

Methods

In the case of substantial clinical or statistical heterogeneity, study results will be combined in a narrative review only. Without substantial clinical and statistical heterogeneity, study results will be combined in a meta-analysis, following the approach described below. The subsequent reporting of the systematic review will be conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) statement (16).

Criteria for considering studies for this review

Types of studies

Studies will be eligible for inclusion if they are a randomised clinical trial (RCT). Only studies that have assessed outcome measures six months or more from baseline will be investigated.

Types of participants

Individuals, regardless of gender and ethnicity, with diagnosed T2DM with or without one of the following comorbidities, assessed and reported at baseline:

- mental health problems (stress, depression, anxiety),
- cancer,
- cardiovascular disease,
- osteoporosis,
- rheumatic arthritis,
- chronic obstructive pulmonary disease,
- neurological diseases, and
- kidney diseases.

Ideally, the diagnostic criteria for T2DM are described in the study and were established using the standard criteria that were valid at the beginning of the trial (ADA 1997, NDDG 1979, WHO 1980, WHO 1985, WHO 1999), in order to be consistent with changes in T2DM classification and diagnostic criteria throughout the years.

We will include only studies in which the average age of the study population is ≥60 years, given that this is the usual age of diagnosis for most patients in Europe.

Type of interventions

Chronic care models/programmes that meet the following criteria:

- specific for individuals with T2DM,
- based on guidelines,
- providing integrated (multi-disciplinary) care,
- addressing patient empowerment,
- providing quality management (e.g., patient registry systems, recording of process measures/adherence to guidelines, achievement of treatment goals), and
- delivered in primary care and secondary care.

Type of controls

The intervention group will be compared with those participants undergoing routine diabetes care (standard care recommended in that particular country, e.g., regular follow-up with the required health professional and a full diabetes annual review).

Types of outcome measures

Primary outcomes.

Biophysical outcomes:

- Metabolic control: hypoglycaemia, serum HbA1c concentrations, serum lipids levels (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), blood pressure, and glomerular filtration rate.
- Change in BMI and other anthropometric measures (waist circumference, waist to hip ratio).

Patient-reported outcomes:

- Diabetes-related quality of life.
- Participation in life style changing programmes.
- Communication.
- Patient empowerment.

Diabetes complications:

- Microvascular complications: retinopathy, nephropathy, and neuropathy.
- Macrovascular complications: cardiovascular disease, cardiovascular risk scores, and cerebrovascular disease.
- Diabetes-related mortality: total mortality and mortality due to major adverse cardiac events.

Secondary outcomes.

Mental Health:

- Depression.
- Cognitive dysfunction or dementia.
- Anxiety.

Functionality:

- Frailty index.
- Self-management skills: dietary habits, physical activity, medication administration, use of equipment.
- Nutritional status.
- Dependency on care.

Contact to Healthcare System:

- Number of yearly hospital visits.
- Hospitalization: number of emergency admissions, and number and duration (days) of hospital stays.
- Adherence to treatment recommendations.
- Quality of care.
- Polypharmacy.

Search methods for identification of studies

Electronic searches.

Electronic databases will be searched from January 2000 until January 2014. We will use the following sources for the identification of trials:

- CENTRAL (the Cochrane Central Register of Controlled Trials).
- MEDLINE (PubMed).
- EMBASE.
- CINAHL.

Searching other resources.

We aim to further identify studies by searching the reference list of each relevant trial and systematic review identified. First authors are contacted whenever additional information is required.

Data collection and analysis

Selection of studies

To determine which studies are to be assessed further, two reviewers (BB, WR) will independently scan the titles, abstracts and key words of every record retrieved. Full text articles will be retrieved if the title/abstract/key words suggest that the trial:

- included patients with T2DM, and
- evaluated a chronic diabetes care model.

In case of any doubt regarding these criteria from the information given in the title and abstract, or if the abstract was absent, the complete article will be retrieved for clarification. Studies will be eliminated if both reviewers agree that the criteria for considering studies for the review are not being met. Inter-rater agreement for study selection will be measured using the Kappa statistic (17). Any differences in opinion will be discussed and, if necessary, resolved by a third reviewer (KM).

Data extraction and management

A structured data extraction form will be developed including the following information:

- General information: published/unpublished, title, authors, source/reference, contact address, country, language of publication, year of publication, sponsoring.
- Trial characteristics: design, duration, (method of) randomisation, use of validated questionnaires, (method of) blinding (if appropriate).
- Intervention: comparison group included (routine care/no intervention), intervention (duration, timing).
- Participants: method of sampling, exclusion criteria, total number (also for comparison group(s)), sex, age, body mass index, ethnicity, pre-existing comorbidities/other medical conditions, standards of diabetes care (HbA1c concentration, serum glucose levels, lipid profile, blood pressure), diagnostic criteria T2DM, duration of T2DM, baseline comparison of the groups (including comorbidities), withdrawal from study/losses to follow-up, assessment of subgroups.
- Outcome: as specified above, main outcome as assessed in the trial, other outcomes/events assessed, quality of reporting the outcomes.
- Results: reported for outcomes and times of assessment.

If there is missing information, the authors of the article will be contacted. Differences in data extraction at item level will be resolved by discussion and if consensus is not reached, the third reviewer (KM) will take the final decision.

Assessment of risk of bias in included studies

The quality of reporting of each experimental trail will be assessed by two review authors independently (BB, WR). Risk of bias will be assessed using the Cochrane Collaboration's tool (18). In particular, the following factors will be studied.

Minimization of selection bias:

- Randomisation procedure (if applicable): the procedure will be scored adequate if the resulting sequences were unpredictable (computer generated schemes, coin tossing, and tables of random numbers).

Minimization of attrition bias:

- Handling of drop-outs: will be considered adequate when the trial reports a complete description of all patients failing to participate until the end of the trial and if the data were analysed on intention-to-treat (ITT) (thus with all randomised patients included). An overall drop-out rate less than 15%, and a selective drop-out rate less than 10% (the at-risk groups), will be considered justifiable.

Minimization of detection bias:

- Method of blinding for the outcome: will be considered adequate if the outcome assessors were completely blind for the intervention.

Assessment of heterogeneity

Variation between studies (heterogeneity) will be examined to answer the question whether the combination of the different studies is meaningful.

Clinical heterogeneity of the selected studies will be evaluated according to key characteristics of the study participants (age, gender, diabetes duration, blood glucose levels), the intervention, and study outcomes. Statistical heterogeneity will be estimated by visual inspection of the forest plots (the less overlap of confidence intervals, the more likely the presence of heterogeneity). Furthermore, heterogeneity will be assessed using the I^2-statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance or sampling error (19). It allows for

calculation across studies of varying sizes, study types and with varying outcome data. In case there is significant heterogeneity (I^2 values >75%), more emphasis will be placed on the results of a random-effects model, despite that the given model cannot overcome the problem of heterogeneity.

Data synthesis

Data will be summarized statistically if they are available, sufficiently similar, and of sufficient quality.

Subgroup analysis and investigation of heterogeneity

To explore potential source of (clinical) heterogeneity, subgroup analyses will be performed. Where performed, subgroup analysis will have a tentative (hypothesis-generating) purpose. The following subgroup analyses will be considered:

- Gender.
- Duration of the intervention.
- Duration of diabetes below and over five years (individuals who have diabetes for a longer time are likely to have more advanced disease and increased insulin resistance, and more complications; hence any forms of care may have a smaller effect in more advanced disease).
- Number of comorbidities.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of certain factors on effect size:

- Repeating the analysis excluding unpublished studies (if selected and included).
- Repeating the analysis taking risk of bias into account.
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
- Repeating the analysis excluding studies by using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

The robustness of the results will further be tested by repeating the analysis using different measures of effects size (risk difference, odds ratio, etc) and different statistic models (fixed and random effects models).

Outlook

As the population ages, the burden of chronic disease is expected to grow continuously. While healthcare organisations need to find effective ways to deal with increased care demands, the CCM has been developed to advocate evidence-based changes in healthcare of patients with chronic disease. The findings of the current systematic review will contribute to our understanding of the relationship between application of CCM and qualitative and quantitative T2DM outcomes in European primary care settings. Finally, the results can provide insights into new approaches to further integrate the CCM into primary healthcare initiatives in diabetes.

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