Adherence to antihypertensive or antihyperlipidemic co-medications in diabetes: patterns, predictors, and intervention

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CHAPTER 9

GENERAL DISCUSSION

The first part of this thesis describes non-adherence and non-persistence to cardiometabolic medications in patients with type 2 diabetes using pharmacy databases in the Netherlands. The second part focuses on developing and testing a targeted and tailored pharmacist-led intervention to improve adherence to antihypertensive drugs among patients with type 2 diabetes in Indonesia. Main findings, implications, methodological considerations, and future perspectives will be discussed for each part below. An overall conclusion is presented at the end of this chapter.

Part I: Non-adherence and non-persistence to cardiometabolic medications in patients with type 2 diabetes: pharmacy data measurement

Main findings

In **Chapter 2**, we reviewed the measures that have been proposed or used to estimate medication adherence and persistence to multiple cardiometabolic medications.[1] Five distinct adherence measures were identified, including adherence to "all" (at least 80% adherence to each medication), to "any" (at least 80% adherence to any –at least one- medication, usually from the same therapeutic level), to "both" medications (calculating adherence based on the number of days when both medications were available), "average adherence" (calculating adherence for each individual medication and presenting the overall average), and "highest/lowest adherence" (calculating adherence for each medication and presenting the highest and lowest number as measure of adherence). Three distinct persistence measures were identified, including persistence with "all" (persistent when each medication is without a gap), with "both" (persistent when no gaps in two medications concurrently), and with "any" medication (persistent when no gap in at least one medication, usually from the same therapeutic level).

In **Chapter 3** and **4**, we focused on the patterns and pharmacy-based predictors of non-adherence, non-persistence, and/or re-initiation of antihypertensive medications and statins in Dutch patients with type 2 diabetes. In **Chapter 3**, we used previously reported measures (see also **Chapter 2)** to assess non-adherence to *any* antihypertensive medication and non-persistence to *all* antihypertensive medications, measures which consider multiple medications and medication switches.[2] The advantage of these measures is that they do not overestimate non-adherence or non-persistence when patients switch to another class of antihypertensive drugs. We observed that the first year after initiation is the most crucial with regard to non-adherence and non-persistence, and that the predictors are clearly different for both processes. Predictors of non-adherence were receiving medications for secondary cardiovascular prevention and the drug class diuretics as initial medication class, while predictors of non-persistence were female gender, older age and diuretics, and the drug class beta-blocking agents or calcium channel blockers as initial medication class. Early non-persistence was a predictor for not reinitiating drug treatment. In **Chapter 4**,

we looked at statins and observed that non-persistence was the foremost problem in the first year after statin initiation, while non-adherence became more of an issue in the second and third year.[3] Predictors of non-adherence were younger age, low socioeconomic status, and not receiving medications for secondary prevention. Predictors of non-persistence were older age, starting on standard or low dose statin treatment, receiving only few other medications, and receiving no other cardiovascular medications.

Implications for research and practice

Precise estimates of adherence and persistence are important in research and clinical practice. In intervention research, inaccurate estimations may influence the validity of adherence and persistence rates and, subsequently, lead to inefficient or even ineffective interventions which hinders optimal personalised medicine.[4] In clinical practice, invalid estimations may lead to several problems, including the fact that effective treatments may be judged as ineffective which may lead to inappropriate actions such as early stopping, switching or treatment intensifications.[5–7] Healthcare providers may also not be triggered to start a discussion about a patient' medication-taking behaviour, since they incorrectly assume that a patient is adherent.[8] For patients who use multiple medications for the same indication, adherence and persistence assessments are even more complex, particularly when drugs can be switched or added over time. Our systematic review (**Chapter 2**) can help researchers and healthcare providers in choosing the measures to estimate adherence and persistence to multiple medications from pharmacy data. For example, the adherence and persistence to "any medication'' measures are helpful to monitor adherence and persistence as well as to identify patients in need of an intervention. The adherence and persistence to ''all medication'' measures are more useful for assessing the effect of interventions. Using different definitions, these measures will result in different estimates.[9,10] Furthermore, we observed that a substantial number of studies were flawed because of inadequate description of the methods or how switching or additions were dealt with. More attention should be paid to both the quality of the studies and the quality of the reporting, since the need for and type of interventions should be supported by sound evidence.

Our findings in **Chapter 3** and **4** highlight the need for pharmacists and other healthcare providers to monitor patients with type 2 diabetes closely during the first year after antihypertensive or statin initiation.[2,3] We observed that 18% out of 6,669 antihypertensive initiators and 20% out of 12,741 statin initiators discontinued antihypertensive or statin treatment in the first year, whereas non-adherence rates in the persistent patients were 11% and 13%, respectively. Of note, we observed that 22% of patients who discontinued antihypertensive reinitiated treatment within one year, indicating that initiatives had been taken to counter unwanted discontinuation of these drugs.[2] For statins, attention should also be given to patients in the subsequent years, because the rates of non-adherence increased to more than 18% over the first

three years. It could be that the motivation to take statins decreases over the year, which may be fuelled by statin scepticism or experiencing side effects without clear benefits.[11]

For routine implementation, pharmacy data can be used as an alert to indicate when patients refill medications later than expected. This is an opportunity for pharmacists to start discussions about the patients' adherence and persistence. Our findings that predictors of antihypertensive or statin non-adherence and non-persistence are not the same (**Chapter 3** and **4)** is important. It illustrates that different subgroups should be targeted for interventions to reduce non-adherence and non-persistence; a personalised targeted approach is warranted over a one size fits all approach.

Methodological considerations

Measuring medication adherence and persistence from pharmacy data is prone to methodological pitfalls, which warrant further consideration.[12] Pharmacy data do not consider lost medications or medications that were dispensed in other pharmacies. However, most patients in the Netherlands (94%) usually collect all their medication from one pharmacy, where they are registered.[13]

In **Chapter 3** and **4**,[2,3] an interval-based approach -with a fixed period as denominator- was used, as this has been recommended as the preferred measurement for adherence.[14,15] Eligibility information regarding the medication use is essential for this approach to be interpreted correctly, because the period of time with no prescription at the end of the observation period is included in the calculation.[16] For cardiometabolic medication, we have assumed that continuous use is required. A prescription-based approach -with a variable period ending with a prescription- has been shown to overestimate adherence, since it provides adherence information only for the period of time when patients are receiving medications.[14,15] Therefore, the prescription-based approach does not provide information on those who discontinue or interrupt therapy, which is common in clinical practice. The distinction between these approaches is relevant when medication is switched, because the interval-based approach may lead to overestimation of non-adherence or non-persistence when medication switches are not taken into account. This issue was addressed by including switches in the calculations when assessing adherence and persistence to antihypertensive medications in **Chapter 3**. In **Chapter 4,** patients were allowed to switch to another type of statin, but patients who switched to another lipid-lowering drug were censored at the moment of switch.

We interpreted non-adherence in **Chapter 3** and **4** as a dichotomous variable with a threshold for optimal adherence equal or higher than 80%, as a lower rate was associated with a higher rate of hospitalization for chronic diseases.[17] For multiple medications, however, different thresholds may be used depending on the adherence measures (**Chapter 2)**. When using the more stringent ''all medication'' or ''both

medications'' adherence measures, a lower threshold, such as 70%, might be preferred, assuming that this is sufficient to achieve the desired clinical effect. Furthermore, the association of adherence level with clinical outcomes may differ based on the type and characteristics of diseases, type of medication, dose, and drug formulation.[18–20] For example, a higher adherence threshold for low-dose medications might be preferred than for high-dose medications to obtain a similar clinical effect.[19] Higher adherence thresholds might also be needed in resistant hypertension to obtain the expected clinical benefits of a treatment.[21] On the other hand, a lower threshold might be preferred for some medications with a long half-life or with extended release formulation in which missing a dose may be less clinically relevant.[20]

It is important to pay attention to the distinction between patients new to therapy (incident patients) and patients already taking a medication of interest before the measurement period (prevalent patients). Incident patients are at the greatest risk of non-adherence and non-persistence due to the early potential side effects or other problems with a new drug treatment.[22] Prevalent patients who have settled into more routine with taking their medication are more likely to have higher adherence rates.[22] Therefore, our findings among incident patients (**Chapter 3** and **4)**[2,3] are not generalizable to those of prevalent patients.

In **Chapter 3** and **4,** we defined patients with type 2 diabetes based on the dispensing of at least two prescriptions for oral antidiabetic medication. Patients only receiving insulin were thereby excluded, which might have resulted in the elimination of some patients with advanced type 2 diabetes. The proportion of type 2 diabetes patients only using insulin, however, is low. Moreover, we expect that the pharmacy-based predictors identified in **Chapter 3** and **4** will differ in a non-diabetes population. Thus, caution should be taken when using these results in a non-diabetes population.

Future perspectives

A variety of measures has been proposed or used to estimate adherence and persistence to multiple medications (**Chapter 2**). However, the association of adherence or persistence measures to multiple medications with clinical outcomes is currently lacking. Previous studies showed that adherence to any blood pressure-lowering medication was associated with lower odds of having elevated systolic blood pressure or with lower odds of death.[23,24] The study by Tang et al.,[24] also showed that the average of the class-specific adherence with an 80% cut-off level to blood pressure-lowering medication was inversely associated with death. Therefore, future studies are needed to relate various measures of adherence and persistence to multiple medications with clinical outcomes. Notably, such relations should be examined for different subgroups to gain insights into possible disparities which may require personalised approaches.

Using pharmacy data (**Chapter 3** and **4)**, underestimating non-adherence may occur when the initial prescription is filled too late or never dispensed (primary non-adherence).[25] On the other hand, overestimation of non-persistence is an issue when patients discontinue treatment on their doctor's recommendation. Therefore, future studies are required to overcome these limitations by linking pharmacy data with prescribing data and with information on active stopping of prescriptions. It has been reported that linked pharmacy and prescribing data allow for more precise adherence estimates than pharmacy-only data among patients treated with osteoporosis drugs.[26]

In **Chapter 3** and **4**, we included mostly non-modifiable factors as predictors for non-adherence and non-persistence, and observed that the overall predictions were not very strong.[2,3] This indicates that there are possibly other factors, which are not readily available or known to a pharmacist and might be modifiable, such as a patient's comprehension of the treatment regimen and its benefits, fear of side effects or level of forgetfulness.[27,28] A review of systematic reviews showed that interventions to improve adherence to cardiovascular medication should be developed to address modifiable factors.[29] The associations of these modifiable factors with non-adherence were mostly assessed during the implementation phase.[28,29] Further studies are needed to clarify the influence of modifiable predictors on different phases of medication-taking behaviour, including primary non-adherence, non-adherence, non-persistence and reinitiation of cardiometabolic medication. In addition, more attention should be paid to different moments or changes in medication which may influence adherence, such as after experiencing treatment failure or following hospital discharge.[30–32]

Part II: Developing and testing a targeted and tailored pharmacist-led intervention to improve adherence to antihypertensive medications among patients with type 2 diabetes in Indonesia

Main findings

To develop a targeted and tailored pharmacist-led intervention, we identified factors associated with non-adherence to antihypertensive and antihyperlipidemic medications among patients with type 2 diabetes in community health centres (CHCs) in Indonesia **(Chapter 5)**.[33] In this observational multicentre cross-sectional survey, around half of 571 diabetes patients who were prescribed antihypertensive and/or antihyperlipidemic medications were non-adherent to this medication. We observed that medication beliefs were a potentially modifiable factor associated with non-adherence to antihypertensive as well as to antihyperlipidemic medications. Beliefs about necessity of the medication were important but concerns about the medication were important particularly for antihyperlipidemic medication. There were not much differences in factors associated with the subtypes of non-adherence to antihypertensive or antihyperlipidemic medications, indicating that necessity and/or concern beliefs are relevant for both unintentional and intentional non-adherence.

We described the study protocol for evaluating a targeted and tailored pharmacist-led intervention in a cluster randomised trial, and the details of the intervention procedures in **Chapter 6**.[34] Importantly, we developed simple support materials for the pharmacists and patients, and a procedure that could be easily implemented in routine care in Indonesia, making this a low-cost intervention. In **Chapter 7,** we observed that this low-cost, targeted and tailored pharmacist-led intervention significantly improved medication adherence. There was a non-significant positive difference in the medication necessity-concerns beliefs between the intervention and control group. The effectiveness of intervention can be explained by its good implementation in the trial setting, and the appreciation of the tailored intervention by both the pharmacists and the patients (**Chapter 8)**.

Implications for research and practice

The implementation of universal health coverage in Indonesia in 2014 has improved patients access to health care,[35] yet it did not appear to lead to optimal medication adherence rates for the preventive medication that is important for patients with type 2 diabetes **(Chapter 5**). We observed that Indonesian patients with type 2 diabetes reported suboptimal adherence rates of 45.5% for antihypertensive and 52.7% for antihyperlipidemic medication.[33] Our study showed that associations between medication beliefs and adherence differ across the therapeutic groups. Of note, we focussed on medication beliefs without considering other potential modifiable factors, such as a patient's comprehension of the treatment regimen or level of forgetfulness.[27,28] The most common adherence barriers identified by the pharmacist during counselling were forgetfulness and lack of knowledge, whereas medication beliefs and other drug related problems (e.g., difficulty to refill antihypertensive drugs in time) were less common (**Chapters 7** and **8**). It is important for pharmacists to address these potential modifiable adherence barriers during counselling in order to reduce both unintentional and intentional non-adherence. The importance of unintentional non-adherence may lie in its potential prognostic value for future intentional non-adherence.[36] Furthermore, we observed that the developed training and support tools were considered helpful for both pharmacists and patients (**Chapter 8**).

Our findings reported in **Chapter 7** and **8** are encouraging since they show that non-adherence can be reduced with a relatively simple and low-cost intervention. The intervention aligns with the current workflow and resources in daily clinical practice in Indonesia and does not require a substantial change to the current care system. Several strategies may be required to optimize and maintain the effects of this intervention, such as:

1. **Adapting guidelines on medication adherence during counselling**
   In Indonesia, the guidelines emphasize the importance of addressing medication adherence during patient counselling in the pharmacy[37], CHC,[38] and hospital[39]. However, there is no clear information or guidance on how to identify and improve

medication non-adherence. Integrating knowledge generated from adherence and behavioural change research, as well as evidence from longer-term studies focusing on clinical outcomes may help to adapt the guidelines on medication adherence.[40] Furthermore, the guidelines need to emphasize the period when monitoring and supporting adherence are particularly important based on different phases of medication-taking behaviour (e.g., when initiating treatment, after experiencing treatment failure, or following hospital discharge).[30–32]

2. **Providing pharmacists with training and practical decision support tools for patient counselling**
   Since 2010, the Indonesian government has initiated a chronic disease management programme, PROLANIS (*Program Pengendalian Penyakit Kronis*). The results of our low-cost, targeted and tailored pharmacist-led intervention confirmed the need for pharmacists to regularly counsel patients with chronic diseases during their monthly regular visits to CHCs. This regular counselling is important since developing patients' habits may take up to one year.[41]

   Furthermore, pharmacists need to be well equipped to easily and consistently identify non-adherence patients who would benefit most from intervention. Incorporating the use of our practical decision support tools (simple question-based flow-charts and the adherence intervention wheel) are needed to support and guide pharmacists when identifying the patient's adherence barriers and tailoring the intervention to these barriers in a time saving manner. While some patients may change their behaviour to adhere to medication after verbal counselling, others may benefit from both verbal and written information.[42] Moreover, high workloads and time constraints can prevent effective verbal communication with patients during counselling.[43] Therefore, counselling needs to be supplemented with personalised written information about the agreed goal and recommended strategies to improve adherence. Personalised written information can improve better understanding of the information provided during counselling.[44] In addition, pharmacists may need training to conduct more efficient counselling, and would also be helped with having consultation rooms for more effective counselling.

Methodological considerations

We used a self-reported questionnaire for the measurement of adherence for the studies reported in **Chapter 5** and **7**, which may be prone to socially desirable answers and lead to underestimation of the true rate of non-adherence.[45] Therefore, a triangulation of two or more different methods to measure medication adherence is recommended.[46] Although pharmacy databases also come with limitations, such information would allow for a more objective assessment of adherence. Unfortunately, these sources were unavailable for our studies in Indonesia. In addition, using a self-reported questionnaire could influence a patient's behaviour and create a Hawthorne effect. The Hawthorne effect may result in "white coat adherence" effects, for instance,

patients taking more punctual dosings in the days before their blood pressure was measured.[47] In **Chapter 7**, some improvements in adherence scores were indeed observed in both the intervention and control group which may have led to an underestimated intervention effect.

In **Chapter 8**, the results of the pharmacist group discussion about the adoption, implementation, and maintenance of the intervention were analysed by one researcher. Within the time-frame and resources of this study, it was not possible to conduct this analysis with two researchers.

Future perspectives

Most self-reported questionnaires to assess medication adherence and medication beliefs, which we used for the studies reported in **Chapter 5** and **7,** have been developed in high-income countries. Therefore, it is recommended to begin adherence research in low- and middle-income countries with a qualitative approach, such as in depth-interview or focus group discussion. Based on the findings on qualitative studies, one might add the questions that are most appropriate for that specific patient group, type of medication, and type of disease. For example, individual, face-to-face interviews conducted among 30 non-adherence patients in rural villages, Indonesia, showed that their preference to use alternative medicines and limited understanding of their blood pressure targets might influence their necessity to take antihypertensive medications.[48]

In **Chapter 7**, a tailored pharmacist-led intervention delivered face-to-face to patients has been shown to effectively improve medication adherence. The key aspects of the intervention included identifying the patient-specific problems for non-adherence, and subsequently delivering and implementing personalised adherence strategies which is supported by paper-based decision support tools. The use of mobile devices for delivering digital health interventions is currently increasing.[49] It would be worthwhile to test whether the use of our paper-based decision support tools could be improved by using mobile apps. A previous study showed that an iPad-delivered intervention focusing on documentation of medication intake and blood pressure values resulted in greater improvement in medication adherence than the pen and paper journal.[50] However, many of the existing mobile apps to improve medication adherence are delivered as a one-size-fit-all intervention, assuming that the reasons for non-adherence are the same for the patients. A recent meta-analysis showed that apps tailored to the patient's specific problems for intentional and non-intentional non-adherence are more effective for supporting medication adherence than apps that were only tailored to the prescribed medication regimen.[51] Future studies could focus on further development and investigation of the effectiveness of a mobile app that can guide pharmacists or other healthcare providers to identify patients' individual adherence problems and to deliver the recommended personalised strategies.

In **Chapter 5,** the associations between medication beliefs and adherence were different across therapeutic groups, confirming findings from previous studies.[52,53] Within individuals, beliefs vary across different medication but also across different medication-taking behaviours.[54]. A previous study indicates that patients who persist in using chronic medication have higher necessity and lower concern beliefs in comparison to those who do not initiate or do not persist in taking their medication.[54] Further studies could clarify the different associations between medication beliefs and different phases of medication-taking behaviour for different types of medication. Moreover, we observed that necessity and/or concern beliefs were relevant for both unintentional and intentional non-adherence (**Chapter 5**). In patients with chronic diseases, perceived need may affect both unintentional and intentional non-adherence, such that the unintentional behaviour may mediate intentional non-adherence.[36] Therefore, better understanding of the mechanism between the potential prognostic value of unintentional non-adherence for future intentional non-adherence is needed.

Our pharmacist-led intervention programme was found to be effective to improve adherence to antihypertensive drugs at 3-months follow-up (**Chapter 7**). However, whether the effects of the intervention on medication adherence are transient over time needs to be evaluated in future studies. Longer duration of outcome assessment is also needed to observe the impact of the intervention on necessity and concern beliefs. Previous studies among patients with hypertension showed a significant effect of repeated counselling on the necessity beliefs after nine months[55] and on necessity and concern beliefs after twelve months.[56] Given the increasing rate of polypharmacy in general,[57] better understanding of the effects of our pharmacist-led intervention to improve adherence to other dispensed medications is relevant. Moreover, in order to evaluate whether implementation of the intervention represents an efficient use of health care resources, further studies on cost-effectiveness of this targeted and tailored pharmacist-led intervention are needed. A previous systematic review showed that community pharmacist-led interventions aimed to improve adherence in high-income countries are either cost-saving or cost-effective.[58]

Overall conclusions

Part I of this thesis illustrated the relevance of defining distinct adherence and persistence measures to multiple cardiometabolic medications, which can be applied using pharmacy data. Furthermore, it was shown among Dutch patients with type 2 diabetes that pharmacy-based predictors and patterns of non-adherence, non-persistence, and/or re-initiation to antihypertensive drugs and statins were not the same. **Part II** of this thesis showed among patients with type 2 diabetes in Indonesia that the association of medication beliefs with non-adherence varied between antihypertensive and antihyperlipidemic drugs. A low cost, tailored pharmacist-led intervention targeted at non-adherent patients with type 2 diabetes was well accepted and resulted in a significant improvement in medication adherence to antihypertensive drugs.

Based on our findings in **Part I** and **Part II**, it can be concluded that both non-modifiable and modifiable factors are relevant for interventions to improve non-adherence and/or non-persistence to cardiometabolic medications. Non-modifiable factors, including the drug classes involved and the time since medication initiation, are important for targeting interventions. Modifiable factors, including lack of knowledge, motivation and forgetfulness, can be addressed in a tailored intervention. While the extent of pharmacist involvement in patient care may vary between the Netherlands and Indonesia, a targeted and tailored pharmacist-led intervention that is effective and can be integrated into the community pharmacy workflow is needed in both countries.

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