Chapter 9

General discussion
From the real world to research
Main findings and summary of results

The research underlying this thesis has been carried out to reach a greater understanding of the variation in current glucose and BP goal attainment rates and its association with risk factors on diabetic retinopathy and other complications of T2DM in a real-world setting.

T2DM patients are at increased risk for both micro- and macrovascular complications. However, not every T2DM patient has the same risk profile. Guidelines do not take individual characteristics into account and recommend fixed targets for both blood glucose and BP levels. These targets are based on outcomes of RCTs, which do not always reflect real world clinical practice. Since T2DM is a heterogeneous disease, and evidently “one size does not fit all” T2DM patients, there was a need to look at subgroups with distinct trajectories of both blood glucose (Chapter 2 & 3) and BP control (Chapter 5), to investigate if there were any changes over time and to help identify patients at high or at low risk of developing complications. Furthermore, we evaluated whether high proinsulin levels could identify patients at high risk of cancer mortality (Chapter 4) and if retinopathy could be a useful risk marker to identify patients at high risk of left ventricular dysfunction (Chapter 6) or cognitive impairment (Chapter 7). Finally, we evaluated whether use of a personalized screening model for retinopathy could be of help to reduce screening frequency in clinical practice (Chapter 8).

Long-term blood glucose and blood pressure control in real world T2DM patients

Most T2DM patients within our study population were well controlled, with 83.1% having stable HbA1c levels at or around the target (7%/53 mmol/mol [Chapter 2]) and 86% showing adequate SBP control (at or around 140 mmHg [Chapter 5]), both after a mean follow-up of 5.7 years.

By using Latent Class Growth Modeling, an innovative statistical technique, four subgroups based on glycemic control were identified and labeled; “good glycemic control,” “fast responders,” “reduced glycemic control,” and “non-responders.” There were 83.1%, 8.2%, 5.2%, and 3.4% in each subgroup, respectively. The good glycemic control subgroup maintained HbA1c levels at or around the target throughout follow-up. Patients within the fast responders group experienced a rapid drop in HbA1c in the first 2 years of treatment, and then maintained adequate glycemic control for the duration of follow-up. Patients with reduced glycemic control exhibited an initial HbA1c decrease very close to target, but the HbA1c subsequently increased further away from the target during follow-up, and the non-responders failed to achieve glycemic control throughout the course of their treatment.

Higher HbA1c levels; a longer diabetes duration and younger age at baseline were associated with a more unfavorable course of glycemic control over time (Chapter 2).

In terms of treatment, most patients were doing well on metformin alone, sulfonylureas, or on both of those, with about a quarter of them using or initiating insulin during follow-up. T2DM patients on insulin were typically less controlled as compared to patients with good glycemic control on metformin and/or sulfonylureas alone. For clinical practice it is important to understand which factors influence the effectiveness of insulin therapy. Therefore we selected patients who initiated insulin and studied the course of HbA1c levels within identified subgroups of this specific subset of T2DM patients. One of the major findings was that, even within centrally organized diabetes care, none of the identified subgroups reached stable levels at or around the target HbA1c level (≤ 53 mmol/mol) after the initiation of insulin. The largest subgroup (88.7%) did show a stable course of glycemic control over time, but HbA1c levels remained elevated and the target was not reached in 60.9% of the patients (Chapter 3).

Four subgroups of patients with a distinct SBP course over time were identified. While the majority (85.6%) of patients fell into the “adequate SBP control” group and achieved SBP levels at or around the SBP target (≤ 140 mmHg), three subgroups with inferior SBP control were also identified; 5.6% were “delayed responders,” 3.4%
were “insufficient responders” and 3.4% were “non-responders.” Subgroups with inferior SBP control were significantly older, comprised more women and used more antihypertensive medications as compared to the adequate SBP control group (Chapter 5).

**Subgroups in the real world at increased risk of developing complications**

After having identified subgroups of T2DM patients with insufficient glycemic and BP control, the question remained what the consequences of those subgroups within clinical practice were. Were the identified subgroups also at increased risk of microvascular complications and of mortality?

For glycemic control, we found that both retinopathy and microalbuminuria over time were statistically significantly more prevalent in all subgroups with insufficient glycemic control as compared to the good glycemic control subgroup. The non-responders subgroup further showed an increasing prevalence of microalbuminuria over time, while other subgroups either showed a stable or diminishing prevalence over time (Chapter 2).

Within the subgroups of patients who initiated insulin, only those with the highest baseline HbA1c (>80 mmol/mol) level had a significantly increased risk of retinopathy and of microalbuminuria (Chapter 3).

As for BP control, microalbuminuria was significantly more present in all other subgroups, compared to the adequate SBP control group. The insufficient SBP control and the non-responders subgroup showed a significantly increased risk of retinopathy over time. Furthermore, patients within the insufficient SBP control group had an almost twofold risk of cardiovascular mortality (Chapter 5).

**Retinopathy as a risk marker to stratify patients at risk for other diabetic complications**

With the shift from “one size fits all” towards personalized diabetes care, it is necessary to be able to stratify patients at risk of developing irreversible and progressive complications. Retinopathy is an early microvascular complication of T2DM and might even be developing 4 to 7 years before a patient is actually diagnosed with T2DM.3,4 Retinopathy at the time of diagnosis could be due to longstanding periods of mostly symptomless hyperglycemia (the “legacy effect” as outlined in Chapter 1). Therefore, retinopathy may as well contribute to personalized care as it might stratify between those patients at risk for other complications. Consequently, we studied whether retinopathy was associated with the development of left ventricular (LV) systolic and diastolic dysfunction after 8 years (Chapter 6) and with cognitive dysfunction (Chapter 7).

We observed that retinopathy was significantly associated with an 8% reduced LV ejection fraction in men. However, no significant associations between retinopathy and changes in LV function in women were found (Chapter 6). Furthermore, retinopathy was unrelated to cognitive functioning. However, a small subset of patients with severe retinopathy had worse cognitive functioning than patients without severe retinopathy (Chapter 7).

**Personalized screening for retinopathy in the real world**

Many countries have adopted an annual or biannual screening program for retinopathy, which is usually integrated within regular diabetes care.5–8 However, as only a minority of the T2DM patients eventually develops sight threatening retinopathy (STR) this “one size fits all” approach is costly and time consuming. A more personalized screening frequency, taking into account individual risk factors, might be a more appropriate method to screen for STR. Therefore, we validated a new model for personalized retinopathy screening and demonstrated that a reduction in screening frequency ranging from 23% to 61% could be achieved, compared to biannual or annual screening, respectively (Chapter 8).

**Methodological considerations**

**RCT versus Observational Study Design**

RCTs count as the golden standard to prove effectiveness for interventions because the strict selection criteria and the randomization procedure minimize the risk that confounding factors influence the results.9 Therefore, the outcomes of RCTs are considered to be close to the true effect. However, patients enrolled in RCTs are
typically not representative for the actual patient population within clinical practice. For example, RCTs exclude patients with comorbidities as well as patients of higher age. Moreover, standardized RCT protocols do not reflect usual care, where physicians usually make numerous individualized treatment decisions according to clinical, psychosocial, patient preference, and economical factors. Observational studies have the potential to provide more relevant and realistic information on the true effectiveness of the guidelines within clinical practice. However, using real world observational data comes along with its own challenges. Firstly, because of the observational nature, the results from observational studies do not necessarily imply causality and therefore cannot prove the mechanisms underlying the observed associations. Secondly, small sample sizes and measurement errors might influence the precision of the reported data. Nonetheless, observational studies are necessary to test the validity of RCT outcomes in the real world. For this PhD thesis, we used two specific observational studies; the Diabetes Care System (DCS) and the Hoorn Study. Within the next paragraphs, methodological considerations for the specific studies are described.

Diabetes Care System
The DCS consists of a well-controlled group of T2DM patients, who were treated according to a managed care plan. Starting at diagnosis, patients receive an annual extended diabetes assessment at the DCS in addition to the diabetes care offered by the patients’ GPs. Patients have a central role in their own care and self-management is stimulated by providing education and information programs. Moreover, individual care plans are discussed with the patient and patients are encouraged to make their own choices with respect to treatment options and lifestyle behavior. The highly protocolized organization of care within the DCS may be an important reason why the studied patients are so well controlled. Furthermore, probably because of the particularly well-controlled population, the incidence of sight threatening retinopathy and kidney dysfunction was low. Therefore, these results might not be generalizable to other clinical populations where blood glucose and BP levels are controlled to a lesser extent. Nonetheless, clinical characteristics of patients who reached the recommended targets are comparable to other observational studies, as were the clinical characteristics of those patients that were of increased risk of complications. It is likely that the identified subgroups also exist in other T2DM populations, probably with dissimilar proportions across subgroups. Nonetheless, our findings need to be confirmed in other long-term, real world study populations. Furthermore, the DCS consists of a mainly Caucasian population. Before extrapolation of the results to patients of other ethnic origins, they should be validated in such patients first. Another limitation of the DCS is that the proportion of medication use might be an underestimation, since information about medication use was obtained via self-reporting. However, comparison of the diabetes medication with data from the PHARMO network, showed an almost complete agreement. The PHARMO network is a comprehensive record linkage system in which drug-dispensing data in a regional/national catchment area are linked to a registry of hospital discharge diagnoses and other registries. Therefore the degree of underestimation is probably negligible. Nonetheless, information on intensified treatment was lacking, hampering the possibility to study whether treatment intensification influenced our results.

Hoorn Study
The Hoorn Study is a population-based study on the prevalence and determinants of diabetes and outcomes. Since study participants were selected from the municipal registry, the study population is likely to be representative of the general population. Strengths of the Hoorn Study include the detailed recording of vascular and retinal determinants and extensive neuropsychological assessment. In the ageing population of the Hoorn Study, 879 (35.4%) of the 2484 original participants had died in 2009. As in the real world, mortality also occurs in an observational cohort study. Therefore, dropouts due to mortality does not necessarily influence the representativeness of the Hoorn study. Furthermore, selective non-response in cohort studies does not influence the direc-
The use of Latent Class Growth Modeling as a method to define subgroups has some limitations. The first limitation concerns the complexity and flexibility of the model. There are numerous, somewhat arbitrary, choices to make and each decision could potentially influence the final number of subgroups. Furthermore, the extraction of the subgroups from the data does not prove the existence of multiple subgroups, but is a simplification of reality. However, an advantage is that categorization is not based on subgroups determined a-priori, but on trajectory characteristics derived from the data. Further, LCGM is focused on relationships among individuals, and makes it possible to categorize them in statistically homogenous subgroups.

Statistical methods
Several statistical techniques were used in this thesis, all chosen on their specific advantages. Thereby we sought to answer the studied research question in an optimal manner. Associations between determinants and outcomes were studied using linear (Chapter 6) and (multivariate) logistic regression (Chapter 2, 3 and 5) analyses. Associations between determinants and mortality (Chapter 4 and 5) were studied using Cox proportional hazards analyses. Subgroups were identified using Latent Class Growth Modeling (Chapters 2, 3 and 5). Associations of subgroups with long-term microvascular complications were analyzed using binomial mixed modeling (Chapter 2, 3 and 5). Lastly, the predictive accuracy of the personalized screening model was performed using calibration (Poisson regression for survival data) and discrimination (Harrell’s C-statistic) techniques (Chapter 8).

Interpretation of results and comparison with existing literature
In this thesis, we showed that the majority of the T2DM patients reached adequate glycemic and/or BP control. However, we also showed that there are certain groups that have insufficiently controlled blood glucose and/or SBP levels over time. Our results complement the results of several cross-sectional studies within clinical practice showing suboptimal glycemic \cite{14-16,21} and BP control \cite{11,22,23} and urge the need to consider long-term real world studies within the T2D guidelines.

Yet, how could the results of this thesis be used to complement the current guidelines? And, did we find proof for the existence of the concepts on which the current guidelines are heavily grounded?

The lower, the better
The adequate SBP control subgroup showed stable SBP levels at or around 140 mmHg and showed lower rates of microvascular complications and a decreased cardiovascular mortality risk as compared to patients with inferior SBP control. These results are in line with the UKPDS study in which lowering SBP levels to a mean of 144 mmHg markedly reduced the incidence of micro- and macrovascular complications compared to the group that achieved mean SBP levels of 154 mmHg during follow-up.\cite{24} Therefore, these results may favor the concept “the lower,
the better.” However, as the adequate SBP control group had the “best” controlled SBP levels and showed a mean SBP of 140 mmHg over time, we did not study whether SBP levels were linearly associated with a decreased risk of complications. Recently, a retrospective cohort study from the Kaiser Permanente health system showed that both higher and lower achieved SBP levels compared with 130-139 mmHg were associated with an increased risk of mortality in both diabetic and non-diabetic patients, thereby validating the evidence from the ADVANCE and the ACCORD studies that “lower SBP levels are not always better.”

**The earlier, the better**

Longer diabetes duration with accompanying high levels of glycemia at the start of diabetes treatment was associated with worse glycemic control during follow-up and with an increased risk of retinopathy and other microvascular complications (Chapter 2 and 3). In comparison, the fast responders subgroup consisting mainly of newly diagnosed T2DM patients, showed a fast response to diabetic treatment and the prevalence of microvascular complications immediately decreased following tight glycemic control (Chapter 2). These findings confirm that strict glycemic control in newly diagnosed T2DM patients has a beneficial effect on glycemic control risk and developing microvascular complications. Our results are in line with the UKPDS and favor the concept “The earlier, the better.” How periods of hyperglycemia impact on the vascular fate of diabetic subjects remains to be elucidated. Mechanisms may include hemodynamic anomalies or be more biochemical in nature. It may be that hyperglycemia alters function and perhaps structure of the vascular endothelium, and that periods of hyperglycemia affect the genome, leaving an imprint on the future of organisms, especially regarding vasculature.

**Personalized care**

Which subgroups may be entitled to receive, more intensive, personalized diabetes care?

Higher HbA1c levels, a longer diabetes duration and younger age at baseline were associated with a more unfavorable course of glycemic control over time in patients entering the DCS (Chapter 2) and those initiating insulin (Chapter 3). Furthermore, these subgroups showed a higher risk of microvascular complications. A recent study showed similar results and observed that the greatest risks of microvascular complications occur in the group with the youngest age at diagnosis (<50 years) and with the longest diabetes duration (>10 years). Further, glycemic control was less often achieved in the younger age groups. It could be that patients who develop T2DM at a younger age have a different, more aggressive phenotype than those who develop T2DM at a more advanced age, so that worse glycemic control and a greater microvascular risk are experienced. These results may indicate that younger patients need to receive more intensive, diabetes care in order to achieve glycemic control and to prevent microvascular complications.

Subgroups with suboptimal SBP control were significantly older (mean age 66 years), more likely to be female and had higher BP levels at baseline (Chapter 5). Particularly older T2DM patients are mainly not included in RCTs and have an increased risk of vascular complications and death. Older T2DM patients with uncontrolled hypertension represent an important subgroup to target in order to improve SBP control and to minimize the excessive risk of vascular complications and death.

**Is retinopathy useful as a risk marker for other complications?**

Retinopathy has been associated with an increased risk of CVD complications. In our study, any retinopathy was associated with a significantly reduced LV ejection fraction. Since this effect was only observed in men and in one aspect of LV dysfunction only, using retinopathy as a risk marker for LV dysfunction does not seem useful. However, the small sample size and selection that occurred most likely led to an underestimation of the observed association between retinopathy and LV function. Therefore, and considering other studies that did show convincing results, we cannot exclude the possibility that retinopathy might be a useful risk marker to identify patients at risk for CVD complications.

Retinopathy and cognitive functioning were unre-
Physicians make treatment decisions that are as relevant as possible to the individual patient. In doing so, they balance their own skills with the treatment of T2DM and supplement this with the T2DM guidelines and evidence from scientific research. Currently, this type of personalized care may lead to a large variety of T2DM treatment policies, largely depending on a physician’s own experience with T2DM. Use of personalized screening models for T2DM and its complications as a whole, such as the screening tool for retinopathy, will probably decrease treatment variation across clinical practices. However, a limitation of personalized screening is that it is dependent of the accuracy and punctuality of the care system and care professionals, making the system more prone to errors. Therefore, computerized medical systems that send automatically generated reminders for screening might ensure safe follow-up procedures whilst using personalized care strategies.

The increasing number of T2DM patients has driven the development of several sorts of glucose lowering medications that may ultimately result in increased glycemic control among T2DM patients, thereby reducing the risk of developing complications.40 Because of the numerous availability of glucose lowering medications, one of the major challenges for clinicians currently is to choose the therapy that fits best and has the highest chance of achieving glycemic control in a specific patient, taking into account individual characteristics. However, few studies examined which patients do better or worse with specific medications. As a result, T2DM patients are currently treated without taking into account individual characteristics that might influence the effectiveness of a particular therapy. Therefore, improved understanding of environmental, phenotypic and genotypic aspects that may influence the response to glucose lowering medications is important in order to reduce the chance of treatment failure.41 Comparative effectiveness research (CER) holds a promise to identify the best strategies towards personalization by reaching a better understanding of the question “What works for whom and in what context?” In CER, groups of real world patients are analyzed to compare the effectiveness of for example, glucose lowering medications, with the intent to more precisely match the optimal

Can personalized screening reduce screening frequency for retinopathy?

Using the personalized screening model for retinopathy, a reduction in screening frequency ranging from 23% to 61% could be achieved, compared to biannual or annual screening respectively. This number is comparable to a Danish population used to test the fit of the model, where 59% of the screenings could be safely omitted.36 Other studies already showed that annual screening intervals could be safely prolonged for individuals at low risk of developing STR.5,6,37 Use of a personalized screening showed to be safe and also increases the likelihood to diminish the time to detect STR, by also integrating shorter (≤ 12 months) screening intervals for patients at high risk of STR. If this is also the case for ethnic groups with a much higher risk of developing diabetes and its complications, must still be evaluated. Momentarily, our group is validating the personalized screening model in small ethnic groups in a secondary care unit.

**Perspectives of Type 2 Diabetes**

An increasing number of people is being diagnosed with T2DM, with the greatest number of patients nowadays aged between 40 years and 59 years.38 Given the shifting age distribution among T2DM patients and the accompanying increase in costs of diabetes care, there is a need to reform care for T2DM patients. A refocus towards intensive management of hyperglycemia at diagnosis, particularly in younger people, seems useful to minimize the long-term risk of complications. On the other hand, patients with consistently well-controlled glucose and BP levels might be currently over screened by the “one size fits all” guidelines. In those patients, lowering of the monitoring frequency might be cost-effective while not hampering glycemic control.39
therapy with the individual patient. By doing so, more dynamic statistical models might be used, such as marginal structural models, which allows adjustment for time-dependent confounders. By adjusting for time-dependent confounding more valid results on the real world effectiveness of several treatment strategies for long-term glycemic and BP control in T2DM patients might be achieved.43–45

Conclusions
This thesis provides long-term proof for the clinical effectiveness of the current T2DM guidelines. Although most patients reached glycemic and/or BP control, we also identified subgroups of patients with insufficient glycemic and/or BP control over time. For those patients, the current guidelines might not provide the best treatment strategy and personalized care strategies may be required to achieve glycemic and/or BP control and thereby prevent complications. We showed that younger age groups might need to receive more intensive diabetes care in order to achieve glycemic control and to prevent microvascular complications. Personalized screening for retinopathy could reduce costs and screening frequency by up to 61% whilst still ensuring safety. Evidence-based personalized screening schemes might be the next step to improve T2DM care in the real world.
References

5. Chalk D, Pitt M, Vaidya B, Stein K. Can the retinal screening interval be safely increased to 2 years for type 2 diabetic patients without retinopathy? *Diabetes Care* 2012; **35**: 1663–8.


