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

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# CHAPTER 1

GENERAL INTRODUCTION

Medication adherence is defined as the process by which patients take their medication as prescribed.<sup>1</sup> Medication adherence has three components, referring to different phases in medication-taking behaviour: initiation, implementation, and discontinuation (Figure 1).<sup>1</sup> The process starts with initiation of the treatment, when the patient collects the medication and decides to take the first dose of a prescribed medication. The process continues with the implementation of the dosing regimen, defined as the extent to which a patient's actual medication-taking behaviour corresponds to the prescribed dosing regimen. Discontinuation or non-persistence marks the moment when the patient decides to end the treatment. Another term used in relation to medication adherence is persistence, which is the length of time between initiation to discontinuation.

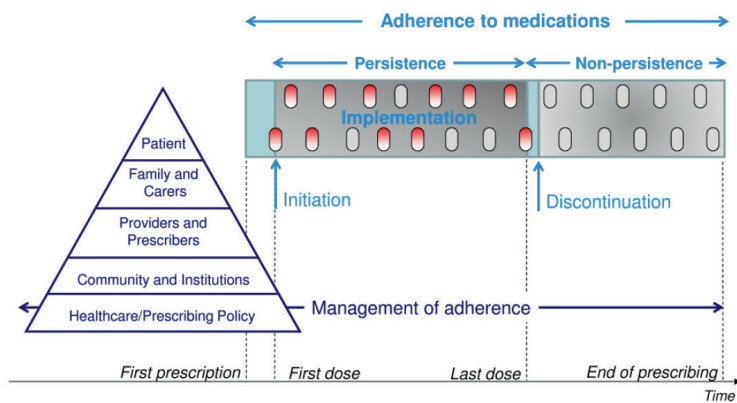


Figure 1. Different phases of medication-taking behaviour<sup>1</sup>

Adherence and persistence to chronic preventive medications remain poor in high- and low-middle-income countries,<sup>2-5</sup> despite the development of many interventions to address this behaviour. In patients with type 2 diabetes, medication taking is particularly complex since they often need not only antidiabetic medication, but also antihypertensive and antihyperlipidemic co-medications. More insight is therefore urgently needed into the patterns of non-adherence and non-persistence among these patients and which risk factors predict a poor adherence. With these insights, innovative strategies for reducing non-adherence and non-persistence can be developed. The studies in this thesis are focused on patient populations in the Netherlands as example of high-income countries and Indonesia as example of low- and middle-income countries.

### Treatment to prevent cardiovascular complications in diabetes

The prevalence of type 2 diabetes is increasing in the Netherlands and Indonesia as in many countries worldwide.<sup>6</sup> In 2013, 4.5% (around 750 thousand people) of the Dutch population was reported to have diabetes.<sup>7</sup> In Indonesia, the number of patients with diabetes was 10.3 million in 2017, and this number is expected to increase to 16.7 million by 2045.<sup>8</sup> Patients with diabetes have a higher rate of developing cardiovascular

disease (CVD) than adults without diabetes.<sup>9</sup> Hypertension and hyperlipidaemia are common in patients with diabetes and contribute significantly to an increased risk of CVD.<sup>10</sup> Antihypertensive and antihyperlipidemic medications are known to be effective in preventing CVD among patients with diabetes.<sup>11–14</sup> Therefore, antihypertensive and antihyperlipidemic medications are commonly needed among these patients.<sup>10</sup>

### **Non-adherence and non-persistence with antihypertensive and antihyperlipidemic medications**

Among patients with type 2 diabetes, antihypertensive and antihyperlipidemic medications can be considered as co-medications which may give particular adherence and persistence problems. While much research has been conducted to assess adherence and persistence to antidiabetic medication and its underlying factors,<sup>15,16</sup> there is limited knowledge regarding their adherence and persistence with cardiovascular co-medications among these patients. A study in the Netherlands showed that at least 1 in 5 patients with type 2 diabetes were non-adherent to antihypertensive and antihyperlipidemic medications.<sup>17</sup> Non-persistence rates to antihypertensive and antihyperlipidemic medications among patients with type 2 diabetes have been observed between 25% and 30%.<sup>18,19</sup> The risk of non-adherence and non-persistence to antihypertensive and antihyperlipidemic medications is high due to the asymptomatic nature of these diseases, that is, the lack of noticeable efficacy by the patient in everyday life.<sup>20,21</sup>

### **Predictors of non-adherence and non-persistence with antihypertensive and antihyperlipidemic medications**

To target the patients most in need of an intervention, insight in the predictors of non-adherence and non-persistence is required. Using pharmacy databases, non-modifiable predictors of non-adherence and non-persistence with antihypertensive or antihyperlipidemic medication include age, gender, marital status, or level of education.<sup>22,23</sup> Furthermore, self-reported medication beliefs were found to be among the important modifiable predictors of non-adherence to antihypertensive medications.<sup>24–27</sup> However, the findings on non-modifiable and modifiable predictors are not consistent in the literature.

One of the main problems, particularly when it comes to identification of predictors from pharmacy databases, is that overlapping definitions for non-adherence and non-persistence are often used. For example, non-persistence was defined as a short gap of more than 30 days after the last prescription,<sup>22</sup> which is likely to include patients who did not discontinue medication but were just taking less medication than prescribed. Shorter gap lengths lead to higher non-persistence rates as they also include non-adherent patients. Disregarding this distinction can lead to conflicting results when assessing predictors of non-adherence and non-persistence.

## **Interventions to improve adherence and persistence among patients with type 2 diabetes**

Factors leading to non-adherence and non-persistence are classified into five categories: socioeconomic (e.g. low level of education or lack of family support<sup>28</sup>), therapy-related (e.g. complexity of medication regimen), patients-related (e.g. perception,<sup>29</sup> beliefs,<sup>30</sup> or forgetfulness<sup>31</sup>), condition-related (e.g. severity of symptoms), and health system/health care team-related factors (e.g. communication between health care provider and patient).<sup>32,33</sup> The reasons underlying non-adherence or non-persistence are not entirely independent and are heterogeneous. As such, there are no one-size-fits-all solutions to address non-adherence or non-persistence.

Numerous interventions to improve medication adherence and persistence have been studied in high-income countries.<sup>33–35</sup> Six main types of interventions can be identified: patient education, medication regimen management, clinical pharmacist consultation, cognitive behavioural therapies, medication-taking reminders, and incentives to promote adherence.<sup>35</sup> However, a Cochrane review showed that most interventions are often not particularly effective and too complex to implement in low- and middle-income countries.<sup>34</sup> Previous studies suggest that effective interventions to improve adherence should be led by a pharmacist, delivered face-to-face, administered directly to patients, and behaviourally-targeted instead of cognitively-targeted interventions.<sup>36</sup> In addition, interventions involving monitoring and feedback, as well as interventions delivered over multiple sessions, are probably more effective.<sup>37</sup> The paucity of healthcare and economic resources in low- and middle-income countries poses challenges to proper implementation of such interventions. Moreover, a thorough process evaluation of implementing such interventions is not often provided, thus, limiting their potential for replication and scaling-up.<sup>38–40</sup>

Community pharmacists are in the ideal position to address non-adherence, since they are highly accessible healthcare providers in primary care. However, in Indonesia, there is no clear information or guidance to identify non-adherence and to counsel patients regarding their medication-taking behaviour.

### **Thesis objectives and outlines**

This thesis aims to get more insight in the patterns and predictors of non-adherence and non-persistence to antihypertensive and antihyperlipidemic medications among patients with type 2 diabetes. Further, these insights were used to develop a targeted and tailored pharmacist-led intervention to improve adherence to antihypertensive medications among patients with type 2 diabetes in Indonesia. To achieve these aims, the following studies were conducted in the Netherlands (Part I) and in Indonesia (Part II).

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

The aims of Part I are:

- To systematically review the measures that are used to calculate adherence and persistence to multiple preventive medications from prescription data.
- To describe patterns and identify predictors of non-adherence, non-persistence, and/or reinitiation to antihypertensive medications and statin as discrete processes in patients with type 2 diabetes.

For clinical decision-making, health care providers need to have precise adherence and persistence estimates. **Chapter 2** presents a systematic review of the measures used to calculate adherence and persistence to multiple preventive medications from prescription data. To develop effective interventions for reducing non-adherence and non-persistence, it is important to describe the patterns of different phases of medication-taking behaviour and identify which patients at risk of becoming non-adherent or non-persistent. **Chapter 3** and **Chapter 4** focus on the patterns and predictors of non-adherence, non-persistence, and/or reinitiation to antihypertensive medications and to statins in Dutch patients with type 2 diabetes.

**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**

The aims of Part II are:

- To identify factors associated with non-adherence to antihypertensive and antihyperlipidemic medications among patients with type 2 diabetes in Indonesia with a focus on their medication beliefs.
- To develop a targeted and tailored pharmacist-led intervention to improve adherence in Indonesian population that can be integrated into the community pharmacy workflow.
- To assess the process and effects of implementing the intervention in a real-world primary care Indonesian setting.

**Chapter 5** identifies factors associated with non-adherence to antihypertensive and antihyperlipidemic medications among patients with type 2 diabetes in Indonesia. **Chapter 6** describes the study protocol of a targeted and tailored pharmacist-led intervention programme and the detailed procedure of the cluster randomised controlled trial. **Chapter 7** evaluates the effectiveness of the pharmacist-led intervention as compared to usual care. **Chapter 8** describes the process evaluation of the implementation of the intervention from both a pharmacist and patient perspective. In **Chapter 9**, we summarise and discuss the main findings of the chapters.

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# PART I

NON-ADHERENCE AND  
NON-PERSISTENCE TO  
CARDIOMETABOLIC MEDICATIONS IN  
PATIENTS WITH TYPE 2 DIABETES:  
PHARMACY DATA MEASUREMENT

