IVD Selftests for Therapy Management in Chronic Conditions

"Can IVD selftests for therapy management contribute to the quality of care for patients with chronic conditions?"

A Literature Review

UNIVERSITEIT TWENTE.

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Abstract

Patient self care has the potential to contribute to the quality of care. One of the realisations of self care interventions is the possibility for chronic patients to use in vitro diagnostic selftests (IVD) for therapy management. The possibility to manage therapy in a more easy and convenient way will potentially result in higher patient satisfaction and by this increase adherence to therapy which consequently increases the accuracy of therapy. In addition, selftests can be very important to the quality of life of chronic patients because they allow them to monitor their condition and manage their therapy, without having to make frequent doctors and lab visits or risking their health. Because of the increasing prevalence of chronic conditions and the high burden associated with it, this study aims to answer to following question:

"Can IVD selftests for therapy management contribute to the quality of care for patients with chronic conditions?".

To answer this question a systematic literature review is conducted in the electronic database PubMed based on a condition-specific search strategy. This strategy combined terms for different chronic conditions and related therapies with a collective terminology for selftests. Search limits that are used are full text items, human study subjects, publication date range from 2004/01/01 – 2009 and articles in English or Dutch language. The retrieved articles are assessed against in- and exclusion criteria with inclusion criteria on the therapy management function, home use purpose and study population and exclusion criteria on the choice of chronic conditions and the exclusion of review articles. The two staged process for article selection (1. titles and abstracts, 2. full text) resulted in 10 included articles on the therapy management of oral anticoagulation therapy (OAT).

In the 10 included articles three types of OAT management procedures on INR control were studied. These can be classified as routine care, self-monitoring and self-management. IVD selftests are used in the last two procedures and therefore the results from these procedures are compared with the results with routine laboratory care. The findings on the statistical data on INR control were evaluated and combined in a review. Also, the data on patient acceptability and quality control of the selftesting devices is evaluated and combined in this review.

Although there are some points of discussion it can be concluded that IVD selftests for OAT management provide patients a convenient, accurate, safe and suitable option to manage their therapy. Inherently, IVD selftests for OAT management can contribute to the quality of care for anticoagulated patients, on condition that adequate education is provided.

Keywords:
IVD, selftest, therapy management, chronic conditions, review, oral anticoagulation therapy, INR control

Preface

This report is the final presentation of my research on in vitro diagnostic selftests for therapy management in chronic conditions. I am satisfied that with this research I will complete the bachelor phase of the study health sciences at the University of Twente.

When I started the research for this report several months ago, I was a stranger to most of the concepts I was going to study and to most of the methods that I was going to use for it. In this inexperienced start I struggled a lot and this made it difficult at certain times. On the other hand this situation challenged me to learn about all these new concepts and to learn about the methods to conduct a systematic literature review. Besides these theoretical and methodological lessons I have also learned some interesting and important things about myself. These personal lessons will probably be very helpful in other struggles and challenges that I may experience as a researcher, and maybe even in life.

I would like to thank Prof. Dr. Maarten IJzerman and Dr. Carine Doggen for their time, enthusiasm, feedback and helpful advices with additionally special thanks to Carine for kindly taking on the role as second supervisor in a very late stadium of the research.

Heleen Hofland
Utrecht, December 2009

Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
BNP	B-type Natriuretic Peptide
CCM	Chronic Care Model
CE	Conformité Européenne
COPD	Chronic Obstructive Pulmonary Disease
CRD	Centre for Reviews and Dissemination
CT	Computer Tomography
DALY	Disability Adjusted Life Year
ECAA	European Concerted Action on Anticoagulation
EDMA	European Diagnostic Manufacturers Association
EQA	External Quality Assessment
FCSA	Federation of Centres for the diagnosis of thrombosis and the Surveillance of Anti-thrombotic drugs
FOB	Faecal Occult Blood
HIV	Human Immune Deficiency Virus
IGZ	Dutch Health Care Inspectorate (Inspectie voor de Gezondheidszorg)
INR	International Normalised Ratio
IOM	Institute of Medicine
ISO	International Organisation for Standardisation
IVD	In Vitro Diagnostic
IVDD	In Vitro Diagnostic Medical Device Directive (EU)
KEMA	Dutch Notified Body for conformity assessment (Keuring Elektrotechnische Materialen Arnhem)
LINH	Netherlands Information Network of General Practice (Landelijk Informatie Netwerk Huisartsenzorg)
MeSH	Medical Subject Headings
MRI	Magnetic Resonance Imaging
OAT	Oral Anticoagulation Therapy
POCT	Point of Care Test(ing)
PSA	Prostate Specific Antigen
PSM	Patient Self Management
PST	Patient Self Testing
PT	Prothrombin Time
QA	Quality Assessment
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RIVM	Dutch National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu)
RCT	Randomised Controlled Trial
TC	Thrombosis Centre
TIR	Time In Range

Contents

1. Introduction

Innovative medical technologies and techniques are being developed at a rapid pace. Likewise, they are found more widely distributed in both clinical settings as non-clinical ones. Instruments, diagnostic tools and techniques are acquired and diffused through medical institutions as well as the patients' home. Technologies ones found only in hospitals are reconfigured for use in primary care, the home, the gym, and even the shopping mall where "health shops" provide whole-body readouts on the apparent state of our health (Webster, 2006).

Because more and more is possible to achieve, both professional and patient expectations increase, resulting in a growing need and demand for high quality healthcare (Muir Gray, 2001). In addition, the suggestion came up that orienting the healthcare system around the preferences and needs of patients has the potential to improve patient's satisfaction with care as well as their clinical outcomes. This theory that 'patient-centred care' improves the 'quality of care' is applied by the Institute of Medicine (IOM) which defines these two concepts as follows:

- *"Patient-centred care encompasses qualities of compassion, empathy, and responsiveness to the needs, values, and expressed preferences of the individual patient."* (IOM, 2001).
- *"Quality of care" is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with the current professional knowledge. Good quality means providing patients with appropriate services in a technically competent manner, with good communication, shared decision making, and cultural sensitivity. Quality can be measured by assessing appropriateness of care and adherence to professional standards."* (IOM, 2001).

From this perspective, patient self care has the potential to contribute to the quality of care. One of the realisations of self care interventions is the possibility for consumers or patients to use selftests for a diagnosis whenever and wherever they like. If this intervention matches the needs, values and expressed preferences of the individual patients and increases the likelihood of desired health outcomes based on the current professional knowledge than it definitely has the potential to contribute to the quality of care. Nevertheless, there are still other factors influencing the success of an intervention.

§1.1. Study objective and significance

The focus of this study is on in vitro diagnostic (IVD) selftests for therapy management in chronic conditions. In brief, this intervention comes down to the diagnostic tests that are performed on body samples by the patient himself with the purpose to provide information about a particular health status by which a chronic condition can be monitored and managed accordingly. These selftests can be very important to the quality of care and consequently, the quality of life of chronic patients because they allow them to monitor their condition and manage their therapy, without having to make frequent doctors and lab visits or risking their health.

The possibility to use IVD selftests for therapy management can result in a growing need and demand for this intervention. The associated quality requirements, costs, and other benefits and problems, induce a growing need for evidence based decision making in healthcare. To accomplish this, decisions in healthcare need to be based on a systematic appraisal of the best evidence available relating the particular decision. Therefore, the evidence needs to be found, appraised and applied (Muir Gray, 2001). Build on this idea, this study will review, summarise and discuss the available evidence in the literature regarding IVD selftests for therapy management in chronic conditions.

Supported by the literature, the different IVD selftests that are used for this purpose will be identified. For the identified selftests, the findings about the impact of these tests on therapy management in chronic conditions will be presented. In addition, the barriers and support factors for its use will be examined. This study aims to answer the question if IVD selftests can contribute to the quality of care for patients with chronic conditions. Inherently, it provides a useful overview of the evidence found in the literature about this subject. Therefore, it can be used as a basis for decision making or further research.

§1.2. Choice for chronic conditions

Latest years there has been a rapid increase in the prevalence of chronic conditions (Wagner et al., 2005) and managing the quality of care for chronic conditions is one of the primary concerns of healthcare systems throughout the world (Epping-Jordan, Pruitt, Bengoa & Wagner, 2004). In a study from February 2004 by the Centres for Disease Control and Prevention, it is stated that chronic conditions are the leading cause of disability and dead in the United States. Every year, they claim the lives of more than 1.7 million Americans and cause major limitations in daily living for more than 1 of every 10 Americans. Consequently, healthcare for people with chronic conditions accounts for 75% of the Nation's total healthcare costs (Centres for Disease Control and Prevention, 2004).
In the Netherlands, more than 25% of the population suffers from chronic conditions, and of this group of patients one third even has more than one chronic condition (co-morbidity). This information is based on data available from Dutch general practitioners (LINH) during the period from 2003-2007 (Nationaal Kompas Volksgezondheid, 2009). Chronic conditions happen to have a very high prevalence among older people, e.g. half of the people being 65 years or older suffers from at least one chronic condition (Nationaal Kompas Volksgezondheid, 2009). According to a RIVM report by de Hollander et al. (2006), the number of chronic patients will therefore increase in the next years influenced by growth and ageing of the population.

Although a very important task in withstanding these problems is in the prevention of chronic conditions by changing people's unhealthy lifestyle that is causing risk factors, this study focuses on secondary prevention of chronic conditions which are already present in patients. Logically, accurate therapy management contributes to better health outcomes. The possibility to manage therapy in a more easy and convenient way will potentially result in higher patient satisfaction and by this increase adherence to therapy which consequently increases the accuracy of therapy. Consequently, the quality of care for chronic patients could improve and healthcare costs could decrease. Because of the increasing prevalence of chronic conditions and the high burden associated with it, this study investigates the contribution that IVD selftests for therapy management could bring to the quality of care for patients with chronic conditions.

§1.3. Research questions

This study aims to answer the following research question:

> ***"Can IVD selftests for therapy management contribute to the quality of care for patients with chronic conditions?"***

To answer this question, three sub-questions will be answered in this study:

1. *What IVD selftests are currently used for therapy management in chronic conditions and what do they measure?*
2. *How do IVD selftests for therapy management in chronic conditions influence the therapeutic control?*
3. *What influences the success of IVD selftests for therapy management in chronic conditions and how?*

The second and third sub-question are answered for the tests identified in the first sub-question.

§1.4. Study restrictions

Within the focus on chronic conditions restrictions have been made in the number of conditions that are included in the study. There are numerous chronic conditions and this makes the scope of the study very large. To restrict this study to a feasible scope, only a selection of chronic conditions is included in the exploration for IVD selftests. To decide on this selection, other studies on chronic conditions are used as an example and starting point (i.e. Van den Brink-Muinen & van Dulmen, 2004; Sabate, 2003; Herings et al., 2002;). In addition, two chronic conditions are excluded from the review for particular reasons. In the first place, diabetes and related concepts as blood glucose, glycaemic control and kidney failure, are excluded from this study. Diabetes has already been studied a lot, also in the combination with IVD selftests for therapy management. The exclusion enables this study to focus on newer and therefore more interesting selftesting applications. The second condition that is excluded from this review is cancer. The main reason for this is that there are too many different types of cancer with different characteristics. A preliminary explorative search for cancer showed that IVD selftests can be used for screening of some types of cancer (PSA – prostate cancer, FOB – bowel cancer), but there were no studies retrieved about the use of selftests for the particular purpose of therapy management. To be certain that there are no such tests for all the different types of cancer, a systematic search needs to be conducted for every specific type of cancer separately. This is beyond the scope of this study. In accordance with these decisions, the chronic conditions included in this study are presented in Table 1.

Asthma and COPD	Depression	Epilepsy
HIV/AIDS	Hypertension	Tuberculosis
Cardiovascular diseases	Arthritis	Osteoporosis

Table 1. included chronic conditions

§1.5. Overview of the report

This report continues with an explanation of the different terms from which the concept of IVD selftests for therapy management in chronic conditions is composed. After this explanation, the third chapter describes of the methodology that is used for the data-collection in this study. Chapter 4 presents the review findings that came forward from the retrieved articles and provides answers to the research sub-questions. Finally, the report finishes with the discussion and conclusion of the study. In this final chapter the research question will be answered and recommendations for further research are proposed.

2. IVD Selftests and Chronic Conditions

This chapter provides a stepwise explanation of the different terms from which the subject of study is composed. Paragraph 2.1. gives a brief impression of the overall concept of diagnostic testing, in vitro diagnostics and the regulation concerning in vitro diagnostic medical devices. To gain insight in the concept of selftesting, paragraph 2.2. starts with the explanation of a related technique called point of care testing and continues with the principles of selftesting. The chapter ends with paragraph 2.3. wherein the specific use of IVD selftests for therapy management in chronic conditions will be explained.

§ 2.1. Diagnostic testing and in vitro diagnostics

§2.1.1. Diagnostic testing

Diagnostic tests are able to provide a source of objective information about the body and how it functions. Therefore they can be seen as the basis for clinical decision making which makes them of vital importance for the quality of healthcare. Diagnostic tests can be used in many ways but the three main fields of use are diagnosis, monitoring and screening. A medical *Diagnosis* can be translated as an identification, analysis and conclusion with the purpose to determine what is wrong with a patient. Early and correct diagnosis is a prerequisite for effective and relevant therapy and without an accurate diagnosis resources will be wasted on incorrect therapy. In the field of *monitoring* the purpose of a diagnostic test can be twofold. The test can be done to examine biochemical parameters to assess if the given therapy has the required effect, and the test can be performed to measure therapeutic levels of prescribed medication. Based on the information from the test results, therapy can be adjusted to the appropriate level when this is necessary and the effect of therapy can be improved. The use of diagnostic tests in *screening*, makes it possible to detect diseases and abnormalities or increased risks for these conditions, even before there are significant symptoms. This enables people to react on this information in a very early stage of the condition and potentially prevent it from getting severe (EDMA, 2009; Diagned, 2009).

There are different technologies used for diagnostic testing. For examination inside the body technologies for diagnostic imaging are applied. These technologies refer to procedures such as X-rays, CT scans, MRI scans and endoscopies (Medline Plus, 2009). This study focuses on in vitro diagnostic testing for the examination of body samples outside the body. An explanation of this technology is given in the next section of this paragraph.

§2.1.2. In-vitro diagnostics

Diagnostic tests performed on samples (for example blood, tissues or urine) taken from the human body are referred to as in vitro diagnostic (IVD) tests. ‘In vitro’ is Latin and means literally ‘ in glass’, many of the diagnostic tests on body samples were originally performed in a test tube and that is where the technology derives its name from (EDMA, 2009). A more specific definition is stated in the legislation concerning in vitro diagnostics. IVD tests are regulated by the European Council Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDD, 1998) which is covered by the Decree on In Vitro Diagnostics (IVD decree, 2001) in the Netherlands.

According to this legislation, an in vitro diagnostic medical device is defined as *"any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:*

- *Concerning a physiological or pathological state, or*
- *Concerning a congenital abnormality, or*
- *To determine the safety and compatibility with potential recipients, or*
- *To monitor therapeutic measures."* (Section 1, paragraph 2b).

In Europe, manufacturers of medical devices need to follow a conformity assessment procedure in order to certify for a CE mark before they can bring their products on the market. This approval procedure depends on the risk-classification of the device (I, II or III). According to this classification, medical devices can be approved by self-certification (low risk) or by certification of a notified body (high risk). The Dutch notified body for approval is KEMA Medical, which is under supervision of the Dutch Health Care Inspectorate (IGZ, 2009).

A reasonably innovative utilisation of IVD tests is a technique called 'point of care testing'. The principles of this technique are explained in the next paragraph.

§2.2. Point of care testing and selftesting

§2.2.1. Point of care testing

Traditionally, most IVD tests were performed in the controlled and regulated environment of a laboratory. Currently, new technologies make it possible to test at, or close to, the patients' site with compact, easy-to-use instruments that provide test results within a few minutes. Innovative techniques have been developed that enable a wide range of tests to be done quickly and simply without the need for sophisticated laboratory equipment (EDMA, 2009; Lab Tests Online, 2009; Price, 2001). This technique is commonly referred to as 'point-of-care testing' or in short 'POCT', but also other terms as near patient test, bedside test or extra laboratory test are used. In this report, the term point-of-care test or POCT will be used. The key objective of POCT is to provide fast results so that appropriate treatment can be implemented immediately, potentially leading to improved clinical outcomes (Price, 2001). However, as POC testing is likely to be done by persons with limited laboratory background, training and quality control is critical in the prevention of incorrectly performed tests or inappropriately interpreted results. In addition, any test will only be beneficial if appropriate action is taken on the result (Price, 2001). There is an International Standard that gives specific requirements for quality and competence applicable to point-of-care testing, the ISO 22870:2006. According to this standard from the International Organization for Standardization (ISO), point-of-care testing can be defined as *"testing that is performed near or at the site of a patient with the result leading to possible change in the care of the patient"*. Despite that the requirements of this standard officially only apply when POC testing is carried out in a healthcare facility and explicitly not for patient self-testing in a home or community setting, elements of the standard can be applicable.
The official requirements for IVD selftests are stated in the IVDD (1998) which pays special attention to the definition of a selftest and the specific safety requirements. The next section of this paragraph will continue on IVD selftests and their specific characteristics.

§2.2.2. Selftesting

The definition in the IVDD (1998) for a 'device for selftesting' is: *"any device intended by the manufacturer to be used by laypersons in a home environment"* (Section 1, paragraph 2d). Because the intended purpose of selftesting devices is the use by laypersons, the directive specifies special safety requirements for IVD selftests:

- They must be designed and manufactured in such a way that they perform appropriately for their intended purpose in all stages of the procedure, taking into account the skills and the means available to users and the influence resulting from variation that can reasonably be anticipated in users' technique and environment;
- They must , as far as practicable, reduce the risk of user error in the handling of the test and in the interpretation of the results;
- They must, where reasonably possible, include user control, i.e. a procedure by which the user can verify that, at the time of use, the test will perform as intended;
- The information and instructions provided by the manufacturer should be easy for the users to understand and to apply. The suitability of these instructions should be substantiated by studies carried out with laypersons;
- The conformity assessment procedure always requires the approval of a notified body; self certification is not an option

IVD selftests are mostly hand held devices that have been developed with the use of micro- or nanotechnology techniques. These tests are internally complex but simple from the outside and able to do several tasks as for example separating cells from plasma, add reagents and read colour or other endpoints (Price, 2001). However, the use of IVD selftests can result in both benefits and problems. To start with the benefits:

- IVD selftests bring convenience, privacy and control. Aspects that fit the principle of the autonomous patient. Moreover, they can bring valuable relief for concerned individuals;
- Carrying out faster results with consequently more accurate implementation of treatment can improve clinical and consequently economic outcomes;
- The option to execute the test at home leads to the possibility to move care to the outpatient setting and to shorter and fewer visits to healthcare facilities which may reduce healthcare costs. (EDMA, 2009; Canterbury Health Labs, 2009; Lab Tests Online, 2009, Price, 2001).

Despite the special requirements in the legislation concerning IVD selftests and the sophisticated devices, there are also problems concerning IVD selftests. This starts with one problem which is inherently to its purpose: laypersons easily make mistakes because they are not specially educated in using a diagnostic test. Mistakes often happen in the storage of the test device, the sample collection, the timing of the test and the interference of results by other substances (e.g. patient medication or bad hygiene) (Lab Tests Online, 2009). If these mistakes have taken place somewhere in the selftesting procedure, they can cause incorrect test results with problematic consequences. Examples of these problems are:

- An inaccurate dosage of medication based on incorrect values;
- A false negative test result that causes a deceptive feeling of relief and absence of therapy that is actually needed;
- A false positive test result that causes unnecessary concern and unnecessary therapy

These consequences may have serious and severe clinical implications and can be very costly. Healthcare costs can increase because of these clinical implications but also because of a needless increase in visits to healthcare facilities where a doctor needs to disconfirm the results of a false positive test result. Finally, another concern with IVD selftests is the question if a layperson without medical education and understanding is capable of dealing with important health decisions based solely on selftest results, intellectually as well as psychologically. So, if the result of a selftest is correct, it is very important to notice that any test is only beneficial if appropriate action is taken on the result (Price & Kricka, 2007).

Nevertheless, when these problems are considered seriously and appropriate actions are taken to prevent them from happen, the benefits of the use of IVD selftests for therapy management in chronic conditions may bring a significant contribution to the quality of care for these patients. The reasons for this suggestion are further clarified in the next paragraph.

§2.3. Therapy management in chronic conditions

In the definition from the Medline Plus encyclopedia, "*chronic refers to something that continues or persists over an extended period of time. A chronic condition is usually long-lasting and does not easily or quickly go away".* Accordingly, chronic conditions are different from acute illnesses and injuries in their time course and severity, but also in their requirements for nearly continuous decision making and adjustments to changing circumstances by patients. Therefore, it is important for chronic patients to adequately control their condition and hence, to control the therapy they need for their condition (Wagner, Bennett, Austin, Greene, Schaefer & Vonkorff, 2005). Nevertheless, about 50% of the chronic patients who use medication do not adhere to their therapy, which results in poor health outcomes and increased healthcare costs (Sabate, 2003; Herings et al., 2002). In addition, it was claimed by Price (2001) that adherence to therapy could be one of the most valuable contributions of point of care testing. This claim by Price (2001) and the high number of therapy non-adherence suggests that IVD selftests may have the potential to contribute to therapy adherence and therapy management in chronic conditions.

In an attempt to improve the quality of care for this large group of patients, Edward H. Wagner and his colleagues developed the Chronic Care Model (CCM), an evidence based conceptual framework based on six elements: health care organisation, community resources, self-management support, delivery system design, decision support and clinical information system (Wagner, Austin, Davis, Hindmarsh, Schaefer & Bonomi, 2001). Most of these elements apply to changes at the organisational level, but the element of improving self-management competences in chronic patients fits with the opportunities that IVD selftests can bring. The element of self-management support in the CCM is concerned with behavioural aspects as for example problem-solving and coping-skills training, patient self-efficacy and overcoming barriers to complement traditional didactic patient education (Glasgow, Funnell, Bonomi, Davis, Beckham & Wagner, 2002). By making it possible for patients to carry out tests and act on the results themselves IVD selftests may play an important role in patient self-management, resulting in higher satisfaction, better health outcomes, and decreasing healthcare costs.

Based on these perspectives about selftesting, chronic conditions and patient self-management, this study aims to answer the research question: *"Can IVD selftests for therapy management contribute to the quality of care for patients with chronic conditions?".* The next chapter describes the methodology that is used to provide an answer to this question.

3. Methodology and Search Results

This chapter provides an outline of how this systematic literature review is conducted. First a short introduction into the theory of the systematic literature review is given, followed by the research strategy that is used in conducting this study. Special attention is given to the criteria that are used for article selection and the search terms that are used in the search process.

§3.1. Systematic literature review

Conducting a systematic search to identify relevant articles of studies is a key factor in minimizing bias in the review process. Therefore, the search process should be as transparent as possible and documented in a way that enables it to be evaluated and reproduced. One very important aspect of the justification the validity of a systematic review is the decision on the selection criteria. A literature search may result in a large number of articles, for which it is impossible to review all of them. Therefore there are two complementary methods that can be used sequentially in the selection process of relevant articles; the insertion of limits and deciding on in- and exclusion criteria. Limits are restrictions on specific general characters of articles and with this option the number of search results can be reduced to a manageable amount. After this reduction there is still a number of potentially relevant articles that needs to be assessed for inclusion against predetermined criteria, and only a small proportion of these articles may eventually be included in the review. The aim of the selection process is to ensure that all relevant articles are included in the review (Centre for Reviews and Dissemination (CRD), 2009; Etten-Jamaludin & Deurenberg, 2008).

§3.2. Search strategy

The systematic literature review for this study is conducted in the electronic database PubMed. PubMed is a service of the U.S. National Library of Medicine and the National Institutes of Health that includes over 19 million citations from MEDLINE and other life science journals for biomedical articles back to 1948. PubMed includes links to full text articles and other related resources (PubMed Homepage, 2009).

§3.2.1. MeSH search

A typical systematic search for articles in the PubMed database starts with an exploration in the MeSH database (Etten-Jamaludin & Deurenberg, 2008), which is one of the special services from PubMed. The MeSH terminology provides a consistent way to retrieve information that may use different terminology for the same concepts (MeSH Homepage, 2009). This way, there won't be articles missed because of terminology errors (Etten-Jamaludin & Deurenberg, 2008). This study's exploration in the MeSH database guided to the following MeSH terms that could be applicable for the subject of study: "Medication Therapy Management"[Mesh], "Reagent Kits, Diagnostic"[Mesh], "Monitoring, Physiologic"[Mesh]. With the use of these MeSH terms, combinations of these MeSH terms, or combinations of these MeSH terms with free text words as for example selftest, point of care test or home test, the retrieved articles frequently had the subject 'diabetes or blood glucose', 'anticoagulation therapy' or 'HIV/AIDS'. Before even assessing these articles against the inclusion criteria, it seems that this search strategy misses out on other chronic conditions for which the therapy might be managed with an innovative selftesting technique. Because one of the targets of this study is to identify all the IVD selftests that are currently used for therapy management in the included chronic conditions (defined in sub-question 1), a more condition-specific search strategy is set up.

§3.2.2. Condition-specific search strategy

The condition-specific search strategy has two component parts. The first part of the search term consists of terms for the included chronic conditions and related therapies (§1.4.) and the second part is a collective terminology for selftests composed from a selection of applicable expressions for selftests. This second part of the search term is set in parentheses in order to process the several expressions as one unit. Besides that, the expressions are attached by the Boolean operator OR, so that results will be retrieved about any of these expressions for selftests. The two components of the search term are combined with the Boolean operator AND, so that only articles will be retrieved about the combination of a chronic condition and a selftest and not about these subjects independently.

Construction of the first part of the search term

Preliminary to this condition-specific search strategy an explorative search for information about the different chronic conditions has been performed. Based on this exploration, a list of most appropriate terms for the included chronic conditions and therapies could be constructed. This is presented in Table 2. All of these terms are used separately as the first part of the complete search term. The construction of the second part of the search term will be explained on the next page. In conclusion there will be an example of what a complete search term would look like.

Conditions:	Terms:				
Asthma and COPD	(Asthma OR COPD)	Anti-inflammatory drugs	Corticosteroids	-	-
Depression	Depression	Mood disorders	Antidepressants	Psychiatric drugs	-
Epilepsy	Epilepsy	Antiepileptic drugs	-	-	-
HIV/AIDS	(HIV OR AIDS)	(HIV OR AIDS) medication	-	-	-
Hypertension	Hypertension	Antihypertensive drugs	-	-	-
Tuberculosis	Tuberculosis	Antibiotic drugs	-	-	-
Cardiovascular diseases	Cardiovascular disease	Heart disease	Anticoagulation	Platelet function	BNP
Arthritis	Arthritis	Arthrosis	Rheumatoid arthritis	Anti-rheumatic drugs	-
Osteoporosis	Osteoporosis	-	-	-	-

Table 2. terms per condition

Construction of the second part of the search term

The construction of the second part of the search term, the collective terminology for selftests, is build up from expressions that are regularly used for selftests in the medical literature. In these keywords, truncation (*) is used to include different expressive structures of the concepts. For example, the keyword self test* results the following PubMed query translation: *self test[All Fields] OR self tested[All Fields] OR self tester[All Fields] OR self testers[All Fields] OR self testicular[All Fields] OR self testing[All Fields] OR self testing/patient[All Fields] OR self tests[All Fields] OR self tests/day[All Fields] OR self tests/week[All Fields]*. The terms that are used for the second part of the search term are presented in Table 3.

Self test*	Point-of-care test*	Point of care test*	POCT
Home test*	Near patient test*	Rapid test*	Over the counter test*
Self monitor*	Self screen*	Self collect*	Home collect*
Self diagnos*	Home diagnos*		

Table 3. selftest terminology

As mentioned, all of these terms are used in combination as a collective terminology for selftests and they are set in parentheses in order to process the several expressions as one unit. An example of a search term that is imported in the PubMed database is:
(Asthma OR COPD) AND (self test OR point-of-care test* OR POCT OR home test* OR near patient test* OR rapid test* OR over the counter test* OR self monitor* OR self screen* OR self collect* OR home collect* OR self diagnos* OR home diagnos*)*.
This combined search is carried out for all of the terms for the included chronic conditions and therapies. Examples of the search terms that retrieved relevant results are given in Table 4, Table 5 and Table 6.

Extra rule

For some of the conditions, IVD selftests will turn out not be a practiced procedure for therapy management. Consequently, a search for information about these conditions in combination with IVD selftests for therapy management, will not retrieve any relevant articles. On these grounds, an extra rule is established to stop searches for which it can reasonably be accepted that relevant articles will not be retrieved to prevent from wasting time. This rule comes down to: **'if there are no relevant results for a search term within the first 20 articles retrieved, the search process with that search term can be stopped'**.

§3.3. Selection criteria

§3.3.1. Search limits

The limits that are used in this study are:

1. Items with links to full text
2. Humans
3. Publication date range from: 2004/01/01 – 2009
4. English and Dutch language

Justifications for these limits:

1. The full text of an article must be accessible in order to decide on inclusion of the article and to use it in the review
2. Animals are not subject of study
3. The articles must be published recently in order to be up-to-date. This is important because the field of IVD selftests is a rapidly changing and developing field.
4. Only English and Dutch articles can be interpreted by the researcher

§3.3.2. In- and exclusion criteria

The results of the search strategy after the insertion of limits are assessed for inclusion against the following criteria.

Inclusion criteria

- The function of the IVD selftest must be therapy management in a chronic condition
- The purpose of the IVD selftest must be home use. Articles wherein the selftest is examined in conditions other than the home situation are only included when the future purpose of the selftest is that it can be used by the patient at his home.
- Study participants should represent the intended users who need to perform each procedural step without medical assistance

Exclusion criteria

- Articles about IVD selftesting interventions for diabetes, diabetes related concepts or cancer.
- Review articles

Justification for the second exclusion criterion:

A review article can be seen as a summarisation of other articles in order to provide a conclusion based on a number of studies. It would be invalid to use review articles in this review study on its own because the existing reviews could be conducted with a different study objective and consequently with different selection criteria than the criteria used in this study.

§3.3.3. Process for study selection

According to the methods used by the CRD (2009), the process for study selection with in-and exclusion criteria is conducted in two stages:

1. A first decision is made based on titles and, where available, abstracts. These are assessed against the predetermined inclusion criteria and if an article does not meet the criteria it can be rejected immediately.
2. For studies that appear to meet the inclusion criteria, or in cases when a definitive decision cannot be made based on the information in the title and/or abstract alone, the full paper is obtained for detailed assessment against the inclusion criteria.

§3.4. Search Results

§3.4.1. First selection of articles

In this comprehensive search, the search process was frequently stopped by the extra rule that was set up. In addition, only three search terms retrieved relevant articles based on the titles and abstracts. These searches are documented in Table 4, Table 5 and Table 6, with a presentation of the number of articles remaining at each stage of the search process.

first part of the search term	second part of the search term	number of results
anticoagulation	(self test* OR point-of-care test* OR POCT OR home test* OR near patient test* OR rapid test* OR over the counter test* OR self monitor* OR self screen* OR self collect* OR home collect* OR self diagnos* OR home diagnos*)	163
limits	items with links to full text	138
	humans	126
	Publication date	60
	English and Dutch	56
total with limits		56
further selection	based on title/abstract	24
	based on content	10
final selection		10

Table 4. search process anticoagulation

first part of the search term	second part of the search term	number of results
platelet function	(self test* OR point-of-care test* OR POCT OR home test* OR near patient test* OR rapid test* OR over the counter test* OR self monitor* OR self screen* OR self collect* OR home collect* OR self diagnos* OR home diagnos*)	64
limits	items with links to full text	53
	humans	48
	Publication date	28
	English and Dutch	25
total with limits		25
further selection	based on title/abstract	3
	based on content	0
final selection		0

Table 5. search process platelet function

first part of the search term	second part of the search term	number of results
antidepressants	(self test* OR point-of-care test* OR POCT OR home test* OR near patient test* OR rapid test* OR over the counter test* OR self monitor* OR self screen* OR self collect* OR home collect* OR self diagnos* OR home diagnos*)	26
limits	items with links to full text	20
	humans	19
	Publication date	8
	English and Dutch	8
total with limits		8
further selection	based on title/abstract	1
	based on content	0
final selection		0

Table 6. search process antidepressants

Last search date: August 24, 2009.

The other search terms retrieved irrelevant articles generally for the following reasons:

- Not IVD selftests but educational and behavioural 'self care' techniques and training.
- IVD selftests for screening or diagnosing purposes as opposed to therapy management.
- Point of care tests used by healthcare professionals and not by patients themselves.
- Self-collecting devices with results from the laboratory.
- Correlation of the condition with diabetes resulting in articles about blood glucose tests.

In addition, the terms cardiovascular disease and heart disease did retrieve some potentially relevant results, but the number of results turned out to be high and the search still retrieved a lot of irrelevant results as well. The terms related to the therapies that are used in cardiovascular conditions give a much more specific search and a higher density of relevant results. For this reason, only the search for these keywords was maintained.

§3.4.2. Final selection of articles

With these three remaining search terms 28 articles were identified for potential relevance, of these 10 also passed the second selection stage wherein the full paper is obtained for detailed assessment against the inclusion criteria and are included in the final selection. A striking detail of this final selection is that only articles about anticoagulation are included. After detailed assessment of the full text of the articles it turned out that the articles about platelet function describe new point of care tests that make it easier to monitor the effects of antiplatelet drugs in cardiovascular diseases. However, none of the articles mention these tests in combination with selftesting or home use which makes them irrelevant for this study (Michelson et al., 2006; Wong et al., 2006; White et al., 2004). The article about antidepressant therapy (lithium) describes an IVD technique which is still in an early developmental phase (Vrouwe et al., 2007). This makes it a promising IVD selftesting method for the future, but in a unusable state for this study.

The 24 articles that passed the first selection stage are documented in Table 1Table 10 in Appendix A. In this table the reasons for exclusion of 14 of the 24 articles are specified.

As a consequence, the next chapter will only represent the review findings of the systematic literature search with the keyword 'anticoagulation'.

4. Review Findings

This chapter integrates the most important findings of the 10 included articles. Based on these findings, the three sub-questions will be answered. A complete overview with summaries of the 10 included articles can be found in Appendix B. For a recapitulated overview, the main facts of the articles are presented in Table 11 in Appendix C.

§4.1. IVD selftests for OAT management

Because the included articles are all on the topic of oral anticoagulation therapy (further referred to as OAT), the focus of this literature review has transformed from chronic conditions in general to conditions for which OAT is indicated. Therefore, the questions are answered for IVD selftests that are used in the management of OAT. The first sub-question will be answered in this paragraph and in the following paragraphs the other two sub-questions will be answered sequentially.

Starting with sub-question 1:

- *What kind of IVD selftests are currently used for therapy management in chronic conditions and what do they measure?*

In the included articles three different IVD selftesting devices are used. As a result, the first part of this question can be answered very straightforward with the names of these three devices and their manufacturers. The currently used IVD selftests for OAT management are:

- CoaguChek® (Roche Diagnostics)[1];
- INRatio™ (HemoSense Inc.);
- ProTime Microcoagulation System (International Technidyne Corporation)

With these three considerably similar types of IVD selftesting devices for OAT management, the answer on the second part of this question can be given for these three devices together. The three IVD selftests are all hand-held PT/INR (Prothrombin Time/International Normalised Ratio) measurement devices, which determine the prothrombin time (clotting time) from capillary whole blood using a programmed algorithm to calculate the INR value. The INR value is introduced as a standardised measure for the highly variable prothrombin time to make the PT results from different laboratories comparable. A drop of finger puncture capillary blood is applied to the sample application area on a disposable test strip where the blood mixes with specific reagents. After certain minutes, the INR value is shown on the display. Based on the INR value the appropriate OAT dosage can be determined. OAT is of vital importance in the prevention and treatment of blood clots, causing thromboembolic complications. Long-term OAT can be necessary for various indications such as atrial fibrillation, deep vein thrombosis, stroke, ischemic heart disease, prevention of complications after mechanical heart valve replacement, and many others. Different therapeutic ranges for the INR value have been set for patients with these various indications and strict control of the INR value within the target range (INR control) is required to ensure good efficacy of treatment and minimising the rate of complications (thromboembolic or hemorrhagic).

[1] *The different CoaguChek devices can be considered as one because these are part of a series of similar products under one brand name (Roche Diagnostics, 2009).*

Because there are many factors that can influence anticoagulation (e.g. other medications, alcohol use) it is important to measure the INR value frequently and make the necessary dose adjustments concordantly (Gadisseur et al., 2004). Because the three IVD selftesting devices are all similar types of IVD selftests for OAT management, no differences will be made among them for answering sub-question 2 and 3 in the next two paragraphs. The following paragraph continues with the influence that IVD selftests have on therapeutic control, based on the statistical data that can be found in the included literature.

§4.2. INR control

§4.1.2. OAT management procedures

The 10 included articles represent 8 studies that assess the influence of different OAT management procedures on the INR control (i.e. the other 2 articles focus on quality assessment of the device and quality of life of patients). The OAT management procedures can be classified in three types:

- Routine care – INR values are determined by laboratory tests on venous blood samples and OAT dose adjustments are made by healthcare professionals in specialised anticoagulation clinics, hospital-based anticoagulation clinics or general practice;
- Self-monitoring – INR values are self-measured by the patient but dosing decisions are made by healthcare professionals (in some articles this procedure is referred to as selftesting);
- Self-management – INR values are self-measured and dosing decisions are made by the patient (self-dosing)

Logically, IVD selftests for OAT management are used in the last two of these three management procedures wherein INR values are self-measured by the patient.

In a broader methodological spectrum, these three different types of OAT management procedures can be seen as manipulable variables in a causal relationship. In a causal relationship the independent variable (OAT management procedures) causes an effect in the dependent variable (INR control). In a causal experiment, the presumed cause is manipulated and the resulting outcome is observed. This way it can be examined if variation in the cause is related to variation in the effect, which points to a causal relationship. An important factor in these types of experiments is that the plausibility of other explanations for the effect which are called confounding variables, needs to be reduced. A central task in conducting research is identifying the different kinds of confounders that can operate in the research area and identify the strengths and weaknesses of a particular study (Shadish, Cook & Campbell, 2002). As mentioned above, in the 8 studies assessing the influence of different types of OAT management procedures on INR control, the OAT management procedures are the presumed cause for the accuracy of the INR control. If the INR control is affected by manipulation of the OAT management procedures it can indicate a causal relationship and the particular type of influence of the different management procedures on the INR control can be determined. This way, the influence of IVD selftests on the therapeutic control can be determined accordingly because this intervention is used in both management procedures.

§4.2.2. Influence of OAT management procedures on INR control

The 8 studies use different designs and different patient populations. In the study designs, some researchers use real patient groups assigned to the different management procedures, some only use a laboratory reference test to determine agreement between the selftesting device and the reference test, and some studies do both. In addition, the study designs also differ on the number of OAT management procedures that are investigated. Some compare all three types of procedures, some compare only two of them. The differences in the patient populations can be attributed to the different indications for which patients are on OAT, the different types of medication,
and the differences in years of age of the study groups. A complete overview of these study differences per article can be found in Table 12 in Appendix D. However, to evaluate and combine the findings of these studies in order to determine the general influence of INR self-measurement with IVD selftests on the INR control, these study differences are not taken into account. Accordingly, a study with a laboratory reference test to determine agreement will be considered as a comparison with routine care because the INR measurements in routine care are also laboratory based. Nevertheless, the consequences of the inconsistent study designs will be considered in the discussion at the end of this study.

This paragraph describes the literature findings about the influence of the different OAT management procedures on the INR control. Statistical data about this influence has been gathered from the 8 articles wherein this is investigated. This data is presented in Table 7. Based on this information an answer will be given on the second sub-question:

- *How do IVD selftests for therapy management in chronic conditions influence the therapeutic control?*

Author	INR control
Gardiner et al. (2009)	%TIR significantly higher in self-monitoring than in routine care (71% vs. 60%). % time outside critical control limits significantly lower in self-monitoring than in routine care (0.45% vs. 2.04%).
Thompson et al. (2008)	INR results from self-monitoring show agreement with reference lab results.
Dauphin et al. (2008)	%TIR not significantly different between self-monitoring and routine care (therapeutic range 91% vs. 86% and target range 57% vs. 53%). INR values significantly more stable in self-monitoring group for both therapeutic range and target range (mean deviation 41 vs 62 and 11 vs 39).
Sunderji et al. (2005)	Paired INR measures both inside or outside target range in 62% of the time. Fair correlation between self-management values and lab results with r=0.62. Overall, 76% of the paired INR values within 0.5 INR units of each other, 86% within 0.7 INR units.
Gardiner et al. (2005)	%TIR not significantly different between self-management and self-monitoring (70% vs 72%). %TIR not significantly different with routine care in previous 6 months (self-management 70% vs 62% and self-monitoring 72% vs 63%). %TIR significantly higher for the combined results from self-management and self-monitoring than the combined results from routine care in previous 6 months (%TIR 71% vs 62.5%). % time outside critical control limits not significantly different between self-management and self-monitoring (2.21% vs 1.06%). % time outside critical control limits not significantly different with routine care in previous 6 months (self-management 2.21% vs 2.56% and self-monitoring 1.06% vs 1.96%). Small reduction in self-management results attributed to patients showing poor compliance. An analysis excluding these patients shows a reduction to 1.34% vs 2.56%.

Gardiner et al. (2004)	Excellent correlation between self-monitoring values and lab results in self-monitoring group with r=0.95. Overall, 85% of the paired INR values within 0.5 INR units of each other in self-monitoring group. %TIR not significantly different between self-monitoring and lab results in self-monitoring group (61% vs 66%) and not significantly different between self-monitoring group and control group (61% vs 64%).
Taborski et al. (2004)	Excellent correlation between self-monitoring values and lab results for INRatio with r=0.95 and for CoaguChek with r=0.94. Concordance with lab results in 81% for INRatio and in 79% for CoaguChek.
Khan et al. (2004)	Good correlation between self-monitoring values and lab results in self-monitoring group with r=0.75. %TIR significantly higher in self-monitoring than in routine care in previous 6 months (71% vs 57%) and also significantly higher in routine care with education than in routine care in previous 6 months (70% vs 61%). %TIR not significantly different between control routine care group and routine care in previous 6 months (63% vs 60%). Compared with routine care in previous 6 months the standard deviation (SD) of the INR values decreased significantly with 0.24 in the self-monitoring group, with 0.26 in the routine care with education group and with 0.16 in the control group. Differences in %TIR and in SD are not significantly different between the three study groups.

Table 7. INR control per article

Because IVD selftests are used for self-monitoring and self-management of OAT, the answer on the question: *how can IVD selftests for therapy management in chronic conditions influence the therapeutic control?*, can be derived from the influence of these two management procedures on the therapeutic control. In the 8 articles, the INR control is illustrated with different methods (i.e. % time in range (%TIR), % time outside critical control limits, stability, and agreement with lab results).
The comparison of the outcomes from these 8 articles, shows that many differences in the INR control caused by the manipulation of OAT management procedures are not significant. This makes it difficult to generate solid conclusions with this information. However, in most of the studies the %TIR is higher for patients in self-monitoring and self-management groups than for patients in routine care groups, either significantly or not significantly. Only the article by Gardiner et al. (2004) encountered a result wherein the patients in the routine care group had a slightly higher %TIR than the patients in the self-monitoring group, but also this difference was not significant. In addition, the % time outside critical control limits was less for patients in self-monitoring and self-management groups than for patients in routine care (never significantly), in the articles that included this calculation. Furthermore, the INR values were significantly more stable for patients in the self-monitoring group when compared with patients in routine care, which was demonstrated in the study by Dauphin et al. (2008). At last, in five of the included articles the researchers investigated the agreement between the INR values derived with a selftesting device compared with the INR values derived with a reference laboratory test. The findings from these studies show that INR values from selftests agree with the INR values from laboratory equipment, varying from excellent agreement to fair agreement.

In addition to these results, it is worth to mention that in the article by Khan et al (2004) a fourth OAT management procedure was included in the study. This fourth procedure can be classified as 'routine care with education'. In this management procedure, patients received the same education as patients in selftesting procedures but they did not actually use a selftesting device. In fact, they received the same care as patients in routine care with laboratory tests and dose adjustments by healthcare professionals. This management procedure was included in the study to investigate if the education might be a confounding variable in the effect of selftesting. The findings from this article show that for both the patients in the self-monitoring group and the patients in the routine care with education group, the INR control is significantly better than the INR control from the same group of patients in the previous 6 months when they were still in routine care (respectively 71% vs 57% and 70% vs 61%). Even more, it is very likely that this finding is valid because it was tested against a routine care control group which showed that the INR control was not significantly different at times of the study from their results in the previous 6 months (63% vs 60%). Supported by this information, it must be noticed that education improves the INR control and as a consequence could be a confounding variable.

In general, it can be concluded that the findings from the 8 articles support the idea that the use of IVD selftests can contribute to accurate therapeutic control and consequently the quality of care for anticoagulated patients by decreasing incorrect OAT dosages and the risk of complications. However, since many of the differences in INR control are not significant and with the potential confounding variable of education, this conclusion is not extremely strong.

§4.3. Success factors for IVD selftests

The contribution of IVD selftests to the establishment of accurate control of the INR values of anticoagulated patients supports the use of IVD selftests for OAT management. However, there are other factors influencing the success of this intervention as well. These factors can be support factors as well as barriers. To estimate the potential success of IVD selftests for OAT management, the data on these other factors is gathered from the included articles. With this information an answer will be given on sub-question 3:

- *What influences the success of IVD selftests for therapy management in chronic conditions and how?*

In this context, success can be defined as the accepted, safe and appropriate use by satisfied patients.

§4.3.1. Acceptability

An important determinant for the success of an intervention is the acceptability of the patients using the intervention. With the data that is used in this study, an estimation of patient acceptability can be derived from aspects that are officially investigated in the articles as ability to use the device and patients preferences as well as from other aspects that come forward as patient participation in the studies, and drop-out rates. This is based on the idea that patients who are not willing to participate, probably do not accept the intervention neither. In combination, a second estimation of patient acceptability comes from the idea that a chronic condition influences the quality of life of patients. Quality of life (QoL) can be measured with special surveys on this topic and this measurement encompasses the effects of a condition and its treatment on the patient's life, as perceived by the patient (Gadisseur et al., 2004).

Of the 10 included articles, 2 articles investigated the influence of OAT management procedures on the QoL of anticoagulated patients (i.e. Khan et al., 2004; Gadisseur et al., 2004). Because these articles did not use a standardised measure to demonstrate the QoL (as for example QALYs or DALYs), the information about the influence of the management procedures on the QoL could be integrated within the acceptability estimation of IVD selftests. The gathered data on acceptability aspects is presented in Table 8.

Author	Acceptability
Gardiner et al. (2009)	44% of eligible patients elected self-monitoring (of 188). 14% of self-monitoring group dropped-out during or after training. 94% of patients who started with self-monitoring completed treatment course and continued self-monitoring after end of study.
Thompson et al. (2008)	91% of eligible patients agreed to participate (of 55). After one month 98% of patients able to self-monitor. Survey returned by 88% of patients reported that: - 82% agreed with early start of self-monitoring education. - 4.5 % felt not ready to self-monitor at hospital discharge. - 75% felt excellent or very good about INR self-monitoring. - 86% found INR self-monitoring easier than routine care. - 80% preferred self-monitoring over routine care.
Dauphin et al. (2008)	9% of self-monitoring group dropped-out because 1 patient did not use the system properly, 1 found self-monitoring too restrictive and 1 did not trust the system.
Gardiner et al. (2005)	13% of eligible patients agreed to participate (of 800). 26% of the patients dropped-out, mostly because of difficulty in self-obtaining capillary sample and in the self-management group also nervousness was mentioned.
Gardiner et al. (2004)	11% of eligible patients agreed to participate (of 800). 32% of self-monitoring group dropped-out, mostly because of poor dexterity, but also for various reasons not associated with self-monitoring. 2.5% of control group dropped-out. Survey returned by 100% of self-monitoring patients reported that: - 84% initially had difficulties with obtaining adequate sample but subsequently 55% found it very easy, 32% quite easy, and only 3% found it difficult. Still, most patients found that they occasionally had to repeat tests and 16% still had some difficulties. - 87% felt confident with the obtained results. - 77% preferred self-monitoring over routine care (of those who expressed a preference).
Taborski et al. (2004)	Patients accept self-monitoring as all patients already used a self-monitoring device at home. INRatio scored mainly positive when compared with known standard by patients, larger blood sample was valued most negative.
Khan et al. (2004)	55% of eligible patients agreed to participate (of 154). 1 patient of self-monitoring group dropped-out because unable to self-monitor at home. - Of recorded parameters in UKSF-36 only one variable changed significantly in 24 weeks: in routine care with education there was a difference in emotional role limitation, however not mentioned in which direction and probably result of chance. Euroqol scores recorded no change. - Perceived benefits and barriers not significantly different between self-monitoring and routine care with education. - 75% of self-monitoring group reported no problems with the technique and want to continue with self-monitoring for its ease and convenience. - Other 25% of self-monitoring group report difficulties with the technique. - In this study with older patients, it was reported that there were initial difficulties but with practice they found it convenient.

Gadisseur et al. (2004)	25% of eligible patients agreed to participate (of 720). 12% of study group dropped-out during or after training, no reasons are given. Questionnaire returned by 64% of patients (high drop-out of routine care with education group) reported: - For routine care with education group; significant increase in distress and strain on the social network and decrease in general treatment satisfaction, not significant. - For self-monitoring group; significant increase in self-efficacy and small increase in general treatment satisfaction, not significant. - For self-management group; significant increase in general treatment satisfaction and self-efficacy, significant decrease in daily hassles and distress. - Differences between self-monitoring and self-management are small but in self-management group general treatment satisfaction is a bit higher and there is a significant decrease in distress compared with self-monitoring. - Over the whole study, younger patients report lower quality of life on the different aspects. Younger patients experience more problems in their professional and social lives caused by frequent visits to clinics in routine care.

Table 8. Acceptability per article

Overall, the procedures wherein IVD selftests were used were evaluated positive by most of the patients that were in these study groups. Most of the patients were able to self-monitor after proper education and some of the studies even report that many of these patients preferred self-monitoring over routine care and wanted to continue with selftesting after the end of the study. Given reasons were that self-monitoring is easier and more convenient than routine care.
Moreover, the quality of life questionnaire that was used in the study by Gadisseur et al. (2004) illustrated that self-monitoring increases self-efficacy and if patients were given the possibility to self-manage their therapy, the feeling of self-efficacy increased even more while decreasing daily hassles and distress. On the other hand, it must be noticed that there was still a number of patients who did not felt comfortable with selftesting. Examples of reasons that were given are that these patients were not able to perform the test, had too many difficulties, felt nervous or did not trust the system. Some of these patients even dropped-out during the study because of these problems. Nevertheless, this is a smaller group than the patients who supported the use of selftests. Above all, these supporting patients reported that initially they experienced difficulties with the use of selftests, but subsequently they found selftesting very or quite easy. Another problem that must be considered is the very low uptake of patients when they were asked to participate in the studies. In the two largest studies by Gardiner et al. in 2004 and 2005, of the 800 eligible patients, respectively only 11% and 13% agreed to participate in a selftesting trial. In the study by Gardiner et al. (2009) the participation rate increased to 44% (from 188), maybe directing to the idea that patients are getting more familiar with the intervention which increases its acceptability. Still, this was not even half the group of patients eligible for using it.

About the acceptability aspect can be concluded that a large group of patients is still reluctant to start using IVD selftests. This influences the success of IVD selftests for therapy management because an intervention must be actually used to be helpful for patients and to be successful in contributing to the quality of care. Nevertheless, the other findings from these studies illustrate that *if* patients are *using* IVD selftests for OAT management, most of them *do accept* the intervention. Even more, patient satisfaction is high among these accepting patients and the use of an IVD selftest is improving their quality of life.

A very important task in the improvement of patient acceptability lies in the provision of appropriate and sufficient education. Education would make the patients confident in using the selftesting devices for their therapy management by taking away the initial difficulties as good as possible. If the acceptability of IVD selftests for OAT management increases, the intervention could be very successful in contributing to the quality of care for anticoagulated patients.

§4.3.2. Quality control of the device

A second determinant for the success of IVD selftests for OAT management is the quality of the selftesting device. If there are problems concerning the quality, this could cause inappropriate use and inaccurate test outcomes. This could result in incorrect OAT dosages and consequently the risk of complications. From the 10 included articles, 4 studies report about aspects of the quality control of the device. These findings are documented in Table 9.

Author	Quality control
Barcellona et al. (2009)	Performance of the device can be affected by changing test strips. It is recommended to check devices when test strips are changed.
Sunderji et al. (2005)	Recommended to periodically check device against laboratory equipment because of small failure rate in INR concordance in study.
Gardiner et al. (2005)	Although overall performance is good, quality control is recommended because of small failure rate. Because many patients do not understand importance of quality control, this should be explained in patient education to increase compliance to quality checks.
Gardiner et al. (2004)	Weekly quality checks are felt as not cost-effective. Occasional paired tests with self-monitor and lab could be an alternative for weekly quality control.

Table 9. Quality control per article

From this data about the quality control of the devices it can be concluded that there are some factors influencing the quality of the devices. This can be an identified factor such as changing test strips, but there might also be other factors causing a small failure rate. Based on these outcomes it is recommended to set up a standard procedure for a frequent check of the selftesting devices. In addition, the importance of this quality check must be explained to patients and therefore it should be integrated in the education about the selftesting procedure. With the implementation of a regular quality check it seems safe to use the IVD selftests for OAT management and again, the intervention could be very successful in contributing to the quality of care for anticoagulated patients.

5. Discussion and Conclusions

In this final chapter the review findings from chapter 4 will be discussed which will lead to a critical evaluation of the answers on the three sub-questions. In addition, the quality of this study will be discussed on its strengths and weaknesses. With the different aspects from this discussion in mind a final answer on the research question, *"Can IVD selftests for therapy management contribute to the quality of care for patients with chronic conditions?"*, can be produced and recommendations for further research are proposed.

§5.1. Discussion

§5.1.1. Quality of the included studies

In this first part of the discussion attention is given to the quality of the included studies based on various aspects that may have influenced the results from these studies.

Study design

In clinical research the state of the art is the randomised controlled trial (RCT) because these types of trials have the highest internal as well as external validity. This is due to the methods of randomisation (i.e. random sample of the population and random assignment to the different study groups) and to the controlled study design which gives researchers the opportunity to manipulate the variables in the study (Shadish, Cook and Campbell, 2002). Because these conditions are not always feasible, other designs are used in research as well but the influence of these designs must be considered. In the included studies there are important differences in study designs. For example, in the study by Gardiner et al. (2009) patients were not assigned to the different study groups but were asked to elect a group by themselves. By this selection, patient preferences and characteristics determine in which study group the patients will be. Therefore, the outcomes of this study can be influenced by these patient characteristics which weakens the internal validity of the relationship. In comparison, the earlier study by Gardiner et al. (2005) did use random assignment to decide on the study groups for the participants. Yet, the results show no important differences in study outcomes related to INR control. With this in mind, results from both study designs can be used in the review.

Confounding variables

There are more aspects that can influence the strength of the claim that the use IVD selftests improves INR control and patient satisfaction. As mentioned before in paragraph 4.2. the effect on these variables may be caused by the confounding variable education. Because of the education, patients get more aware of their condition and the consequences of their condition, this awareness can cause an improvement in patients therapy adherence and safety concerns which influences the INR control. A potential confounding variable in the assessment of the acceptability of patients is the clinical trial setting. Many patients have a reluctance for participating in a clinical trial which not necessarily indicates a reluctance for the use of IVD selftests. Studies by Gardiner et al. (2009) and Khan et al. (2004) back up this idea because these studies used patient groups outside trial conditions and showed a high participation rate compared to the other studies (respectively 44% of eligible patients and 55% of eligible patients). The complete overview of these percentages can be found in Table 8.

Other aspects of bias

Other aspects that could have caused bias in the assessment of patient acceptability to use IVD selftests are the use of questionnaires for the estimation of acceptability and satisfaction (patients are tended to answer extremely positive or negative in questionnaires) and the influence of being allocated to a study group which was not the patients preference. An example of the bias that this situation can cause can be seen in the study by Gadisseur et al. (2004). In this study, the routine care with education group reported an extremely low quality of life compared to the normal routine care group and the selftesting groups. This could have been caused by their exclusion from a selftesting group after they did receive the education and were familiar with the use of a selftest for their therapy management.

Patient differences, generalisation and external validity

Another weakness that needs to be pointed out is the problem with the external validity of most of the included studies. As it was mentioned already, most of the studies had a very low rate of patient participation. This could indicate that the participants in the studies are different types of patients than the patients that refused; there has been an unintended selection of patients. This idea that there are differences between people when it comes to the use of an innovative technology agrees with the 'diffusion of innovations' theory from Rogers (2003). This theory demonstrates that there is a consistent pattern of adoption of new ideas over time by people in a social system. The cumulative adoption of innovations by a population shows an S-shaped pattern based on 5 adopter categories: innovators (2,5%), early adopters (13,5%), early majority (34%), late majority (34%) and laggards (16%). These groups follow each other in the adoption of an innovation wherein the laggards need the highest amount of time before they are ready to adopt and use the innovation. In the context of IVD selftests this process can also be recognised in that the acceptability is increasing from a very low percentage of patients willing to participate to a percentage of participants that shows that IVD selftests are now more or less adopted by the early majority (44% in Gardiner et al., 2009).

If there is a difference between the patients in the study and the larger group of patients, this weakens the external validity because the results cannot be generalised for the complete population of anticoagulated patients. This makes it difficult to decide on the actual contribution of IVD selftests to the quality of care for the complete group of patients despite of the generally positive results from the study participants. In addition, it is claimed in one study (Gadisseur et al., 2004) that younger patients will experience more benefits by the use of selftests because they evaluate their quality of life lower because of the restrictions routine care causes on their lifestyle. A study with specifically younger participants could show a larger contribution to the quality of care than the studies that were included in this review. Obviously, results from such a study could not be generalised over the complete patient population.

A final comment on the included studies related to patient differences is the absence of information about education/employment level in all of the studies. This patient characteristic may influence the use of IVD selftests because patients with a higher education level are generally more suitable for self care interventions.

Statistical imperfections

At last there are some statistical imperfections in some of the included studies that need to be mentioned. To start with the lack of statistical significance for a lot of effects in the INR control: the validity of the relationship between selftesting and better INR control can be disputed. In addition, the studies that examined agreement with reference tests from the laboratory used the correlation coefficient. This is a suboptimal method because correlation is useful in demonstrating similarity between two tests but it does not provide a meaningful assessment of agreement (Sunderji, 2005). Besides that, several studies use the INR control results from the same patient group of the previous 6 months to assess these against the results with selftests (Gardiner et al., 2005; Gardiner et al., 2004; Khan et al., 2004). The reliability of this method is not very high.

§5.1.2. Quality of this study

In this second part of the discussion attention is given to the quality of this study. This is based on two aspects of the study: the quality of the review and the quality of the complete study.

Quality of the review

As it was mentioned in chapter 4, §4.2.2., the included studies differ on many aspects. A complete overview of these differences can be found in Table 12 in Appendix D. The consequences of these differences is that conclusions based on the combined results of these studies are not very reliable. When the study designs or measurement procedures differ, the outcomes can also differ because of the differences in designs and procedures. Meaning that outcomes acquired by a combination of different measurement procedures to determine a relationship are not absolute and can be disputed. In addition, the assessment of patient acceptability for this study is based on different types of study data such as questionnaire answers and participation rates. Besides the weaknesses of these methods themselves that are criticised in the first part of the discussion, it can also be disputed if the combination of all these different aspects represent patient acceptability.

Quality of the complete study

The quality of the complete study is largely determined by the quality of the systematic literature review. A major difficulty in conducting this review was the lack of a universally accepted terminology to describe the technology of IVD selftests. There is no MeSH term for in vitro diagnostics and neither for selftests. Studies use a wide variation of expressions for selftesting and a lot of the studies that are retrieved by a literature search related to selftesting but turn out to be about point of care testing for healthcare professionals, or for screening purposes. Also, the studies refer to the specific technologies that are used for the test such as the particular point of care systems or the markers that are examined. This makes it difficult to retrieve all the relevant articles in the literature search. Searching the literature for all kinds of diagnostic tests individually may have resulted in more testing applications and a more complete overview, but it would not have been feasible.

If at the start of this study it would have been known that the only therapy that is actually managed with IVD selftests is oral anticoagulation therapy (besides diabetes), a different search strategy would have been more appropriate to find all the relevant articles about this specific subject. For example, the keywords warfarin, INR, INR control, therapeutic control and INR-monitoring would have been added to the search.

Besides that, a separate literature search for the third sub-question on the factors influencing success would have been beneficial. In this new search special attention would have been given to the factors influencing success by using other keywords such as acceptability, therapy adherence etc.

For several potentially relevant articles, there is no access to the full text which makes it impossible to review these articles and use them in this study. This way, relevant information is missed and the conclusions of this study are actually based on incomplete data.

§5.2. Conclusions

The most important conclusions related to the influence of IVD selftests on the INR control compared to the INR control in routine care are, although not always significant, generally that:

- The %TIR is higher for patients using an IVD selftest
- The % time outside critical control limits is less for patients using an IVD selftest
- INR values are more stable for patients using an IVD selftest
- INR values from IVD selftests agree with INR values from laboratory tests
- Education may be a confounding variable causing better INR results for IVD selftests

The most important conclusions related to the success of IVD selftests for OAT management are generally that:

- After use IVD selftests are evaluated positive by most of the patients
- After education most IVD patients are able to use IVD selftests properly
- After use IVD selftests are valued as easy and convenient
- After use IVD selftests increase self-efficacy and decrease daily hassles and distress
- After use there is still a number of patients who is not comfortable with using IVD selftests
- After use there is still a number of patients who is unable to use IVD selftests properly
- This unsatisfied group is smaller than the group of patients who support IVD selftests
- There is a very low participation rate in studies with IVD selftests but this rate is increasing
- IVD selftests have a very small failure rate. A standard procedure for a frequent quality check of the device would be valuable
- The importance of the quality check should be explained in the patient education

Research question

Based on these conclusions a final answer can be given to the research question: *"Can IVD selftests for therapy management contribute to the quality of care for patients with chronic conditions?"*.

The answer on this question can be given by looking at the agreement with the definition of 'quality of care' as applied by the Institute of Medicine wherein *"Quality of care" is the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with the current professional knowledge. Good quality means providing patients with appropriate services in a technically competent manner, with good communication, shared decision making, and cultural sensitivity. Quality can be measured by assessing appropriateness of care and adherence to professional standards."* (IOM, 2001).

Current professional knowledge shows that IVD selftests, although not always significantly, can improve the INR control of patients on OAT and by this increase the likelihood of desired health outcomes. When IVD selftests are used by patients, the intervention is evaluated positive in most cases because IVD selftests provide an easy and convenient option to manage therapy. Because IVD selftests respond to the needs and preferences of patients it increases the quality of life and patient satisfaction, especially for patients who feel restricted by routine care in their daily lifestyle.
Still, IVD selftests respond only to the needs and preferences of a part of the total population of patients on OAT which demonstrates that it is not an appropriate intervention for every individual patient. Nevertheless, if patients feel confident about selftesting it can be concluded that IVD selftests contribute to the quality of care. The intervention provides these patients with a convenient, accurate, safe and suitable option to manage their therapy. Besides that it gives the patient autonomy and the opportunity for shared decision making. It must be noticed that a very important condition for this successful contribution to the quality of care is the provision of adequate education. Without adequate education patients cannot use IVD selftests in the appropriate way, which would cause safety problems and would bring damage to the quality of care.

Recommendations for current use of IVD selftests

- Adequate education should be provided to patients. To offer patients a safe and suitable intervention, adequate education is very important. With adequate education difficulties in the use of IVD selftests could be taken away and a larger group of patients would be qualified to use IVD selftests. Additionally, with adequate education a larger group of patients would feel confident with using IVD selftests, improving the adoption of IVD selftests for therapy management.
- The importance if a frequent quality check of the selftesting device should be explained to patients. Therefore, this aspect could be integrated in the education about the use of the selftest.

Recommendations for further research on IVD selftests and OAT management

- More studies should be done with large groups of representative study participants to estimate if the influence of IVD selftests on INR control is significant in better study conditions. Special attention should be given to the influence of differences in patient characteristics as age and educational level.
- More studies should be done to identify the reasons for reluctance of patients.
- More studies should be done to estimate if education is a confounding variable.
- More studies should be done on cost-effectiveness of the intervention.
- More studies should be done to identify the groups for which IVD selftests for therapy management would be most valuable.

Recommendations for further research on in vitro diagnostic tests

Because in vitro diagnostic tests are being developed for different innovative purposes they provide a lot of new subjects for research. Studies on the use of IVD selftests in general or the use of point of care tests in healthcare facilities would be very interesting.

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Appendices

Appendix A. In-and exclusion of articles anticoagulation

Title	Author	In- or Excluded?
Evaluation of Point-of-care Activated Partial Thromboplastin Time Testing by Comparison to Laboratory-based Assay for Control of Intravenous Heparin	(Douglas et al., 2009)	Excluded; not patient selftesting
Self-monitoring of oral anticoagulation: does it work outside trial conditions?	(Gardiner et al., 2009)	Included
Validation of the international normalized ratio (INR) in a new point-of-care system designed for home monitoring of oral anticoagulation therapy	(Plesch & Besselaar, 2009)	Excluded; study to confirm accuracy of test strip lots
Point-of-care (POCT) prothrombin time monitors: is a periodical control of their performance useful?	(Barcellona et al., 2009)	Included
Quality assurance for point-of-care testing of oral anticoagulation: a large-scale evaluation of the Hemochron Junior Signature Microcoagulation System	(Maddox et al., 2009)	Excluded; not patient selftesting
Feasibility, cost-effectiveness and patients' acceptance of point-of-care INR testing in a hospital based anticoagulation clinic	(Kong et al., 2008)	Excluded; not patient selftesting
In-patient International Normalized Ratio Self-Testing Instruction After Mechanical Heart Valve Implantation	(Thompson et al., 2008)	Included
Patient self-testing for management of anticoagulation therapy: challenges	(Wurster, 2008)	Excluded; it's a paper
Improving Anticoagulation Therapy Using Point-of-Care Testing and a Standardized Protocol	(Franke et al., 2008)	Excluded; not patient selftesting
Comparison of INR stability between self-monitoring and a standard laboratory method: Preliminary results of a prospective study in 67 mechanical heart valve patients	(Dauphin et al., 2008)	Included
Self-monitoring versus standard monitoring of oral anticoagulation	(Ferretti et al., 2007)	Excluded; it's a letter
Comparison Between International Normalized Ratio Using a Portable Device and Conventional Methodology	(De Piano et al., 2007)	Excluded; not patient selftesting
Quality Assessment of CoaguChek Point-of-Care Prothrombin Time Monitors: Comparison of the European Community – Approved Procedure and Conventional External Quality Assessment	(Poller et al., 2006)	Excluded; evaluation of two quality assessment approaches
The use of a HEMOCHRON® JR. HEMONOX™ point of care test in monitoring the anticoagulant effects of enoxaparin during interventional coronary procedures	(Rouby et al., 2006)	Excluded; not patient selftesting and not for therapy management
Anticoagulation Self-Monitoring	(Pence & McErlane, 2005)	Excluded; it's a paper
The Impact of Patient Self-Testing of Prothrombin Time for Managing Anticoagulation: Rationale and Design of VA Cooperative Study #481 – The Home INR Study (THINRS)	(Matchar et al., 2005)	Excluded; overview, objectives and design of the study -> the study is not completed yet.
Clinical Impact of Point-of-Care vs Laboratory Measurement of Anticoagulation	(Sunderji et al., 2005)	Included
A randomised control trial of patient self-management of oral anticoagulation compared with patient self-testing	(Gardiner et al., 2005)	Included
Patient self-testing is a reliable and acceptable alternative to laboratory INR monitoring	(Gardiner et al., 2004)	Included

Analytical Performance of the New Coagulation Monitoring System INRatio™ for the Determination of INR Compared with the Coagulation Monitor Coaguchek® S and an Established Laboratory Method	(Taborski et al., 2004)	Included
European Concerted Action on Anticoagulation. Quality Assessment of the CoaguChek Mini and TAS PT-NC Point-of-Care Whole-Blood Prothrombin Time Monitors	(Poller et al., 2004)	Excluded; evaluation of two quality assessment approaches
Quality assurance program for whole blood prothrombin time-international normalized ratio point-of-care monitors used for patient self-testing to control oral anticoagulation	(Tripodi et al., 2004)	Excluded; evaluation of a quality assessment approach
The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation	(Khan et al., 2004)	Included
Patient self-management of oral anticoagulant care vs. management by specialized anticoagulation clinics: positive effects on quality of life	(Gadisseur et al., 2004)	Included

Table 10. Article selection anticoagulation

Appendix B. Complete overview of the included articles

List of abbreviations

OAT – Oral Anticoagulant Therapy
INR – International Normalized Ratio
TIR – Time In Range
TC – Thrombosis Centre
PT INR – Prothrombin Time International Normalized Ratio
ECAA – European Concerted Action on Anticoagulation
FCSA – Federation of Centres for the diagnosis of thrombosis and the Surveillance of Anti-thrombotic drugs
EQA – External Quality Assessment
PSM – Patient Self-Management
PST – Patient Selftesting
QoL – Quality of Life

List of definitions

Self-monitoring – self-measurement of INR values but not self-dosing of OAT
Self-management – self-measurement of INR values and self-dosing of OAT

Self-monitoring of oral anticoagulation: does it work outside trial conditions?
(Gardiner et al., 2009)

Audit to determine whether self-monitoring of OAT with the CoaguChek S (Roche Diagnostics, Basel, Switzerland) from the start of treatment and outside trail conditions, is acceptable to patients and a viable alternative to routine care. Study started with 318 patients referred for OAT who had not previously received OAT. Patients were excluded for a-typical target INR ranges (n=11) and after eligibility assessment (n=119). This resulted in 188 patients invited to self-monitor their OAT. Eligibility criteria excluded: short-term anticoagulation, drug/alcohol abuse, language barriers, non-local residency, residential care/district nurse, planned surgery/concomitant illness, no phone, warfarin discontinued, non-compliant/did not attend. Of the 188 eligible patients, 84 patients (44%) elected self-monitoring and the remaining 104 elected routine care. Finally resulting in study groups of self-monitoring (n=68 (of 84, 81%)) and routine care (n=88 (of 104, 85%)). Drop-out during or after training was 14% but 94% of patients who started self-monitoring completed treatment course and continued after end of study. Self-monitoring patients were significantly younger than those electing for routine care (58 vs 68).

Results *Therapeutic INR control*: Median %TIR significantly higher in self-monitoring than in routine care (71% vs 60%) and median % time outside critical control limits (INR <1.5 or >5.0) significantly lower in self-monitoring than in routine care (0.45% vs 2.04%).

Adverse events: For self-monitoring the incidence of major bleeds 1.7 per 100 patient years, minor bleeds 8.4 per 100 patient-years and thrombosis 3.4 per 100 patient-years. For routine care the incidence of major bleeds 5.4 per 100 patient years, minor bleeds 16.2 per 100 patient-years and thrombosis 1.4 per 100 patient-years. Overall, adverse events were less in the self-monitoring group than in the routine care group.

Point-of-care (POCT) prothrombin time monitors: is a periodical control of their performance useful?
(Barcellona et al., 2009)

Study to investigate the quality control of the CoaguChek S (Roche, Mannheim). 95 monitoring devices were assigned to 101 anticoagulated patients at home (median age 59, 23-88 years). All patients were on long term OAT. Eligibility inclusion criteria: patients on OAT for at least 6 months, confined to home because of serious physical illness, advanced age, patients not living within easy reach of TC, lack of time due to working hours. Conditions of the included patients: atrial fibrillation (n=29), deep vein thrombosis with or without pulmonary embolism (n=33), recurrent superficial vein thrombosis (n=3), mechanical heart prostheses (n=23), myocardial

infarction (n=5), cardioembolic stroke (n=4) and peripheral embolism (n=4). The researchers conducted a PT INR comparison for the portable coagulometer CoaguChek S (capillary blood) with an automated coagulometer ACL Futura (International Laboratory, Barcelona, Spain) located at the TC as a reference system (venous blood). Patients were required to bring their devices to the TC on a quarterly basis for a total of three consecutive occasions. Because of dropout, no. of devices examined at first control (n=95), second control (n=93), third control (n=87).

Results *Quality control*: one monitor (~1%) failed all the ECAA quality controls even when the lot of test strips was changed. This finding confirms the utility to periodically check portable monitors to evaluate their performance. The performance of the monitors can be affected by use of different lots of test strips of varying quality. Therefore it is recommended to check an individual monitor every time the patient changes the lot of strips. These quality assessments could be executed by the TCs.

In-patient International Normalized Ratio Self-Testing Instruction After Mechanical Heart Valve Implantation (Thompson et al., 2008)

Study to evaluate the feasibility and efficacy of an in-hospital educational program (early postoperative instruction) for selftesting of INR with the INRatio (HemoSense San Jose, CA) in patients recovering from mechanical heart valve replacement. Of the 55 adult patients scheduled for mechanical heart valve implantation or who were recovering from it, 50 (91%) consented to participate (median age 54 (18-88), all no experience with INR selftesting). Eligibility exclusion criteria: disabilities or language skills that would preclude selftesting education. Selftesting instruction was initiated as soon as patient's clinical status allowed and was completed before hospital discharge. The INRatio INR values were compared with the INR values determined by reference laboratories. Dual INR testing only for the 1-month duration of the study, selftests were performed at the managing physician and at home and INR log-sheet recorded both selftesting results and laboratory results.

Results *Educational program*: Most patients started instructions on postoperative day 4 (1-8). Before going home all patients were able to selftest and record results. At the end of the study month 49/50 patients (98%) were able to obtain INR results from INRatio. This was examined by personal communication with each subject at end of the study.

INR control: INR logs were returned by 30 patients and Bland-Altman plots demonstrate agreement of the INR results obtained by INRatio with the INR results obtained by reference laboratories.

Acceptability: surveys were returned by 44 patients (88% of 50) reporting that 82% agreed they were recovered enough at initiation of selftesting instruction, 4.5% felt not ready to selftest at hospital discharge, 75% felt excellent or very good about INR selftesting, 86% found INR selftesting easier and 80% preferred selftesting to INR determination by laboratories.

Comparison of INR stability between self-monitoring and a standard laboratory method: Preliminary results of a prospective study in 67 mechanical heart valve patients (Dauphin et al., 2008)

Study to evaluate the INR self-monitoring system CoaguChek® by comparing it with standard laboratory methods for mechanical heart valve patients. Primary objective: check whether self-monitoring led to better compliance with the INR therapeutic range (INR: 2-4.5), secondary objective: confirm that INR stability within INR target range (established for individual patients) reduces incidence of clinical events. 67 Participants are randomly allocated to one of two groups (A (control n=34): standard INR monitoring once a month in lab, B (intervention n=33): home INR self-monitoring, combined with standard monitoring once a month in lab. Eligibility exclusion criteria: contraindication tot oral anticoagulants, pregnancy or inability to self-monitor. Patients in both groups received training in anticoagulant treatment monitoring methods and in addition, patients in group B were trained to use the self-monitoring system. The anticoagulant dose was adjusted by the patient's doctor based on lab measurements for group A and on lab and self-monitoring measurements in group B. The mean age of the participants in group A is 55 years and for group B, 58 years. 6 Patients dropped

out (3 in both groups), among self-monitoring group one did not use the system properly, one found self-monitoring too restrictive and one did not trust the system.
Results *Time in range*: average time in INR target range (A: 53±19%, B 57±19%), and in therapeutic range (A: 86±14%, B 91±7%), is not significantly different between the two groups.
Stability: INR values were significantly more stable in group B (self-monitoring) than in group A (control) for the whole study period for both the target range and the therapeutic range (mean deviation 41 vs 62 and 11 vs 39).
Clinical events: 13 haemorrhages were reported in group A (9 mild, 7 serious) and 4 in group B (all mild). There were no thromboembolic events.

Clinical Impact of Point-of-Care vs Laboratory Measurement of Anticoagulation
(Sunderji et al., 2005)
Study to determine agreement between self-management with the ProTime Microcoagulation System (International Technidyne Corporation, Edison, NJ) and the hospital laboratory and its impact on therapeutic decision making. In addition, the need for a quality assurance program for the self-monitoring device will be determined. Eligibility inclusion criteria: older than 18 years, receiving warfarin for at least one month before enrolment with planned anticoagulation for at least one year to a target INR of 2.0-3.0 or 2.5-3.5, exclusion criteria: known hypercoagulable disorder, mental incompetence, language barrier, or inability to attend training sessions. Patients are randomised to warfarin self-management or to routine care. Self-managing patients were required to determine their INR with the ProTime monitor and concurrently at the hospital laboratory within 1 hour to verify concordance at the start of the 8 month study and at the end. The paired INR results were analysed for clinical agreement (both INR measures falling within or outside the target INR range) and numeric agreement (correlation coefficient analysis and mean difference; o.5 INR units or less was used to establish concordance). Final study group of 55 patients with 91 evaluable paired INR measurements (mean age 55.8 (20-79)).
Results *Clinical agreement*: occurred in 56 (62%) of 91 cases (fair strength of agreement).
Numeric agreement: correlation coefficient of 0.62. Overall, 69 (76%) of 91 cases were within 0.5 INR units of each other, and 78 (86%) of 91 cases were within 0.7 INR units.
Quality control: Because there was a small failure rate in INR concordance between test systems observed in this study it is recommended to periodically check POC systems against a laboratory method to monitor performance and make patients alert for unexpected values.

A randomised control trial of patient self-management of oral anticoagulation compared with patient self-testing
(Gardiner et al., 2005)
Study to compare the quality of warfarin control achieved by self-management with that of selftesting against the background of routine care (patient's INR values from previous 6 months) in routine care. Also patient compliance with the self-management program is assessed. Of all patients attending to the anticoagulant clinic, 800 fulfilled inclusion criteria, but only 104 (13%) agreed to participate in the study. Eligibility inclusion criteria: older than 18 years, receiving long term OAT for a period of a least 8 months, exclusion criteria: history of poor compliance, dexterity or sight problems that would prevent successful selftesting, intellectual impairment, known drug or alcohol dependency. Of the 104 participants, 55 (53%, mean age 59) were randomly allocated to self-management and 49 (47%, mean age 61) to selftesting, no significant differences between baseline characteristics. 77 Patients (74%) completed the study (self-management=41, 75%, selftesting =36, 73%), drop out mostly because of difficulty in obtaining capillary sample and in self-management group also because of anxiousness about self-management. Both the self-management and the selftesting patients measured their INR with the CoaguChek system (Roche Diagnostics, Basel, Switzerland) and both attended a training course. The self-management group routinely tested their INR every 2 weeks for 6 months with dose changes based on a treatment algorithm issued to each patient, including other necessary instructions. The selftesting group tested identical, but they contacted the anticoagulation clinic staff with the INR selftest result for advice in

dose changes and other instructions. In addition, all patients were asked to perform an internal quality control (QC) sample once a month and at least one external quality assessment (EQA) exercise during the study.
Results *Percentage time in range*: overall, no statistically significant difference in the %TIR was found between self-management and selftesting (70% vs 72%). Neither, statistically significant differences were found in %TIR for individual patients and their results from the previous 6 months (PSM 70% vs 62% and PST 72% vs 63%). However, a significant improvement was found when the two groups were combined and assessed against previous results (routine care), (%TIR 71% vs 62.5%).
Percentage time outside control limits: for the selftesting group the % time outside control limits was approximately half of that observed in the previous 6 months (1.06% vs 1.96%) though not a significant reduction. for the self-management group similar values could only be observed after exclusion of extreme data resulting from poor compliance (1.34% vs 2.56%), before exclusions reduction of 2.21% vs 2.56%.
Compliance in quality control: many patients did not fully understand the importance of regular quality control and did not comply to the quality control checks. Importance of compliance should be included in the patient education and training sessions.

Patient self-testing is a reliable and acceptable alternative to laboratory INR monitoring
(Gardiner et al., 2004)
Study to investigate the accuracy and acceptability of patient selftesting with the CoaguChek S (Roche Diagnostics, Basel, Switzerland) in a trained and motivated group of patients against a control group and against a background of routine care (patient's INR values from previous 6 months). Of the 800 eligible patients, only 84 (10.5%) volunteered for the study. Eligibility inclusion criteria: older than 18 years, long term oral anticoagulation for at least 8 months, a previous record of good compliance. These patients were randomly assigned to a selftesting group (n=44, 52%) or control group (n=40, 48%) (continuing with lab testing with no specific education/training), no significant differences between baseline characteristics although the median age of the participants of the study (control: 58, selftesting: 58) was lower than that of the anticoagulant population of the clinic as a whole (66). Selftesting group attended training sessions and after this these patients tested at home once a week and recorded results for 6 months. Anticoagulant control was based on lab test performed every 4 weeks (no self-dosage). Selftest and lab tests used for the comparability study were collected within 1 hour from each other. In addition, the selftesting group performed quality control tests and were asked to complete a patient acceptability questionnaire after 3-4 months. At the start of the study, of the 44 patients in the selftesting group, 39 entered the study and all patients of the control group entered the study. During the study, 9 selftesting patients and 1 control group patient failed to complete the study (not a main reason for drop-out).
Results *INR control in comparability study*: excellent correlation between selftesting values and lab values of selftesting patients (r=0.95), no trend with increasing INR value. Overall, 85% of these results was within 0.5 INR units of each other. No significant differences in %TIR between the two study groups, nor between the study period and the previous 6 months for individual patients.
Acceptability: questionnaires were returned by all 31 patients still selftesting after 3 months (this should be 30 patients according to the drop-out data). Initially, 84% found it difficult to obtain an adequate sample, but subsequently most of them found selftesting very easy (55%) or quite easy (32%). Only 1 patient found CoaguChek difficult to use and 16% still had difficulties with obtaining an adequate sample. 87% was confident with the results they obtained and, of those who expressed a preference 77% preferred selftesting rather than attending the clinic. None of the patients had difficulties with the quality control and >98% was compliant, however, it was generally felt that weekly QC testing is not cost-effective. An alternative could be occasional paired selftesting and lab testing for comparison with a controlled instrument.

Analytical Performance of the New Coagulation Monitoring System INRatio™ for the Determination of INR Compared with the Coagulation Monitor Coaguchek® S and an Established Laboratory Method
(Taborski et al., 2004)

Study to evaluate the INRatio™ system (HemoSense Inc., Milpitas CA, USA) for accuracy and precision. Reference testing was performed with the STA Compact (Stago, Paris, France) and the CoaguChek®S (Roche Diagnostics GmbH, Mannheim, Germany). 63 Anticoagulated patients were tested in centre 1, 14 anticoagulated patients and 5 healthy individuals in centre 2. The INR determinations of the reference samples (separated plasma from citrated blood shock frozen in portions) were all analysed in centre 1. Capillary measurements were taken dually with two INRatio instruments with two drops from fingerstick sample which were alternated between the two instruments to level out sampling differences. Same was done with CoaguChek S with another finger. All patients were familiar with INR selftesting using different instruments, they were asked about their opinion comparing their old meter with the new device.

Results *Accuracy*: correlation coefficient r=0.954 for INRatio and r=0.937 for CoaguChek S. Mean relative deviation (MRD) was 6.87% for INRatio and 9.72% for CoaguChek S, variation coefficient of dual measurement found in normal range (INR=1.1) was 7.8%, in high therapeutic range (INR=3.9) 5.4% and in the high range (INR=5.3) 8.4%.

Concordance: based on 62 pairs of values from patients from centre 1 under anticoagulation therapy, concordance with the laboratory method (STA) was 81% for INRatio and 79% for CoaguChek S.

Patient's observations: of the 62 patients, 58 patients gave their opinion. Overall, the patients evaluated the design of the instrument and its in-built quality control as positive, the larger drop of blood that is required and the longer waiting time for a result negative. General observations: no malfunction of the systems and no case of erroneous results generated by any of the meters.

The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation

(Khan et al., 2004)

Study to assess the effect of an anticoagulation education program with or without self-monitoring in older patients with atrial fibrillation against routine care (patient's INR values from previous 6 months) and a control group in routine care, on stability of anticoagulant control and treatment related quality-of-life measures. By computer, 249 patients of the anticoagulation service were identified as eligible. Eligibility inclusion criteria: atrial fibrillation with target INR range of 2-3, taking warfarin for at least 12 months, INR SD ≥0.5 over the previous 6 months and aged ≥65 years. 55 patients were excluded because of eligibility exclusion criteria: general frailty, poor hearing or eyesight, impairment of hand function which precluded the use of a self-monitoring system or when cause of instability of anticoagulation control was apparent (e.g. drug interactions). The control group continued with routine anticoagulation clinic care and were unaware of participation to prevent bias (n=40). The intervention arm of the study resulted in 85 participants (55% of 154 approached) who all attended a 2 hour education session with an interview by a research worker (not clinic staff member) to assess health status and quality-of-life (UKSF-36, Euroqol and a special instrument for anticoagulated patients). Educated patients were then randomised to two treatment groups: routine care with education (n=41, 48%) or weekly self-monitoring (n=44, 52%). Median age patients in control routine care group: 73 years (65-93), routine care with education group: 75 years (65-87) and weekly self-monitoring group 71 years (65-91). Self-monitoring patients underwent training in self-measurement of capillary blood samples using the CoaguChek System (CoaguChek®, Roche Diagnostics, Mannheim, Germany). The study coordinator provided advice about warfarin dosage by phone based on the self-measured INR values (no self-dosage). The active study participants also attended anticoagulation clinic at 6, 12 and 24 weeks to attend an interview about the treatment related quality-of-life. Drop-out: 4 (9%) from self-monitoring group, 2 (5%) from routine care with education group.

Results Good correlation between capillary INR (CoaguChek) and venous INR (lab), r=0.75.

Percentage time in range (%TIR): %TIR for self-monitoring increased significantly from 57 ± 17 to 71 ± 14.5, mean difference 14.1 compared with the %TIR in routine care in previous 6 months. The %TIR for routine care with education increased significant from 61 ± 15 to 70 ± 24.5, mean difference 8.8 and the %TIR for the control routine care group increased from 60 ± 19 to 63 ± 26, mean difference 3.2, which is not significant.

Standard deviation of INR: During the same period the mean SD decreased with 0.24 in self-monitoring, with 0.26 in clinic monitoring, and with 0.16 in control group. The differences between groups are not statistically significant, possibly because of the large amount of variability.
Quality-of-life/acceptability: perceived benefits and barriers to anticoagulation were not significantly different between the self-monitoring group and the clinic monitoring group. Of 40 self-monitoring patients who completed the study, 30 (75%) reported no problems with the technique and an interest to continue for its ease and convenience. The other 10 (25%) reported difficulties with the technique. In this study, specifically on older patients, it was reported in the free text views that some older patients had initial difficulty with the technique of blood sampling, but learnt with practice and all found it convenient.

Patient self-management of oral anticoagulant care vs. management by specialized anticoagulation clinics: positive effects on quality of life
(Gadisseur et al., 2004)
Study to assess the effects on OAT-related quality of life through different treatment modalities: self-monitoring (group A), self-management (group B), routine care with increased patient education (group C), and routine care (group D). After eligibility assessment and the randomisation of 161 patients to the routine care group, 720 patients were contacted for participation in the trial. Eligibility inclusion criteria: long-term OAT with phenprocoumon or acenocoumarol, at least 3 months experience, age range 18-75. Of these 720 patients, only 184 consented to participate, 4 were later unavailable resulting in 180 (25%) patients attending the training sessions. After the training sessions another 21 patients withdrew or were ineligible (no reason is given), resulting in three final study groups (n=159). Group A, n=52 (33%); group B, n=47 (30%) and group C, n=60 (38%). The self-monitoring and self-management group performed a weekly self-measurement of their INR values. The quality of life (QoL) was measured with a questionnaire developed by Sawicki et al (1999). The questionnaire mirrors the most important concerns of patients regarding the condition and treatment based on the 'clinical impact method' wherein importance to items is given by patients themselves. It is translated from German into Dutch and marginally adapted to make it compatible to the situation in the Netherlands. The QoL questionnaire was distributed to all patients assigned to training sessions (n=180) at the start and the end of the study and it measures the impact of the different management procedures at the end of the study compared with baseline. Results were compared at 26 weeks with baseline, as well as between groups at 26 weeks. Only 116 patients (64%) returned both the baseline questionnaire and the end-of-study questionnaire. Group A, n=47 (90% of group), mean age 55; group B, n=41 (87% of group), mean age 54, and group C, n=28 (47% of group), mean age 60, all analyses are restricted to these patients.
Results *Quality of life*: QoL scores are given on a scale from 1-6. The baseline questionnaire presented high general treatment satisfaction (5.11) while showing a moderate degree of daily hassles (1.71), distress (2.05) and straining of the social network (1.46). Daily hassles were scored higher by younger age groups, especially below the age of 50 (+0.24), as was the element of distress (+0.34), which below the age of 40 increased even further (+0.70).
In group C there was a decrease in general treatment satisfaction (-0.23) although not significant and a significant increase in distress (+0.33) and strain on the social network (+0.21). In group A there was only one significant change; an increase in self-efficacy (+0.31), there was also a small increase in general treatment satisfaction. Group B had the most important changes with a significant increase in general treatment satisfaction (+0.49) and the feeling of self-efficacy (+0.32) and a significant decrease in the perception of daily hassles (-0.31) and distress (-0.44), while there was a smaller decrease in strain on the social network. Although differences between group A and B were small, there was a trend towards a further increase in general satisfaction by allowing the patients full self-management (+0.30, not significant p=0.14) and a further significant decrease in the feelings of distress (-0.50, p>0.001).
Over the whole study, younger patients report less general treatment satisfaction than older patients, which may be explained by the higher intrusion into their lifestyle by the frequent blood sampling than is the case in older patients. Based on the discussions with patients it is clear that younger patients experience more problems in their professional and social lives caused by frequent visits to clinics in routine care. Younger

patients also show a higher degree of irritation with daily hassles. Over all age groups the perception of distress is more pronounced in women than in men ($p<0.05$).

Note: the results from patients in group C who were trained for self-management but were assigned to routine care, may have been heavily influenced by feelings of dissatisfaction with the study process, i.e. being denied self-management, resulting in the presented decrease in general treatment satisfaction and the increase in distress and strain on the social network.

Appendix C. Main facts of the included articles

Author	Device(s)	Design	Study Group	N	Setting	Characteristics	Conclusion
(Gardiner et al., 2009)	CoaguChek®S, Roche Diagnostics, Basel Switzerland	Prospective closed cohort audit	patients referred for oral anticoagulation	At start: (n=318), in trial: 188 eligible patients -> self-test (n=67), routine care (n=88)	UK, July 2005 – March 2007, 20 months	Uptake of self-monitoring, INR control, adverse events	Self-monitoring acceptable and efficacious for 26% of unselected patients if offered at the start of treatment
(Barcellona et al., 2009)	CoaguChek®S, Roche, Mannheim	Quality assessment study with 3 control occasions	Patients on long term OAT. Several conditions	101 patients with 95 coagulo-meters (93 at second control and 87 at third control)	Italy, March 2006 - May 2007	Quality control of the portable coagulometer	CoaguChek S is a reliable monitor to control OAT but quality checks should be executed every time lots of strips are changed
(Thompson et al., 2008)	INRatio™ (HemoSense Inc., San Jose, CA)	Selftesting educational program evaluation	Mechanical heart valve patients	50	Minnesota, US, February 2005 – June 2005, 1-month study	Timing educational program, INR control, patient's acceptability	Early introduction of INR selftesting is possible and patients are able to continue selftesting during first month after hospital discharge
(Dauphin et al., 2008)	CoaguChek® System	Single-centre, regional, prospective, randomised, open study	Mechanical heart valve patients	67, routine care (lab) (n=34), self-monitor (n=33)	France, May 2004 - June 2005	INR control, adverse events	Self-monitoring correlates with better anticoagulation, also it appears to be linked to reduction of clinical events

(Sunderji et al., 2005)	ProTime Microcoagulation System (International Technidyne Corporation, Edison, NJ)	Single-centre, Randomised, open-label study	Patients receiving warfarin. Mechanical valve (67%), atrial fibrillation (25%), Venous thromboembolism (4%), other (4%).	55 patients with 91 evaluable paired INR measurements	Canada, 8 months	INR control	Acceptable agreement between INR values obtained with ProTime and laboratory, small failure rate of systems emphasises the need for external quality control systems
(Gardiner et al., 2005)	CoaguChek®S, Roche Diagnostics, Basel Switzerland	Prospective randomised controlled trial	Patients receiving warfarin	At start: n=800, in trial (n=104), PST (n=49), PSM (n=55)	UK, 6 months	INR control, compliance in quality control of the device	PSM is an effective mode or OAT for the majority of suitably trained patients
(Gardiner et al., 2004)	CoaguChek®S, Roche Diagnostics, Basel Switzerland	Prospective randomised controlled trial	Patients on long term OAT	At start: n=800, in trial (n=84), PST (n=44), PSM (n=40)	UK, September 2002 – April 2003, 6 months study	INR control, patient's acceptability	PST offers a reliable alternative to lab determination of INR values and is acceptable for majority of suitably trained patients
(Taborski et al., 2004)	INRatio™ system (HemoSense Inc., Milpitas CA, USA) and CoaguChek®S (Roche Diagnostics GmbH, Mannheim, Germany)	Device evaluation study	Anticoagulated patients and healthy subjects	Anticoagulant patients (centre 1; n=63 and centre 2; n=14), healthy subjects (centre 2; n=5)	Germany, no date or time mentioned	INR control, patient's acceptability of new device	The INRatio™ system is innovative and reliable and fulfils the precision and accuracy requirement while being very easy to use

(Khan et al., 2004)	CoaguChek® (Roche Diagnostics, Mannheim, Germany)	Randomised controlled trial	Patients with atrial fibrillation	At start: (n=249), in trial: education self-monitoring (n=44), education only clinic care (n=41, control group routine care (n=40)	UK, no date or time mentioned	INR control, quality of life	Significant improvements in anticoagulation control after just 1 education session could be a cost-effective initiative
(Gadisseur et al., 2004)	CoaguChek® (Roche Diagnostics, Mannheim, Germany)	Randomised controlled trial	Patients on OAT 9 (phenprocoumon and acenocoumarol)	At start: (n=916), in trial: weekly self-measurement (n=52), weekly self-measurement and self-management (n=47), routine care (trained patients) (n=60) and routine care (n=161)	The Netherlands, 26 weeks	Quality of life	Patient self-management of OAT in motivated patients improves general treatment satisfaction, and decreases patients' perception of treatment related daily hassles, distress and strain on their social network

Table 11. Main facts per article

Appendix D. Study differences

Author	Patient group	Type of medication	Study objective and design	Age (mean or median)
Gardiner et al. (2009)	Patients referred for OAT	Warfarin	Efficacy of self-monitoring vs. routine care	58 vs. 68
Barcellona et al. (2009)	Patients on long-term OAT	Not mentioned	Quality control of the device with reference at lab	59
Thompson et al. (2008)	Mechanical heart valve patients	Warfarin	Feasibility of early post-operative education and self-monitoring agreement with lab	54
Dauphin et al. (2008)	Mechanical heart valve patients	Fluindione and acenocoumarol	Efficacy self-monitoring vs. routine care	58 vs. 55
Sunderji et al. (2005)	Patients on warfarin	Warfarin	Paired INR values agreement self-management with lab	59
Gardiner et al. (2005)	Patients on warfarin	Warfarin	Efficacy of self-management vs. self-monitoring vs. routine care (history)	59 vs. 61
Gardiner et al. (2004)	Patients on warfarin	Warfarin	Self-monitoring agreement with lab and efficacy of self-monitoring vs. routine care (control group and history)	58 vs. 58
Taborski et al. (2004)	Anticoagulated patients	Not mentioned	Paired INR values agreement self-monitoring with lab	Not mentioned
Khan et al. (2004)	Atrial fibrillation patients	Warfarin	Influence of education on INR control by efficacy of self-monitoring vs. routine care with education vs. routine care (control group and history)	71 vs. 75 vs. 73
Gadisseur et al. (2004)	Patients on coumarin drugs	Acenocoumarol and phenprocoumon	OAT-related quality of life of self-management vs. self-monitoring vs. routine care with education vs. routine care	54 vs. 55 vs. 60 (age routine care group not mentioned)

Table 12. Differences in study design and population