Outpatient Subcutaneous Injection Therapy –

Drug Use Problems with Low-Molecular-Weight Heparins

and Impact of Pharmaceutical Care

Inauguraldissertation

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

Seraina Mengiardi

aus Ardez und Chur (GR)

Basel, 2012

creative commons

Namensnennung-Keine kommerzielle Nutzung-Keine Bearbeitung 2.5 Schweiz

Sie dürfen:

das Werk vervielfältigen, verbreiten und öffentlich zugänglich machen

Zu den folgenden Bedingungen:

Namensnennung. Sie müssen den Namen des Autors/Rechteinhabers in der von ihm festgelegten Weise nennen (wodurch aber nicht der Eindruck entstehen darf, Sie oder die Nutzung des Werkes durch Sie würden entlohnt).

Keine kommerzielle Nutzung. Dieses Werk darf nicht für kommerzielle Zwecke verwendet werden.

Keine Bearbeitung. Dieses Werk darf nicht bearbeitet oder in anderer Weise verändert werden.

- Im Falle einer Verbreitung müssen Sie anderen die Lizenzbedingungen, unter welche dieses Werk fällt, mitteilen. Am Einfachsten ist es, einen Link auf diese Seite einzubinden.
- Jede der vorgenannten Bedingungen kann aufgehoben werden, sofern Sie die Einwilligung des Rechteinhabers dazu erhalten.
- Diese Lizenz lässt die Urheberpersönlichkeitsrechte unberührt.

Quelle: http://creativecommons.org/licenses/by-nc-nd/2.5/ch/ Datum: 3.4.2009

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät
auf Antrag von

Prof. Dr. sc. nat. Kurt E. Hersberger
Prof. Dr. med. Dr. pharm. Stephan Krähenbühl

Basel, den 13. Dezember 2011

Prof. Dr. Martin Spiess
Dekan

To my family

Acknowledgements

This work has been carried out at the Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences, at the University of Basel under the supervision of Prof. Dr. sc. nat. Kurt E. Hersberger and Prof. Dr. med. Dr. pharm. Stephan Krähenbühl.

My thanks are offered to all the people who contributed in any way to the completion of this thesis.

First of all, I would like to sincerely thank Prof. Dr. sc. nat. Kurt E. Hersberger for his boundless support, enthusiasm, and helpfulness throughout this period. I am very grateful for all the valuable discussions and ideas, his untiring dedication, and his humanity.

I wish to express my gratitude to Prof. Dr. med. Dr. pharm. Stephan Krähenbühl for assuming the co-reference of this thesis and for supporting this work. His helpful suggestions contributed to the successful completion of this thesis.

My sincere thanks also go to Prof. Dr. med. Dimitrios A. Tsakiris for his essential support and help throughout the thesis, for the inspiring discussions, and for his kindly assistance.

Many thanks are offered to Dr. phil. II Markus L. Lampert for his support and motivation during the thesis, for giving me the opportunity to qualify in Clinical Pharmacy („Fähigkeitsausweis FPH in klinischer Pharmazie“), and for offering a perspective for the time after the PhD.

My thanks go to Prof. Dr. Christoph R. Meier for accepting the function of representative of the Faculty.

Additionally, I would like to thank Prof. Dr. med. Rudolf Bruppacher for his helpful inspiration and comments in the framework of the seminar in clinical pharmacy,

Michael Mittag for his support in analysis and statistics, Paul Lavender for his English reviews, and Joëlle Bader for her assistance.

I would like to thank Pfizer AG for their financial support of the studies (Investigator-Initiated Research Grant).

Many thanks go to all colleagues of the Pharmaceutical Care Research Group, especially to Dr. Patrick Eichenberger, Fabienne Böni, Philipp Walter, Markus Messerli, Esther Spinatsch, Carole Kaufmann, Dr. Isabelle Arnet, Dr. Vera Bernhardt, Corinne Zöbeli, Dr. Jörg Indermitte, Verena Renggli, and Franziska Ankli for the great teamwork and pleasant atmosphere in the team. Many thanks also go to my colleagues at the Clinical Pharmacy & Epidemiology and Clinical Pharmacology & Toxicology units, especially to Dr. Yolanda Brauchli, Dr. Birk Poller, Dr. Dr. Felix Hammann, Dr. Sabin Egger, Dr. Alexandra Rätz Bravo, Dr. Michael Bodmer, Dr. Oliver Kummer, PD Dr. Manuel Haschke, Prof. Dr. Jürgen Drewe, Dr. Cornelia Schneider, Carmen Franz, Patrick Imfeld, Julia Spöndlin, and Saskia Bruderer. Thanks to Stefan Winzap for being the heart and soul of the Pharmacenter.

I would like to thank Judith Kaiser and Raphaela von Grünigen for their excellent work, in the context of their Master's theses, in our team.

At this point, I would like to express my gratitude to my parents, to my brother, and to my fiancé Marek for their empathy and encouragement. My deepest thanks for offering all these opportunities to me, for supporting me wherever life would take me, and for being such a good family to me. Grazcha fich!

The time as a PhD student took me in new directions both from professional point of view and also a personal one. I'm very grateful for this experience, and for all the fortunate coincidences that came my way.

Abbreviations

α	Cronbach's alpha reliability coefficient
CI	confidence interval
ClinS	clinical setting arm
ClinS-C	control group of the clinical setting arm
ClinS-I	intervention group of the clinical setting arm
DailyS	daily life setting arm
DailyS-C	control group of the daily life setting arm
DailyS-I	intervention group of the daily life setting arm
DOT	direct observation technique
DRP	drug-related problems
DVT	deep vein thrombosis
ECMD	electronic compliance monitoring devices
e-MCM	electronic multidrug compliance monitoring
Fig.	figure
FIP	International Pharmaceutical Federation
GP	general practitioner
GP	glycoprotein
h	hour
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
IIRG	Investigator-Initiated Research Grant
i.m.	intramuscular
INR	international normalized ratio
IQR	interquartile range
i.v.	intravenous
l	litre
LMWH	low-molecular-weight heparin
MEMS®	Medication Event Monitoring System
n	number
N	Newton
NHS	National Health Service

NMS	New Medicine Service
NSAR	non-steroidal anti-rheumatic
OTC	over the counter
PC	pharmaceutical care
PE	pulmonary embolism
r	Spearman's correlation coefficient
RCT	randomized controlled trial
s.c.	subcutaneous
SMS	text message
SOP	standard operating procedure
TDM	therapeutic drug monitoring
UFH	unfractionated heparin
USB	Universal Serial Bus
VAS	visual analog scale
VKA	vitamin K antagonists
VTE	venous thromboembolism
WHO	World Health Organization

Table of contents

Summary

Arterial and venous thromboses are important diseases associated with significant morbidity, mortality, and costs. To date, the orally taken vitamin K antagonists are, together with the parenterally administered heparins, still the most frequently used anticoagulants. There is a need for novel agents that are characterized by similar effectiveness, but lack the limitations seen in the well-established antithrombotic drugs.

Pre-filled syringes constitute one of the fastest growing markets in the drug delivery sectors, driven by a marked rise in the success of biopharmaceuticals (e.g., heparins). In Switzerland, all low-molecular-weight heparins (LMWH) and fondaparinux are administered subcutaneously (s.c.) with pre-filled syringes. Besides the selection of the most appropriate injection site for each individual, a proper injection technique contributes to a safe and positive outcome. Self-injections in an outpatient setting are of increasing importance as they strengthen the patient's responsibility for his/her own disease management, grant greater independence, and reduce costs by minimizing visits to the general practitioner, hospital, or nursing service.

Reasons for handling difficulties and drug use problems are diverse and may lead to dosing errors or non-compliance. They are either related to patient's impairment or to the medication, its packaging, or its device. Pharmaceutical care concentrates on the process of 'drug use', characterized by its dynamic and continuous nature. It is based on an active relationship with the patient, and aims to develop an individualized, patient-centered, and goal-oriented treatment plan to optimize safety and effectiveness. The process consists of the assessment of drug-related problems (DRP), the implementation of a care plan to solve and prevent DRP, patient action, and a periodic outcome evaluation.

Poor compliance shows a high prevalence of about 50%, leading to poor clinical outcomes, mortality, and increased health-care costs. Ten types of non-compliance are known, which can be categorized as intentional or unintentional and which are influenced by the patient's beliefs and concerns about the treatment. Potential barriers include patient-related factors, social and economic factors, health-care

system-related factors, condition-related factors, and therapy-related factors. Strategies to improve compliance comprise multifaceted, patient-tailored interventions. Compliance is assessed by indirect or direct methods. To date, there is no established gold standard to measure compliance behaviour. A multi-method approach combining self-reports and objective measures is the current state-of-the-art.

It was the **goal of this thesis** to identify drug use problems and handling difficulties with pre-filled injection systems and to evaluate the impact of pharmaceutical care on outpatient s.c. injection therapies. The thesis consists of three projects:

The objective of **project A** was to investigate one single handling difficulty that, to our knowledge, had not been reported in the literature so far. We aimed at comparing subjectively and objectively measured pull-off forces required to remove the needle shield of commercial LMWH pre-filled syringes (Clexane old and new devices, Fragmin, Fraxiparine, Sandoparin, Arixtra).
Three methodological approaches were used:

- self-assessment by a study population using a visual analog scale (VAS)
- simultaneous observer's assessment using a 3-point scale ('no effort needed', 'effort needed', or 'can not remove the needle shield')
- mechanical pull-off tests (measurements in Newtons)

The study population included 68 persons with a median age of 29 years. The removal of the needle shield was not possible in 5 of 204 cases, involving four subjects and two brands. Significant differences between the VAS scores were detected. The observer's results confirmed these findings, as did the mechanical cap-pull-off tests. Measurements of the mechanical pull-off forces showed a large range of median forces (13.6–29.9 Newtons) were needed to remove the needle shields, with the highest forces needed for Fraxiparine and the old Clexane device. Significant differences between different lots of the same brand were detected only with Fraxiparine.
In conclusion, important differences between brands were observed. Health-care professionals should be aware of these possibly crucial handling difficulties and their consequences for successful therapy and compliance.

A literature search failed to find any studies on application problems pertaining to the self-injection of LMWH in a heterogeneous outpatient population under daily-life conditions. In **project B**, we therefore designed a prospective cross-sectional study using pharmacy customers with the aim of recording drug use problems, patient satisfaction, compliance, problems arising from the injection site (abdomen vs. thigh), and residual drug volumes in used pre-filled syringes.

Data were collected during recruitment and by means of structured questionnaire-based telephone interviews that were carried out at the beginning and the end of the LMWH treatment.

The median age of the 213 patients enrolled in the study was 54 years; of these, 15.5% had their injections administered by a third person. The rate of self-reported non-compliance was 17.1%. At least one relevant problem was recorded in 85.0% of the cases. At the end of the treatment, 38.9% of the patients stated self-administration of the injections required some effort. The preferred injection site was the thigh (68.5%). An overall mean residual drug volume ≥10.0% was detected for 3.9% of the patients. If residual drug was present, a median of 11.2% (IQR 8.6─17.6%) of the total drug volume had not been injected. Patients injecting into the thigh showed a higher risk of leaving residual medication (odds ratio 2.16, 95% confidence interval 1.04─4.51).

The effectiveness of community-pharmacy-based interventions in preventing problems that arise during s.c. self-injections of LMWH was unknown. Therefore, in **project C**, we aimed to:

- develop a standard operating procedure (SOP) for the first instruction in the s.c. injection technique given by a community pharmacist and the subsequent pharmaceutical care provided during outpatient therapy
- compare intensive pharmaceutical care vs. standard care in both a clinical setting under study conditions and a daily life setting

We hypothesized that:

- intensive pharmaceutical care for outpatients self-injecting LMWH results in improved compliance, safety, and satisfaction, as well as in fewer complications
- the interventions used are feasible in the everyday routine of community pharmacies

- the results achieved in the clinical and daily life settings are comparable

In the clinical setting (randomized controlled trial), patients were recruited sequentially in hospital wards; in the daily life setting (controlled trial), recruitment took place in community pharmacies. Interventions were offered according to patient needs. Data were collected by means of a monitored self-injection at home and structured questionnaire-based telephone interviews at the beginning and the end of the LMWH treatment.

The median age of the 139 patients was 54 years. Interventions resulted in improved s.c. injection technique ($p<0.01$) and knowledge ($p=0.03$). Oral instructions were pivotal for improving patients' injection technique. We found no significant differences between the intervention groups of the clinical and daily life settings concerning quality of the s.c. injection technique, knowledge, compliance, and self-assessed assistance quality. Patients' compliance rate was high (95.8%) as were their baseline skills, with the lowest score being 0.86 on a range of −2.00 to +2.00 making further improvement difficult.

In **conclusion** this thesis showed that:

- The pull-off forces required to remove the needle shields of LMWH pre-filled syringes correspond roughly to the force needed to hold a narrow-neck plastic flask containing 1–3 l of water by pinching the neck between a finger and thumb. This seemed to be a so far unnoticed drug use problem.

- Drug use problems with outpatient s.c. injection therapies are very prevalent, diverse, and complex. They may be associated with the injection itself or with the handling of the injection-device. No associations with any factors studied were observed with non-compliance, the injection site (beside residual drug), and discomfort or effort required (beside prior injection use).

- The overall mean residual drug volume was negligible, but the total injection volume seemed to have an influence. If residual drug was present, however, it tended to be of pharmacological relevance. Patients injecting into the thigh showed a higher risk of leaving medication.

- From a patient's point of view, injections require some effort. Patients have concerns with pre-filled syringes, but are aware of their need. Further research should investigate whether compliance is not only disease- and time-dependent, but also device-dependent. We assume that intentional non-compliance might be lower with s.c. self-injections than with oral administration.

- The provided SOP for pharmacist interventions was of good quality, adequate, appreciated by the patients, and feasible in the daily life of community pharmacies. It resulted in improved s.c. injection technique and knowledge, despite high baseline patient skills. The home visits with the direct observation technique (DOT) were valuable in determining patient skills. Patients are capable of managing s.c. injection therapies in a satisfactory way and with high compliance if adequate assistance is provided.

- Overall, we confirmed our hypothesis that intensive pharmaceutical care for outpatients self-injecting LMWH resulted in more safety (objective assessment of the s.c. injection technique during the DOT), but we had to reject our assumptions of improved compliance, more satisfaction, and fewer complications.

- Our recommendations for daily practice are:
  (1) offering each person with a prescription for an outpatient s.c. injection treatment written information (leaflet, manual), application aids (alcohol swabs, sharps collector), and oral instructions (being the pivotal intervention in improving patients' s.c. injection technique)
  (2) the first self-injection should occur in the presence of a health-care professional to ensure proper injection technique (at the patient's own individual injection time)
  (3) injection training into a 'phantom' and further injections in the presence of or administered by a pharmacist are very supportive tools and should be applied if the patient requires lots of effort or has discomfort
  (4) potential needle phobia and handling difficulties should be kept in mind

1 General introduction

1.1 Anticoagulants

1.1.1 Thrombosis and embolism

Arterial (e.g., ischemic stroke, myocardial infarction) and venous thromboses (e.g., deep vein thrombosis (DVT) and subsequent pulmonary embolism (PE)) are important diseases causing significant morbidity, mortality, and costs. The average annual incidence of venous thromboembolism (VTE) is approximately 1 person per 1,000, and this increases with age. Despite appropriate treatment, thrombosis recurs frequently, at a rate of approximately 7% at 6 months. Death occurs in approximately 6% of DVT and 12% of PE patients within 1 month [1]. Only about 20% of DVT are symptomatic [2]. There is strong evidence indicating that appropriately used VTE prophylaxis has a positive benefit-to-risk ratio, and is highly efficacious and cost-effective. Without thromboprophylaxis, 10-40% of the medical or general surgical patients, 20-50% of stroke patients, 40-60% of patients following major orthopedic surgery, and 40-80% major trauma patients would have a hospital-acquired DVT [3].
Under certain circumstances, each of us can be at risk for a thrombosis or embolism. There is a very wide range of risk factors covering inpatients and outpatients as well as unstable (intensive care unit) and stable patients. Examples are:

- trauma, orthopedic, general surgical, or medical patients (e.g., bed rest, acute medical illness)
- acquired risk factors, such as increasing age, previous VTE, heparin-induced thrombocytopenia (HIT) type II, long-distance travel, immobility, pregnancy, and lifestyle (e.g., obesity, smoking)
- inherited conditions, such as thrombophilia
- certain illnesses, such as cancer, varicose veins, diabetes mellitus, hyperlipidemia, and hypertension
- certain medications, such as estrogen-containing oral contraceptives or hormone replacement therapy, selective estrogen receptor modulators, erythropoiesis-stimulating agents, and cancer therapy (e.g., chemotherapy, radiotherapy, thalidomide, tamoxifen)

The individual risk increases with the accumulation of single risk factors [3-19].

1.1.2 Antithrombotic drugs

To date, the orally taken vitamin K antagonists (VKA) are, together with the parenteral administered unfractionated heparins (UFH) and low-molecular-weight heparins (LMWH), still the most frequently used anticoagulants [20]. LMWH are usually used for the initial treatment of arterial or venous thromboembolisms. In contrast, oral anticoagulants are prescribed for long-term use [7]. Due to their parenteral administration, long-term treatment with LMWH is only seen with contraindications to VKA (e.g., pregnancy) [18] or where studies showed better outcomes with LMWH compared to VKA (e.g., cancer) [3, 21]. Arterial thrombi are treated with antiplatelet agents, whereas anticoagulants are used for the prevention and treatment of VTE [7]. Table 1 gives an overview of the antithrombotic drugs licensed in Switzerland with their mode of actions diagramed in Fig. 1. Examples of antithrombotic drugs which are not available in Switzerland are the coumarin derivative warfarin, the thienopyridin derivate ticlopidin, the LMWH tinzaparin, the oral direct thrombin inhibitor Pradaxa (dabigatran etexilate), and the parenteral administered direct thrombin inhibitor Argatra (argatroban). The first oral direct thrombin inhibitor Exanta (ximelagatran) had been withdrawn from the market due to hepatotoxicity [7].

There is a need for new antithrombotic drugs that are characterized by similar effectiveness but lacking the limitations of the well-established heparins (e.g., parenteral administration, risk of HIT type II), VKA (e.g., inter- and intraindividual pharmacokinetics, need of close monitoring, narrow therapeutic window, high potential for drug-drug and drug-food interactions, delayed onset of action, delayed offset of action due to long half-lives of 10 to 160 hours), and antiplatelet agents (e.g., resistance, metabolic activation, delayed offset of action due to active metabolites) [7, 20, 22].
A ‘perfect’ anticoagulant would have the following attributes: oral administration, simple dosing regime, fixed dosing, rapid onset and offset of action, predictable pharmacokinetics, wide therapeutic window, low potential for interactions, no need for routine monitoring, direct inhibition of a clotting factor (no need for a plasma cofactor such as antithrombin), no immuno-allergic reactions, high effectiveness, and good tolerance [22]. Very active research on novel agents is ongoing in this field.

Examples of agents in advanced stages of clinical testing (phase II/III trials) are edoxaban and betrixaban (direct oral factor Xa inhibitors), otamixaban (parenteral administered direct factor Xa inhibitor), bemiparin and semuloparin (newer ultra-low-molecular-weight heparins), tecarfarin (VKA), as well as the thienopyridin derivates cangrelor and elinogrel. Oral direct factor Xa and thrombin inhibitors are in the most advanced stages of development. It is likely that new antithrombotic drugs and new classes of antithrombotic drugs will be approved in the next few years and that their spectrum of indications will continuously be enlarged. Nevertheless, the aim of replacing VKA and LMWH might not be reached very soon due to the long-lasting, extensive, and well documented experience with these medications, their comparatively low prices, and lack of specific antidotes for the new antithrombotic drugs [7, 20, 22, 23].

Table 1 Approved anticoagulants and antiplatelet agents in Switzerland (2011) [20, 24, 25]

type of inhibition	**compound class**	**innovator drug**	**route of administration**
ORAL ADMINISTRATION			
indirect inhibition	vitamin K antagonists	**coumarin derivatives**	
		▪ **Marcoumar** (phenprocoumon)	oral
		▪ **Sintrom** (acenocoumarol)	oral
	antiplatelet agents	▪ **Aspirin cardio** (acetylsalicylic acid)	oral / (i.v.)
		▪ **Asasantin retard** (dipyridamol, acetylsalicylic acid)	oral
		▪ **DuoPlavin** (clopidogrel, acetylsalicylic acid)	oral
		▪ **Brilique** (ticagrelor)	oral
		thienopyridin derivates	
		▪ **Plavix** (clopidogrel)	oral
		▪ **Efient** (prasugrel)	oral
direct inhibition	factor Xa inhibitors	▪ **Xarelto** (rivaroxaban)	oral
		▪ **Eliquis** (apixaban)	oral

continued next page

type of inhibition	compound class	innovator drug	route of administration
PARENTERAL ADMINISTRATION			
indirect inhibition	factor Xa inhibitors	▪ **Arixtra** (fondaparinux; synthetic pentasaccharide)	s.c.
		▪ **Orgaran** (danaparoid; heparinoid)	s.c. / i.v.
	combined factor Xa and thrombin inhibitors	**unfractionated heparins**	
		▪ **Liquemin** (natrium heparinate)	s.c. / i.v.
		▪ **Calciparine** (heparinum calcicum)	s.c. / i.v.
		low-molecular-weight heparins	s.c. / (i.v.)
		▪ **Fragmin** (dalteparin)	
		▪ **Clexane** (enoxaparin)	
		▪ **Fraxiparine** / **Fraxiforte** (nadroparin)	
		▪ **Sandoparin** (certoparin)	
	antiplatelet agents	**glycoprotein (GP)-IIb/IIIa inhibitors**	
		▪ **ReoPro** (abciximab)	i.v.
		▪ **Aggrastat** (tirofiban)	i.v.
		▪ **Integrilin** (eptifibatid)	i.v.
direct inhibition	thrombin inhibitors	**recombinant hirudins / hirudin derivatives**	
		▪ **Refludan** (lepirudin)	i.v.
		▪ **Angiox** (bivalirudin)	i.v.

i.v. Intravenous; *s.c.* Subcutaneous

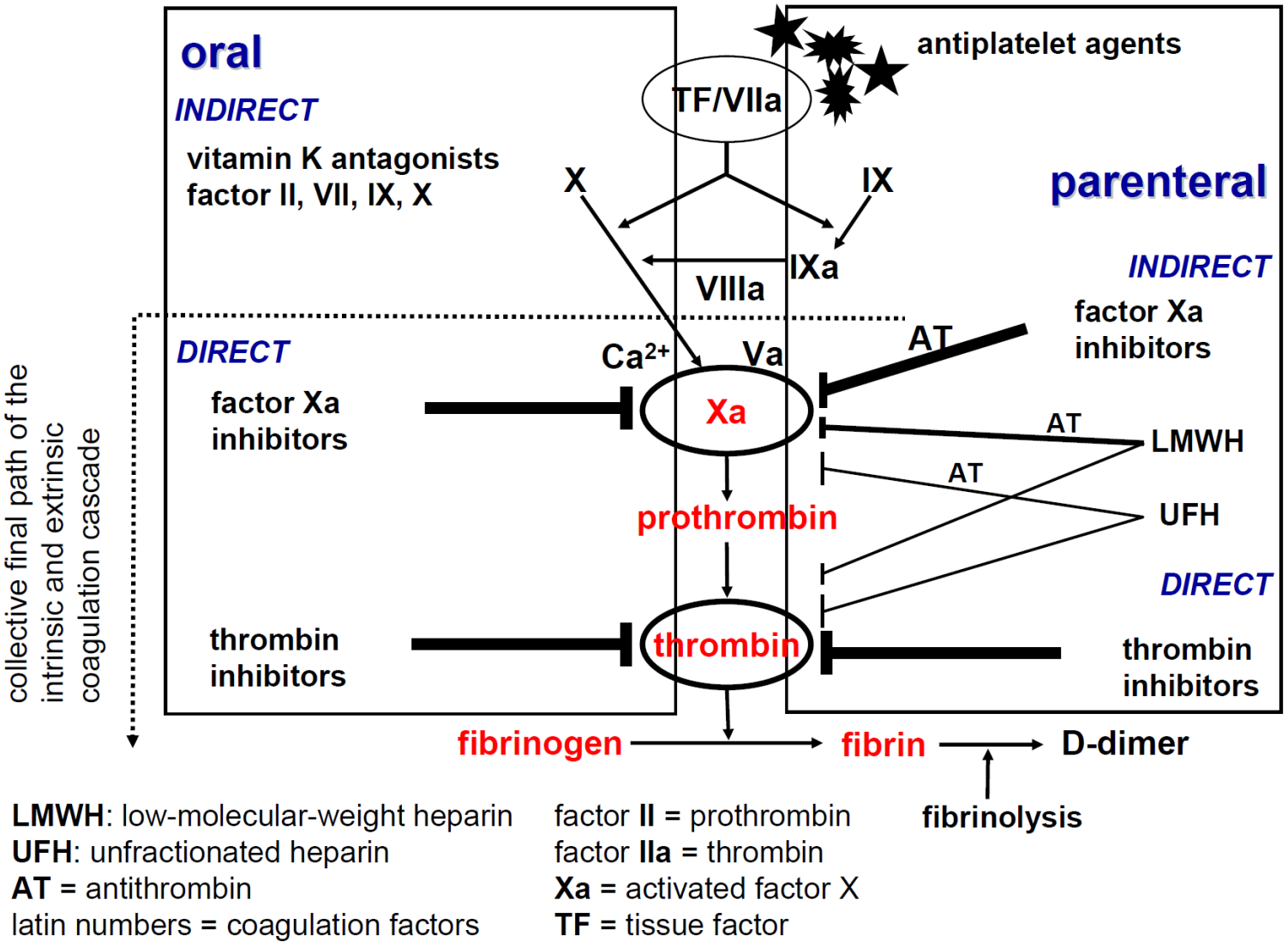


Fig. 1 Diagram of the plasmatic coagulation with the targets of the various anticoagulants and antiplatelet agents. Adapted from [26]

1.2 Subcutaneous injection therapy

1.2.1 Pre-filled syringes and related systems

Most biopharmaceuticals such as proteins, peptides, vaccines, antibodies, heparins, and antisense oligonucleotides are macromolecules. To date, most of these have to be administered parenterally (subcutaneous (s.c)., intravenous (i.v.), or intramuscular (i.m.)). Their oral bioavailability is marginal due to their characteristic large molecular size, high pre-systemic degradation, and physicochemical characteristics (e.g., hydrophilicity) [27].

International conferences on pre-filled syringes with key speakers from the pharmaceutical industry, manufacturers, and researchers emphasize the rising demand for pre-filled syringes in the recent years [28, 29]. It is estimated that 2 billion pre-filled syringe units worth up to 2.5 billion US dollars were sold in 2009. For both new and existing products, there is a trend away from vials/ampules and towards pre-filled injection systems (e.g., glass and plastic syringes, pens, auto-injectors, including refills). They are the format of choice for many parenterally administered drugs as they are ready-to-use. The sector has shown growth of 10-15% in recent years, forming one of the fastest-expanding sectors in the pharmaceutical industry. A broad range of compound classes are administered with pre-filled syringes or related systems, such as vaccines, monoclonal antibodies, hormones, anti-infectives, anti-inflammatory agents, hematological agents, erythropoietin products, obstetric agents, pain relievers, insulins, interferons, interleukins, or biosimilars. These devices are therefore used in the treatment of different diseases, including multiple sclerosis, rheumatoid arthritis, immunological disorders, diabetes mellitus, infectious diseases, cancer, osteoporosis, and hematological or hormone therapies. As the number of products licensed in pre-filled injectables increases, it is expected that the pre-filled drug delivery market will expand steadily and be worth up to 5.5 billion US dollars in 2025 [30]. The market for pre-filled syringes and related systems is also of interest to generic pharmaceutical companies: Filgrastim, for example, is used for the treatment of neutropenia due to chemotherapy or a human immunodeficiency virus (HIV) infection. Pre-filled syringes of Filgrastim are available from 4 different pharmaceutical companies [24].

1.2.2 Low-molecular-weight heparin devices

In Switzerland, all LMWH and fondaparinux are administered s.c. with pre-filled syringes (Fig. 2). Post-injection needle guards have recently been developed for the prevention of needle stick injuries and the transmission of infectious diseases such as hepatitis or HIV. These syringes increase comfort as correctly installed safety systems make sharps collectors no longer mandatory and the used syringes can be disposed of in the garbage. Post-injection needle guards are activated either mechanically using physical effort (Fraxiparine / Fraxiforte, Fragmin) or triggered automatically when the syringe has been emptied by pressing the plunger all the way down (Clexane, Arixtra) (Fig. 3).

The protective shield of Fraxiparine and Fraxiforte is securely locked once a clicking sound is heard after sliding it over the needle. The mechanism is poorly marked and positioning the guard properly requires considerable force and coordination. One has to be aware that patients are exposed to an increased danger of needle stick injuries when the needle guard is activated but has not been locked, as protection is assumed but not given.
Fragmin is equipped with a needle-trap: The red needle-trap is folded toward the side by 50-80 degrees prior to remove the needle cap. After the injection, the needle is secured by placing the trap on a firm surface using one hand. The trap is then pushed down and bent by more than 45 degrees until the needle locks into the red plastic part by a clicking sound.
While *keeping the thumb grip pressed* when withdrawing the needle from the skin fold, the protective shield of Clexane comes out and automatically covers the needle. In contrast, *releasing the thumb grip* of Arixtra withdraws the needle automatically from the skin and retracts it into the protective shield where it is locked. The safety systems of Clexane and Arixtra are only activated when the whole volume has been injected. Sandoparin is not equipped with any special safety system [31].

Fig. 2 LMWH and Arixtra pre-filled syringes in Switzerland (2011)

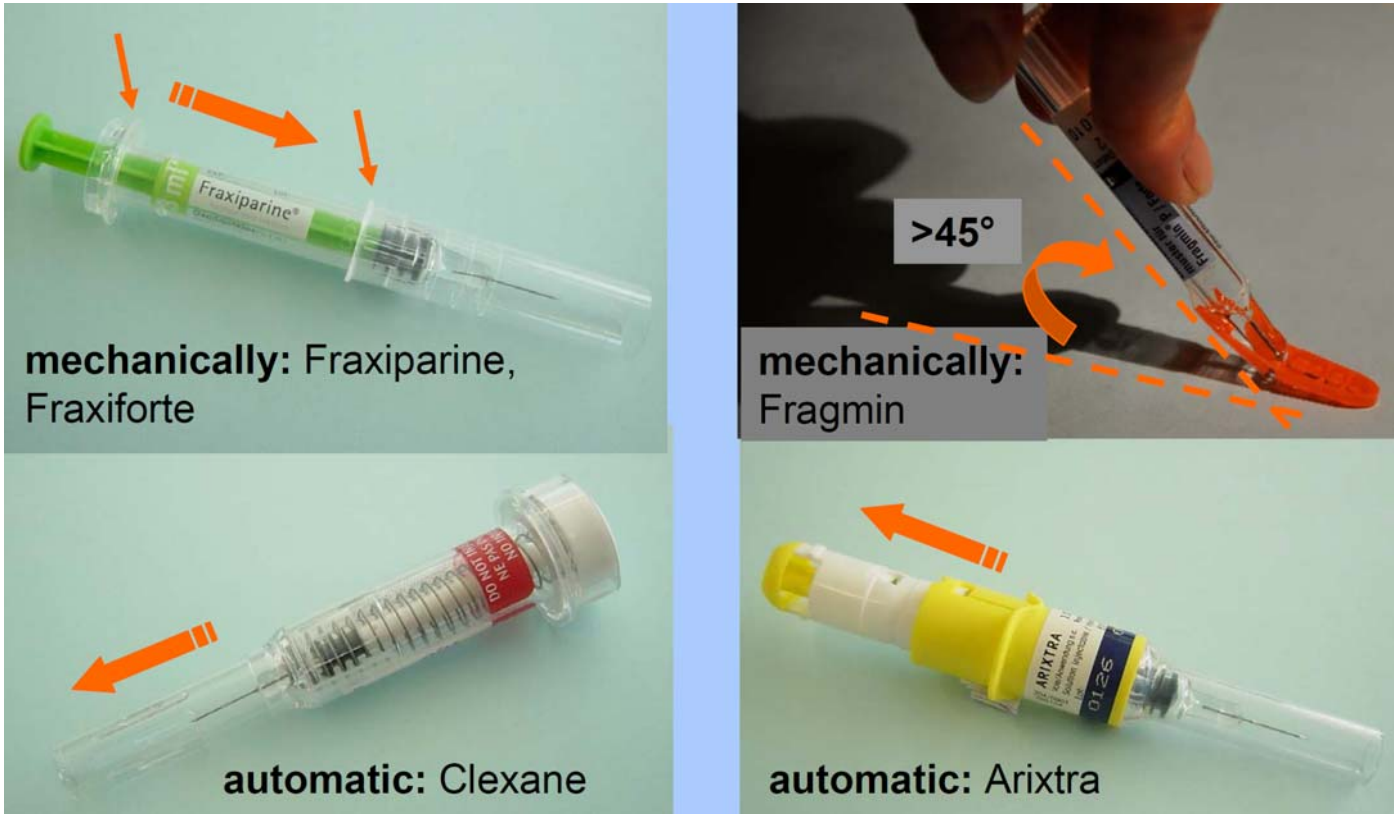


Fig. 3 Activated post-injection needle guards of used LMWH and Arixtra syringes

1.2.3 Subcutaneous injection technique

In the past, great effort has been made to analyze techniques and device characteristics which make an s.c. injection as comfortable as possible (e.g., air bubble, allowing the alcohol to dry before inserting the needle, skin fold, injection angle, aspiration prior to injection, injection duration, waiting before withdrawing the needle, application of ice or pressure at the site of injection; syringe and needle size, injection volume, changing the needle prior to injection) [32-34].

There is no consensus about the preferable injection site for the administration of LMWH. The abdominal skin has a thicker s.c. tissue, is easily accessible, and has a large surface area [33]. Nevertheless, there is a trend towards injections into the thigh, with the intention of reducing the risk of hematomas in the abdominal wall and rectus sheath ─ rare but regularly published complications after s.c. injections into the abdomen [35].

Beside the selection of the individual's appropriate injection site, a proper injection technique contributes to a safe and positive outcome. The individual steps of an s.c. injection can be divided into four aspects:

(1) to ensure that the injection is s.c. and neither intracutaneous nor i.m.: pinch a skin fold, insert the full length of the needle perpendicular into the skin (minimal injection angle of 45°), and release the skin fold after withdrawing the needle

(2) to ensure that the whole volume is injected: do not remove the air bubble (preferably place the air bubble above the fluid level), and wait a second before and keep the thumb grip pressed when withdrawing the needle (to ensure that no fluid is pulled out by an early discontinuation)

(3) to avoid needle stick injuries: put the sharps collector within easy reach, remove the needle shield horizontally using both hands, do not put down the bare needle, do not recap, and dispose of the syringe immediately after withdrawing the needle

(4) to ensure a hygienic injection: wash or disinfect the hands right before injection (and not in advance), disinfect the skin area (a single wipe is sufficient; very hairy skin can be cleansed by a single wipe each with the front and back sides of the alcohol swab; by rubbing, the contamination is

just moved around), wait for the alcohol to evaporate (skin not shiny anymore, i.e. allow the alcohol to react and in doing so, avoid burning), avoid contact with disinfected skin area (i.e. through clothes), do not put down or touch the bare, aseptic needle, do not wipe off a drop on the aseptic needle (but shake it off; leaving the drop might provoke burning), and puncture into the cleansed skin area

Other aspects contribute to patient comfort and to a reduction in adverse drug reactions, such as having the materials within easy reach, making an unhesitant puncture, slowly injecting, swabbing the skin area after injection (rubbing might provoke hematoma), and use of a plaster [31-34].

Self-injections in an outpatient setting are of increasing importance as they strengthen patient's responsibility for his/her own disease management, grant greater independence, and reduce costs by minimizing visits to the general practitioner (GP), hospital, or nursing service. It has been perceived that pharmacists can also play a crucial role in appropriate patient education, training, and support [36]. Good patient education has not only an impact on a proper injection technique, compliance, and clinical outcome, but is also of economic importance: Rebif (recombinant interferon beta) for example is prescribed for the treatment of multiple sclerosis. It is available as pre-filled syringe or auto-injector and can be administered s.c. on an outpatient basis. Following the usual treatment recommendations (injections three times weekly with 184 Swiss francs per pre-filled syringe), the overall costs amount to 28,704 Swiss francs per year [24].

1.3 Handling difficulties and drug use problems with medication

Reasons for handling difficulties and drug use problems with medication are diverse and may lead to dosing errors or non-compliance. They are either related to the medication, packaging, or device (e.g., small size, poor design, poor quality, bad markings, complicated to use, physicochemical characteristics handicapping proper administration) or to the patient's impairment (e.g., poor fine motor skills, impaired vision or hearing, cognitive impairment, deficiency in force). Force impairments might be caused by the patient's position when administering the medication, an injury, or illnesses such as arthritis, gout, diabetes mellitus, stroke, and Parkinson's disease.

With the continuous aging of the population and the promotion of outpatient therapies, the prevalence of handling difficulties and drug use problems with medication is likely to increase [37]. In particular, the use of pre-filled injection systems, inhalers, and spray bottles, the application of nose and eye drops, and the splitting of tablets are challenging [38-41]. These pitfalls have been recognized and led to the development of application aids (e.g., holding chambers or spacers, disk inhalers instead of metered dose inhalers, tablet-splitting devices, rotation aids for opening screw caps, dosing syringes, aids for positioning the eye drop, pill organizers) or the ergonomic optimization of existing devices (e.g., large font sizes, embedded magnifying glasses, or colour changes for the dosage display, larger devices, single-use or automatic pens, tactile signals (vibrations), acoustic feedback) [31, 38, 40-43].

The maximal pinch strength of women under 60 years of age is over 60 Newtons (N), men achieve approximately 100 N (1 N corresponds roughly to 100 grams). Maximal forces decrease with age, resulting in 40 N in men and less than 10 N in women aged 90 years or more [38, 42]. Forces needed to handle the medication, packaging, or device range from 4 to 80 N [38-40, 44].

As low-threshold facilities, community pharmacies are suitable for patient education, training, and support. Patients seeking assistance would rarely communicate their handling difficulties or drug use problems, but appreciate any help. Pharmacists play a crucial role in recognizing and preventing potential handling difficulties by offering an extensive first instruction, by monitoring patient's first self-administration, and by regularly monitoring patient's self-administrations under daily life conditions to ensure a proper technique. Thereby, the pharmacist can determine the patient's most appropriate device, and consult the GP if needed. To offer the best support, it is recommended that community pharmacies are always equipped with the latest placebo devices and education materials [38-41, 43, 44].

1.4 Pharmaceutical Care

Definitions

Pharmaceutical Care (PC) is defined as 'the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life' [45]. These outcomes aim at curing a disease, minimizing or eliminating symptoms,

arresting or slowing a disease progression, and at preventing a disease or symptoms. Suboptimal outcomes might arise from inappropriate prescribing, inappropriate delivery (e.g., drug not available, incorrect or no patient education), inappropriate patient behaviour (e.g., non-compliance, handling difficulties, drug use problems), patient idiosyncrasy, or inappropriate monitoring (e.g., no verification of effectiveness). A drug-related problem (DRP) is 'an event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care' [45]. They include untreated indications, no indication for treatment, inappropriate medication (i.e., no effect, better alternative with respect to patient characteristics or economic considerations), over- or underdosage, failure to receive the medication as intended (e.g., non-compliance, drug use problem, handling difficulties), adverse drug reactions, and drug interactions. [45-47].

Pharmaceutical care process

PC concentrates on the process of 'drug use', and is characterized by its dynamic and continuous nature. It involves cooperation between the pharmacist and the patient and aims at developing an individualized, patient-centered, and goal-oriented treatment plan to optimize safety and effectiveness. The PC process implies an active participation of the patient in making decisions concerning his/her treatment plan. It consists of four levels (Fig. 4):

(1) assessment of patient needs and identification of potential or actual DRP
(2) design and implementation of a care plan: provision of appropriate interventions and patient education to solve and prevent DRP as well as to achieve therapeutic goals
(3) patient action
(4) periodic outcome evaluation: monitoring of the progress in meeting therapeutic goals and reassessment for new DRP [45, 47-49]

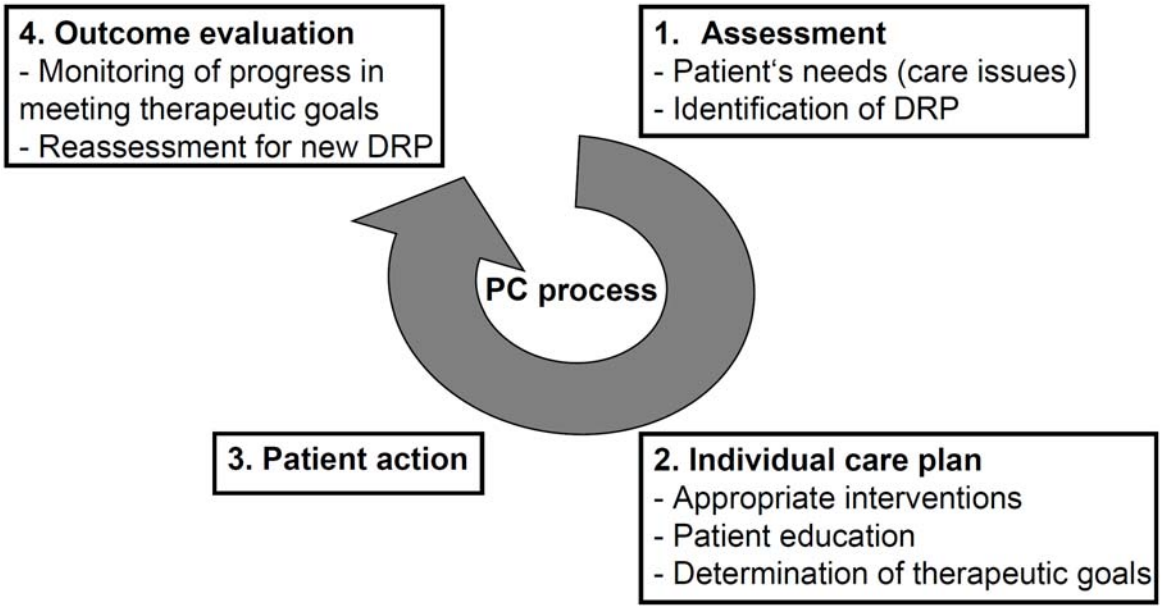


Fig. 4 The pharmaceutical care process ─ continuous teamwork between pharmacist, patient, and physician aiming at optimal patient outcomes regarding safety and effectiveness [45-49]
DRP Drug-related problems; *PC* Pharmaceutical care

Pharmaceutical care ─ a pharmacist's duty

The International Pharmaceutical Federation (FIP) and World Health Organization (WHO) have recently published the 'Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services' [50]. These guidelines comprise PC as a challenging duty of pharmacists, which goes beyond the conventional role of preparing and dispensing drugs. Clinical pharmacy includes PC and can be performed irrespective of the setting by either a hospital or community pharmacist [51]. Transitions between two settings, in particular discharge from hospital to the ambulatory setting, pose critical and vulnerable phases susceptible to DRP. As physicians often fail to communicate essential elements when prescribing new medications [52] and after discharge patients often visit their community pharmacy before seeing their GP, hospital and community pharmacists play important roles in ensuring the continuity of care through a seamless transition from inpatient to outpatient care [53]. The National Health Service (NHS) in the United Kingdom has perceived the need to act and commenced a New Medicine Service (NMS) in autumn 2011. This service provided by community pharmacists supports patients with long-

term conditions receiving a newly prescribed medication. Initially, the service is focused on particular patient groups and conditions, including the treatment with oral anticoagulants and antiplatelet agents [54].

Through the prevention and solution of DRP leading to increased safety and effectiveness, pharmacists may contribute to improved outcomes and to a reduction of costs [45]. An extensive review on the effectiveness of PC, however, revealed inconsistent results [55]. The multidisciplinary communication between pharmacist, patient, and physician is not only for the direct benefit of the patient, but may also promote closer collaboration between health-care professionals [45, 47]. Last but not least, one has to be aware that the provision of PC implies direct contact with the patient, and therefore cannot be offered by mail-order pharmacies [39].

1.5 Compliance

Definitions

A patient is compliant, if he/she administers or takes properly the correct medication at the prescribed time, in the prescribed dosage, over the prescribed therapy duration without unintentional combinations [43, 56]. Poor compliance is a worldwide phenomenon of striking magnitude with a prevalence of about 50%; the degree of non-compliance has been shown to be disease- and time-dependent [57-63]. Consequences of non-compliance are poor clinical outcomes, increased mortality, and increased health-care costs (e.g., emergency department visits, hospital admissions, intensified pharmacotherapy, increased morbidity, waste of medical time and waste of medication dispensed but not taken) [56, 60-67]. Table 2 gives an overview of the terminology used in the literature to describe patient involvement in decision-making about his/her treatment plan and his/her behaviour when following it.

Table 2 Definitions concerning patient involvement in decision-making about his/her treatment plan and their behaviour when following it

compliance	▪ Extent to which a patient follows the health-care professional's advice and takes the treatment [61] ▪ Characteristics: passive, obedient patient [61]; measurable
adherence	▪ Extent to which a person's behaviour ─ taking medication,

	following a diet, and/or executing lifestyle changes ─ corresponds with *agreed* recommendations from a health-care professional [62] ▪ Characteristics: refined definition of 'compliance', intending to break with the picture of the passive, obedient patient [43, 68]; measurable
concordance	▪ Agreement between the patient and health-care professional, reached after negotiation that respects the beliefs and wishes of the patient in determining whether, when, and how their medication is taken, and (in which) the primacy of the patient's decision (is recognized) [69] ▪ Characteristics: process of shared, informed decision-making; partnership approach [61]; not measurable
persistence	▪ Duration of time from initiation to discontinuation of therapy [70] ▪ Period of time being compliant [43]; measurable

Compliance behaviour

Ten types of non-compliance are known:

(1) 'parking place effect': non-acceptance of the treatment (no treatment or discontinuation shortly after filling the prescription) leading to no or reduced effect

(2) 'drug holiday': break in the persistence (e.g., due to economic reasons) leading to potential rebound effects or development of resistances

(3) 'toothbrush effect': a non-compliant patient becomes compliant shortly before the next visit with the GP potentially masking non-compliance (satisfying short-term laboratory-chemical markers, but suboptimal long-term values)

(4) compliant intake/use of a wrong medication

(5 ─ 7) dosing errors leading to reduced effects, potential toxic effects, or adverse drug reactions: over-, under-, or erratic dosage

(8) wrong administration frequency

(9) wrong therapy duration

(10) polypharmacy with additional, over the counter (OTC) medications leading to potential drug interactions [43, 56]

Potential barriers influencing compliance include:

- patient-related factors, such as age, lifestyle, knowledge, attitudes, beliefs, expectations, and mental or physical impairments
- social and economic factors, such as poverty and lack of social support
- health-care system-related factors, such as poor patient/health-care professional relationship, poor medication distribution, lack of knowledge of health-care professionals, short consultations, and lack of electronic information-technology systems (data sharing across health-care professionals and care settings)
- condition-related factors, such as severity of symptoms and degree of disability
- therapy-related factors, such as complex medication regimens, long-term treatment, previous treatment failure, and adverse drug reactions [62, 64, 65, 67]

In order to assess potential barriers and intervene adequately, it is essential to identify patient's beliefs about his/her treatment (Fig. 5).

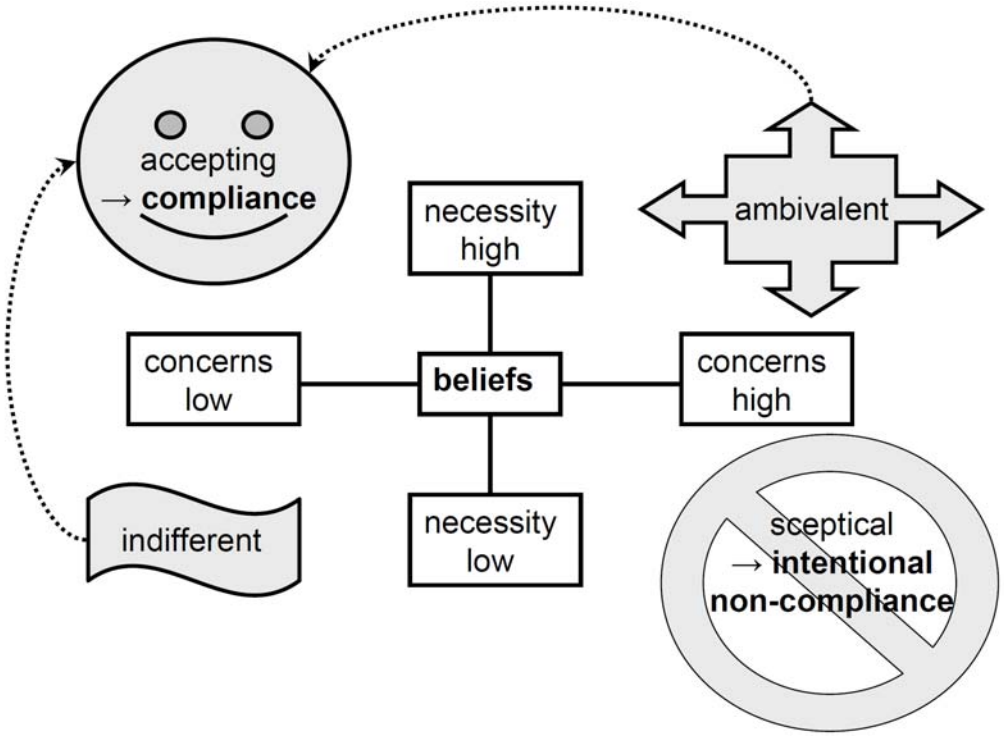


Fig. 5 Balancing the benefits (necessity of treatment) and drawbacks (e.g., concerns about adverse drug events, dependence) of a medication determine patient's likelihood to follow a treatment plan [71, 72]

Another classification of compliance behaviour is the differentiation between intentional and unintentional non-compliance:

- *Intentional* non-compliance is associated with patient beliefs and includes denial of the disease, refusal of the treatment, or changing of dosage without prior consultation [43, 56]. In the study of Jackevicius et al., for example, 87% of patients did not fill their first prescription for an injectable anticoagulant for the secondary prevention after acute myocardial infarction [73]

- *Unintentional* non-compliance is not planed and more diverse. It comprises forgetfulness, bad communication, complex treatment plans, or handling difficulties [43, 56]. Unintentional non-compliance seems to be three times more prevalent than intentional non-compliance with forgetfulness being a major factor [74].

Strategies to improve compliance

Strategies include multifaceted, patient-tailored interventions (Fig. 6), including patient information (oral and written) and education [75], communication skills, active listening, motivational interview depending on the patient's stage of self-change readiness [76], telephone follow-up, active patient involvement such as self-monitoring, use of application aids, electronic reminder systems, pill organizers, rewards for patients and health-care professionals for improved patient outcomes, collaborative team approaches involving multiple health-care professionals, and simplification of medication regimens (e.g., fixed combinations at the cost of flexibility concerning choice of drug substances and dosages) [43, 57, 60, 62, 64-67, 77].

Facing the wide range of factors potentially leading to non-compliance and their complex interplay, appropriate medication use remains a challenge for both patients and health-care professionals [60, 65] and to date, the effects of the interventions remain sparse [57]. Strategies to improve compliance should be considered by insurers, government payers, and patients, as long as intervention costs do not exceed the estimated health-care cost savings. Among others, pharmacist-led counselling has been perceived to be an appropriate approach [66, 67].

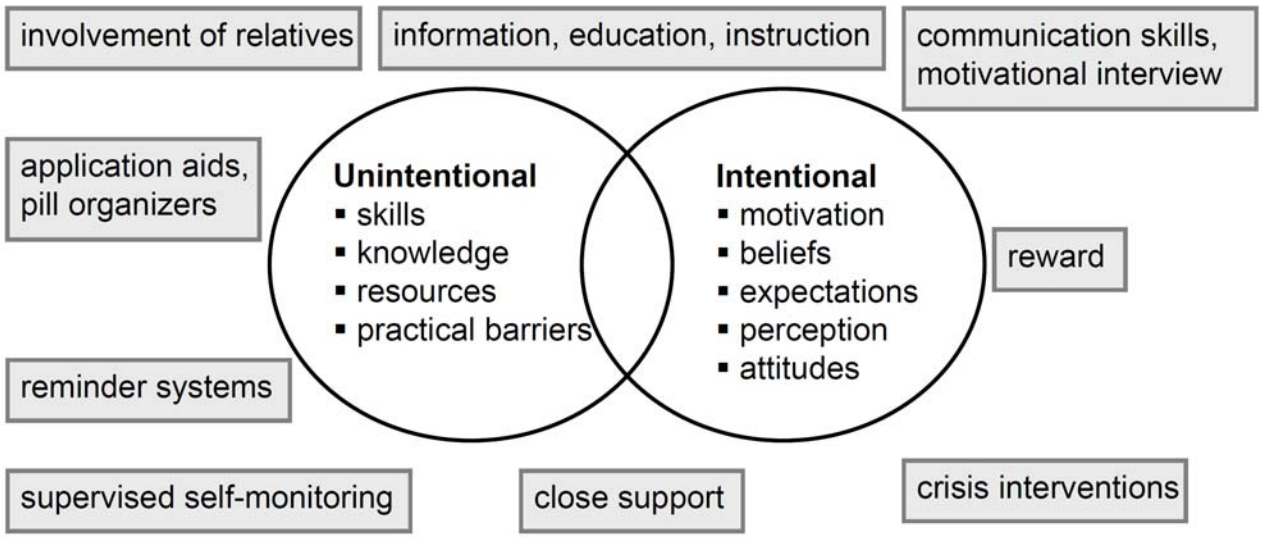


Fig. 6 Examples of patient-tailored interventions to counteract intentional and unintentional non-compliance [43, 56, 60, 62, 64, 65, 78, 79]

Methods to measure compliance behaviour

The response rates to treatments are individual (e.g., due to polymorphisms, non-responders), which limits the assessment of patient's compliance by clinical and laboratory-chemical markers (e.g., blood pressure, pulse rate, blood glucose, HbA1c, peak flow, international normalized ratio (INR)) [56].

Indirect measurement methods to assess patient's compliance comprise patient self-reports [80-82], use of diaries, 'pill count' or 'syringe count' (determination of 'taking' compliance by counting the number of residual tablets or by calculating the number of missing used syringes, respectively), determination of residual drug volumes in used syringes, examination for evidence of recent s.c. injections [83], attendance at appointments (visits with GP, (re)filling of prescription), or estimation of the effect. These methods are simple and mostly cheap at the cost of reliability [56, 62, 65, 68, 84]. Electronic compliance monitoring devices (ECMD) like medication event monitoring systems (MEMS®) record electronically the 'taking' and 'timing' compliance of a single medication. Electronic multidrug compliance monitoring (e-MCM) is a further development allowing the control of the intake frequency of several medications at a time [85]. The market for electronic pill organizers is growing rapidly. Some of them are equipped with acoustic or visual signals or generate a text

message [43, 62]. These new technologies, however, are very expensive and not applicable for pre-filled syringes.

Direct measurement methods to assess patient's compliance involve medication administration under supervision and the testing of blood or urine samples for agents, its metabolites, or marker substances (e.g., therapeutic drug monitoring (TDM)). The direct methods are more reliable on the one hand, but more time-consuming, expensive, and not applicable to all medications on the other hand [56, 62, 65, 68, 84].

To date, there is no established gold standard to measure compliance behaviour [62, 78, 84]. The method of choice depends on the type of non-compliance suspected. A multi-method approach combining self-reports and objective measures is the current state-of-the-art [62].

Therapeutic coverage

There is no universally valid adequate degree of compliance existing that would assure the achievement of definite outcomes. The required extent depends on the pharmacokinetic and pharmacodynamic properties of the individual medication. The time in the therapeutic window (= therapeutic coverage) is crucial. The half-life and duration of action determine if a medication is a 'forgiving drug' (e.g., acetylsalicylic acid) or a 'non-forgiving drug' (e.g., immunodepressants, HIV medication) [43, 56, 68, 86, 87].

1.6 Rationale and aims of the thesis

Pre-filled syringes are increasingly being used for the self-administration of various medications in ambulatory care. They constitute one of the fastest growing markets in drug delivery. One would expect that poor patient acceptance, including needle phobia, would impede successful use and that compliance could be a major issue. Literature on drug use problems and compliance with s.c. injection therapies in outpatients is rare. Previous studies have only investigated specific patient populations recruited from selected clinics or hospitals receiving educational programs. However, neither studies using a heterogeneous patient population

receiving standard care nor studies that were controlled or examined the feasibility of the interventions in daily life were identified.

Therefore, this thesis aimed to identify drug use problems and handling difficulties with pre-filled syringes and to evaluate the impact of pharmaceutical care on outpatient s.c. injection therapies. LMWH proved to be a convenient tool to meet our objectives: To date, they are prescribed frequently and mostly for short-term outpatient treatment; it is a comparatively cheap s.c. injection therapy with high application frequencies; and is used in a heterogeneous, relatively healthy population.

As key steps towards fulfilling these aims, we elaborated the following projects in this thesis:

Handling difficulties and drug use problems with pre-filled syringes

Handling difficulties and drug use problems with medication can either be attributed to patient impairments or to the medication itself, its packaging, or device. The consequences are suboptimal outcomes due to dosing errors and non-compliance. With the continuous aging of the population, the promotion of outpatient therapies, and the fast growing market for pre-filled syringes, handling difficulties and drug use problems are increasing in importance. In order to recognize and prevent DRP in the context of pharmaceutical care, it is crucial to get a detailed overview of their characteristics, prevalence, and variety.

Project A: Pitfalls in patient self-management of subcutaneous drug application: removal of rubber protection caps from ready-to-use syringes

The objective of this project was to investigate one single handling difficulty, which ─ to our knowledge ─ had not been reported in the literature so far. We aimed to compare subjectively and objectively measured pull-off forces required to remove the rubber protection cap (needle shield) of commercial LMWH pre-filled syringes.

Project B: Drug use problems with self-injected low-molecular-weight heparins in primary care

It was the aim of this project to record the spectrum of drug use problems, patient satisfaction, and patient compliance of pharmacy customers treated with LMWH under daily life conditions. The results should highlight potential areas for improvements in patient care through specific interventions. Additional aims were to identify differences in problems arising due to the choice of injection site (abdomen vs. thigh) and to determine residual drug volumes in the used syringes.

Outpatient low-molecular-weight heparin therapy

The provision of patient-centered, pharmaceutical services by community pharmacists are needed in order to justify their future role in the health-care system and to fulfill the community's expectations. The influence of pharmaceutical care on asthma, elevated lipid levels, hypertension, and diabetes has been investigated, but knowledge of the effectiveness of community-pharmacy-based interventions on problems in self-administering s.c. injection therapies is lacking.

Project C: Self-management of outpatient low-molecular-weight heparin therapy: impact of pharmaceutical care

Our aims in this study were:

(1) the development of a standard operating procedure (SOP) for the first instruction in the s.c. injection technique given by a community pharmacist and the subsequent pharmaceutical care provided during the outpatient LMWH therapy

(2) the comparison of intensive pharmaceutical care vs. standard care in both a clinical setting (hospital wards under study conditions) and in a daily life setting (community pharmacies following their daily routine)

2 Handling difficulties and drug use problems with pre-filled syringes

2.1 Project A:

Pitfalls in patient self-management of subcutaneous drug application: removal of rubber protection caps from ready-to-use syringes

Seraina Mengiardi[1], Beat Goepfert[2], Dimitrios A. Tsakiris[3], Kurt E. Hersberger[1]

[1] Institute of Clinical Pharmacy, University of Basel, Switzerland

[2] Laboratory for Orthopaedic Biomechanics, University of Basel, Switzerland

[3] Division of Hematology, University Hospital Basel, Switzerland

Eur J Clin Pharmacol (2009) 65:1061–1062

DOI 10.1007/s00228-009-0681-0

Sirs,

Outpatient subcutaneous therapies are becoming more and more common, such as the use of low-molecular-weight heparins (LMWH) for prophylaxis or for the therapeutic treatment of thromboembolisms, multiple sclerosis, arthritis, anemia, or female infertility. Based on reports from patients and nurses indicating that some ready-to-use syringes require a concerted effort to remove the rubber protection cap, we decided to evaluate cap removal forces of commercial LMWH pre-loaded syringes as we were unable to find an ISO-norm from such syringes nor studies on this topic.

Three methodological approaches was used: (1) self-assessment by a study population, (2) simultaneous observer's assessment, and (3) mechanical pull-off tests.

In parts (1) and (2) of our study, we analyzed Clexane (enoxaparin; old device), Fragmin (dalteparin), and Fraxiparine (nadroparin), three widely prescribed LMWH products in Switzerland. The study population included 68 persons (age range 19-86 years, median age 29 years), of whom 34 were pharmacy students, 18 were hospitalized orthopedic patients, and 16 were pharmacy customers. Persons with obvious disabilities of the upper extremities were excluded. One syringe of each brand within its expiration date was given to each of the subjects in randomized order. In part (1), subjects rated the force needed to remove the rubber protection cap using a visual analog scale (VAS). In part (2), the observer rated the effort needed to remove the cap as: (1) no effort needed, (2) effort needed, or (3) can not remove the protection cap. In part (3), the pull-off forces were investigated on a standard mechanical testing machine. The custom-designed holding fixture allowed an axial pull-off of the cap, measured in Newtons (N), at a constant speed without shear forces. In addition to the syringes used in parts (1) and (2), we enlarged the study sample with Arixtra (fondaparinux), Clexane (new device with an automatic safety system), and Sandoparin (certoparin), which meant that our study included the most important brands. Of each brand, 20 syringes within the expiration date were tested in randomized order (two different lots of ten syringes per lot).

The results of part (1) of this study revealed that the removal of the rubber protection cap was not possible in five of 204 cases involving four subjects and two brands. Figure 1a shows significant differences between the VAS scores (ANOVA $p<0.001$; Tukey-B-test $p<0.05$ for pairwise differences between the mean values) and high interquartile ranges caused by highly individual self-estimations. The observer's results from part (2) supported these findings (Fig. 1b). Measurements of the mechanical cap-pull-off forces (part 3) showed a large range of median forces (13.6–29.9 Newton) were needed to remove the rubber caps, with the highest forces needed for Fraxiparine and the old Clexane device (ANOVA $p<0.001$; Tukey-B-test $p<0.05$). Significant differences between different lots of the same brand were detected only with Fraxiparine (Fig. 1c).

In conclusion, the mechanical cap-pull-off tests confirmed the results from self- and observer's assessments, and important differences between brands were observed. The pull-off forces correspond roughly to the force needed to hold a narrow-neck plastic flask containing 1–3 l of water by pinching the neck between a finger and thumb. Medical staff should be aware of these possibly crucial handling difficulties and their consequences for successful therapy and compliance.

Tables and figures

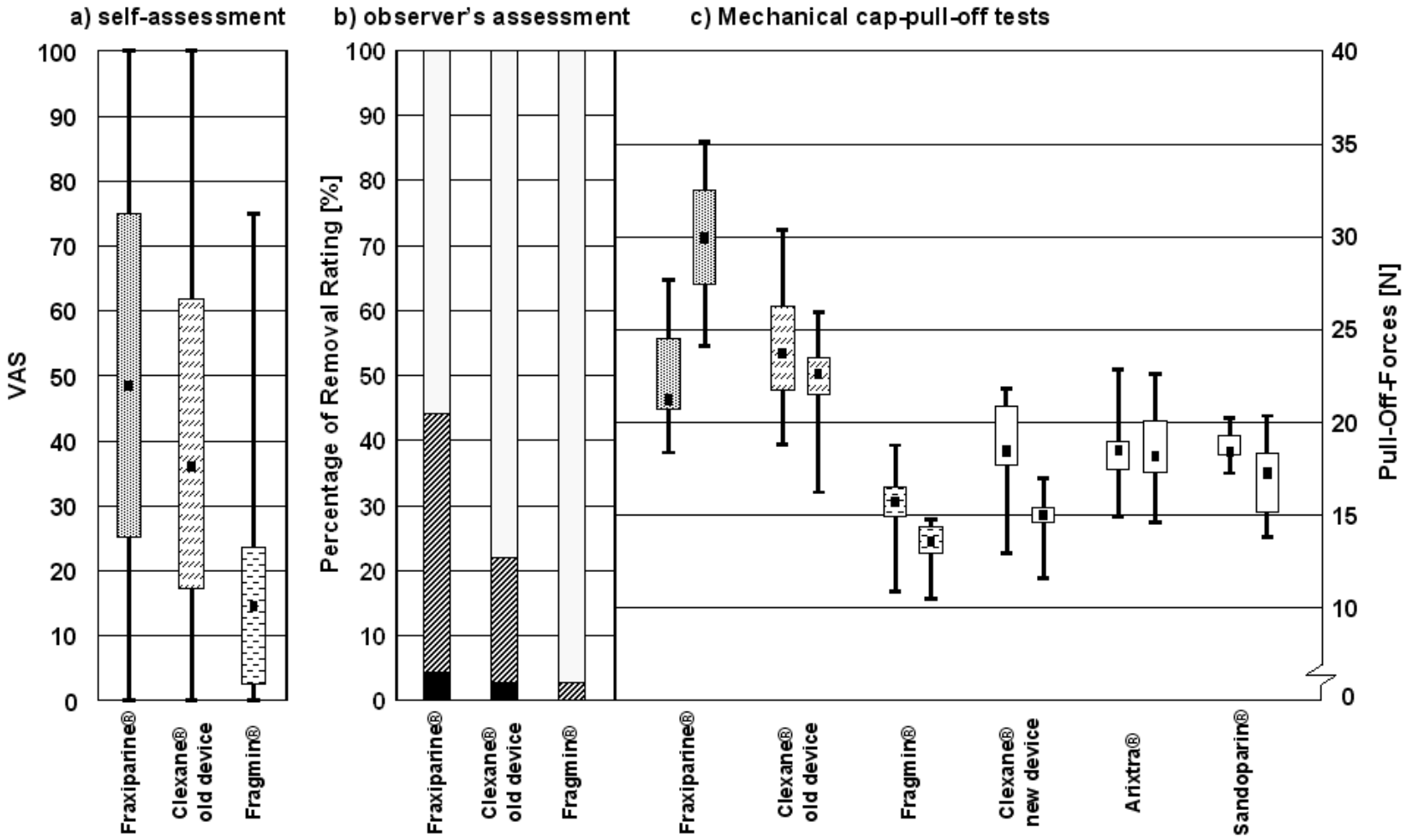


Fig. 1 Determination of the pull-off forces needed to remove the rubber protection caps from ready-to-use syringes.

continued next page

a Self-assessment using the visual anaolg scale: 0 = no effort/100 = enormous effort. Values are presented as the median and interquartile range (IQR): Fraxiparine 48.5 (49.75), Clexane old device 36.0 (44.5), Fragmin 14.5 (20.75).

b Simultaneous observer's assessment using three assessments (%): *black portion of bar* person can not remove the protection cap (Fraxiparine 4.41; Clexane old device 2.94; Fragmin 0), *portion of bar with diagonal stripes* person needs to make some effort (Fraxiparine 39.71; Clexane old device 19.12; Fragmin 2.94), *open portion of bar* person needs no effort (Fraxiparine 55.88; Clexane old device 77.94; Fragmin 97.06).

c Mechanical pull-off tests (N) performed by a standard mechanical testing machine; each *bar* indicates one lot including ten syringes. Values are given as the median and IQR

2.2 Project B:

Drug use problems with self-injected low-molecular-weight heparins in primary care

Seraina Mengiardi[1], Dimitrios A. Tsakiris[2], Markus L. Lampert[1,3], Kurt E. Hersberger[1]

[1] Pharmaceutical Care Research Group, University of Basel, Switzerland

[2] Division of Hematology, University Hospital Basel, Switzerland

[3] Clinical Pharmacy, Kantonsspital Bruderholz, Switzerland

Eur J Clin Pharmacol (2011) 67:109–120

DOI 10.1007/s00228-010-0956-5

Abstract

Purpose

Outpatient subcutaneous therapies are becoming increasingly common. A literature search failed to find any studies on application problems pertaining to the self-injection of low-molecular-weight heparins (LMWH) in a heterogeneous outpatient population under daily-life conditions. We therefore designed a study with the aim of recording drug use problems, patient satisfaction, compliance, problems arising from the injection site (abdomen vs. thigh), and residual drug volumes in pre-filled syringes used in self-injection therapy.

Methods

Patients were recruited in community pharmacies by 95 trained Master's students in pharmacy. Data were collected during recruitment and by means of structured questionnaire-based telephone interviews that were carried out at the beginning and the end of the LMWH treatment.

Results

The median age of the 213 patients enrolled in the study was 54 years (interquartile range (IQR) 39–70 years); of these, 15.5% had their injections administered by a third person. The rate of self-reported non-compliance was 17.1%. At least one relevant problem was recorded in 85.0% of the cases. At the end of the treatment, 38.9% of the patients stated self-administration of the injections required some effort. The preferred injection site was the thigh (68.5%). An overall mean residual drug volume ≥10.0% was detected for 3.9% of the patients. If residual drug was present, a median of 11.2% (IQR 8.6–17.6%) of the total drug volume had not been injected. Patients injecting into the thigh showed a higher risk of leaving residual medication (odds ratio 2.16, 95% confidence interval 1.04–4.51).

Conclusions

Most patients had drug use problems, whereas no clear factors were associated with non-compliance, the injection site (apart from residual drug), and discomfort or effort required (apart from prior injection use).

Keywords

Low-molecular-weight heparin · Outpatients · Drug use problems · Subcutaneous injections · Injection site · Community pharmacy

Introduction

Low-molecular-weight heparins (LMWH) are frequently used for the prevention and treatment of venous thromboembolism [3, 5, 18]. There is strong evidence demonstrating the good benefit-to-risk ratio and cost-effectiveness of venous thromboembolism prophylaxis [3]. Treatments with LMWH are often started during a hospital stay or at hospital discharge and followed up by daily subcutaneous (s.c.) self-injections in an ambulatory setting for a period of time varying from days to weeks. Results from published studies demonstrate that home treatment of deep vein thrombosis with LMWH is at least as safe and effective as inpatient treatment─and may save costs and increase patient satisfaction [88, 89].

Approaches involving outpatient s.c. therapies for the treatment of different diseases are becoming increasingly common. In addition to being used for the injection of the LMWH, *pre-filled ready-to-use syringes* are readily available for the treatment of multiple sclerosis (e.g., interferons), arthritis (e.g., methotrexate, tumor necrosis factor alpha blocker), anemia (e.g., erythropoietin), cancer (e.g., interferons), female infertility (hormones), hepatitis B and C (e.g., interferons) as well as for contraception (medroxyprogesterone acetate). Additional devices are *pens*, which are used by diabetic patients (insulin, exenatide) or for migraine treatment (e.g., sumatriptan), *injectors*, which are often used in the treatment of osteoporosis (recombinant parathyroid hormone analogue), or *vials/ampules*, where preparation is needed before injection (e.g., female infertility, cancer, multiple sclerosis and enfuvirtide in HIV treatment). A search of the literature failed to identify studies focusing on drug use problems and/or the practical aspects of s.c. self-administration beside the LMWH in an outpatient setting. Rather, most of the studies on the self-injection of other agents concentrated on other aspects of this therapeutic approach, such as pharmacokinetics, effectiveness, safety, and patient satisfaction.

Discussions on the preferred injection site are ongoing, especially with LMWH [90-93]. Case reports of hematomas in the abdominal wall and rectus sheath due to s.c. injections into the abdominal wall are rare, but appear regularly in the literature [94-102]. Risk factors seem to be advanced age, female gender, polymorbidity, renal impairment, cough, therapeutic LMWH dosages, and concomitant use of anticoagulants. There is no expert consensus on the preferable injection site, often

not even within one hospital. Patients who have already received LMWH treatment in the past are especially irritated when they receive a complete new set of instructions. Even more confusing is the wording for the abdomen and thigh injection sites: for example, eight different terms pertaining to the abdomen and five descriptions of the injection in the thigh were found in Swiss package inserts and leaflets. Expressions such as “ventral, collateral region of the abdomen” or “outer upside of the thigh” are difficult to visualize, especially by the layperson. The injection sites “back of the upper arm” or the “gluteal area” are rarely used, as these sites are unsuitable for self-injections. In addition to the injection site, a proper injection technique contributes to a safe and positive outcome, i.e., injecting slowly into a skin fold to reduce site pain and bruising [32, 33] as well as to ensuring that the injection is subcutaneous and not intramuscular.

Little information on drug use problems and compliance with LMWH treatment in outpatients is available in the literature [83, 103-105]. Previous studies only investigated orthopedic patients recruited from selected clinics or hospitals. All of these study participants received educational programs that included instruction in the injection technique, performing their first self-injection in the presence of a medical professional (nurse or physician), and (occasionally) written information material or a video tape. Study sizes ranged from 40 to 214 patients. However, we were unable to find any study involving a heterogeneous patient population receiving standard care.

We therefore designed a prospective cross-sectional study using pharmacy customers treated with LMWH as a convenient representative population receiving s.c. therapies with pre-filled syringes under daily life conditions. Our aim was to record drug use problems, patient satisfaction, and patient compliance. The results should highlight potential areas for improvements in patient care through specific interventions. The secondary aims were to identify differences in problems arising due to the choice of injection site (abdomen vs. thigh) and to determine residual drug volumes in the used syringes.

Methods

Setting and study population

Patients were recruited sequentially in community pharmacies by pharmacy students during their internship. Between January and May 2008, 95 Master's students of the two German-speaking universities of Basel and Zurich were instructed to recruit and interview ambulatory LMWH patients. In advance, the students received: (1) a detailed oral study briefing and written information; (2) documents for data collection; (3) instructions in the s.c. injection technique, including clinical training by nursing staff.

A broad range of inclusion criteria was deliberately chosen with the intention of reaching a varied sample of LMWH patients reflecting all aspects of daily life: outpatients aged ≥18 years, all brands of LMWH (pre-filled syringes), prophylactic or therapeutic use, new or long-term prescription, first or previous outpatient s.c. treatment, all therapy durations, self-injection or application by another person (e.g. family member, nursing service), and no comprehension difficulties due to language.

Data collection

Routine prescription validation by each community pharmacy (standard care) was performed when a LMWH was requested. The study was explained to the person bringing the prescription (the patients themselves or another person) and instructions were given on the s.c. injection technique if required. If the patient met the inclusion criteria and oral consent was obtained, written patient information and a sharps collector (E-safe) for the used syringes were delivered.

Telephone interview

At a pre-arranged date—either 1–3 days after the prescription was filled or at start of the LMWH treatment—an extensive structured questionnaire-based telephone interview was carried out. The trained students filled in the questionnaire by interviewing only the patient, even if the injections were carried out by another

person. The survey consisted of open questions wherever possible, and patients' spontaneous answers were recorded. Multiple answers were accepted, but no answer suggestions were allowed. The reason for carrying out this telephone interview at an early point in the LMWH treatment was to evaluate drug use problems, the amount of effort required to self-inject, and discomfort at the beginning of the treatment. Self-estimations were assessed on two different scales: (1) an 11-point scale to rate discomfort (0=very uncomfortable; 10=very comfortable) and (2) a 4-point scale to assess the degree of effort required (1=no effort required at all; 2=nearly no effort required; 3=sometimes effort required; 4=considerable effort required) and drug use problems in general. In addition, the interview gathered information on patient and medication characteristics, self-management, knowledge, quality of care, and patient satisfaction. If participants confirmed being impaired in their daily activities due to any kind of problem, pain, injury, or illness associated with the arm, shoulder, or hand, we rated the patient as being impaired in fine motor skills.

Final interview

After completion of the s.c. therapy, a short, structured questionnaire-based interview was carried out with each patient when he/she returned the sharps collector to their community pharmacy for professional disposal. The questions focused on the amount of effort required to maintain the treatment (none at any time; only in the beginning of treatment; occasionally; during the whole treatment period), on discomfort at the end of treatment, and on self-reported non-compliance. Exactly when this short interview took place depended on each individual's treatment duration. Patients were instructed to return their sharps collector after 6 weeks if the treatment period was longer.

The data collection was anonymized by assigning a code to each patient. Participants were asked to give oral consent each time they were contacted. The study protocol was approved by the local Ethics Committee of Basel (EKBB 95/07).

Analysis of used syringes

The returned sharps collectors were examined for the following: identification of patient code and syringe type; number of used syringes; number of syringes with

recapping (illegitimate replacement of the needle shield─sometimes called needle cap─after injection); number of syringes with a visible residual drug volume; amount of residual drug volume; number of syringes with a correctly installed safety device for the prevention of needle stick injuries after injection.

Because the residual drug had often evaporated (especially in syringes without recapping), its volume could only be reliably determined by measuring the distance between the plunger and the end of the syringe barrel. Accordingly, the residual volume could be estimated by comparison with an unused syringe of the same type (taking the air bubble into consideration). To obtain this reference distance, we calculated the mean values of at least three syringes of each type. The mean residual drug volume (as a percentage) was defined as being equal to the calculated mean residual distance (percentage). Unused syringes were not included in this analysis. We considered a residual drug volume to be relevant if ≥10.0% of the total volume remained in the syringe.

Statistical analysis

The interview data sheets were processed with the automated form-processing software TELE*form* ver. 10.2 (Cardiff Software, Vista CA). To avoid potential errors, we verified the data transfer by visually comparing the written sheet and on-screen data. All data were then checked for plausibility by the first author. Free-text answers and comments were recorded separately and grouped during the plausibility-process by the first author. Missing data were complemented in the database according to the annotations if possible. Statistical analysis was performed using SPSS for Windows ver. 17.0 (SPSS, Chicago, IL).

In the descriptive analysis, medians and interquartile ranges (IQR; 25th to 75th percentile) were calculated. Pearson's chi-square test was used to investigate possible associations between two variables in a four-fold table. For unrelated group analyses, the non-parametric tests Mann-Whitney and Kruskall-Wallis were chosen. Analog tests for normal distribution (Student's *t* test, analysis of variance (ANOVA)) were employed if the results differed. Statistical significance was set at $p \leq 0.05$.

Results

Of the 402 people approached by the pharmacy students when they went to a community pharmacy with a prescription for LMWH, 223 agreed to participate in the study and 144 completed the study (Fig. 1). Drop-outs did not differ from study completers in terms of age (p=0.37, Mann-Whitney test), sex (p=0.93, chi-square test), previous outpatient s.c. injection therapies (p=0.76, chi-square test), injections administered by another person (p=0.06, chi-square test), little instruction (no oral instruction in the injection technique or only by the pharmacy; p=0.66, chi-square test), the degree of effort required (p=0.56, Mann-Whitney test), discomfort (p=0.91, Mann-Whitney test), or fine motor skills (p=0.40, chi-square test). Patient and medication characteristics are listed in Table 1.

Table 2 summarizes patients' self-reports on application problems, self-management, knowledge, non-compliance, and quality of care experienced (including patient satisfaction). We defined drug use problems to be relevant when: (1) patients were insufficiently informed about the injection site or technique; (2) injections were administered by another person; (3) recapping was carried out; (4) difficulties with removal of the needle shield existed; (5) there were discrepancies with prescribed therapy duration, daily injections, and injection time. At least one of these problems was reported in 181 (85.0%) patients. The community pharmacy instructed 10.8% of the patients in the injection technique.

Self-reported non-compliance showed no association with age (p=0.85, Mann-Whitney test), previous outpatient s.c. injection therapies (p=0.94, chi-square test), injections administered by another person (p=0.18, chi-square test), the degree of effort required (p=0.53, Mann-Whitney test), little instruction (p=0.23, chi-square test), discomfort (p=0.15, Mann-Whitney test), or fine motor skills (p=0.24, chi-square test). No significant associations were seen between the estimations of effort required and discomfort experienced with the variables first self-injection under the supervision of a medical professional (p=0.62 and 0.56, respectively; Mann-Whitney test), little instruction (p=0.66 and 0.22, respectively; Mann-Whitney test), injections administered by another person (p=0.32 and 0.83, respectively; Mann-Whitney test), or the injection sites abdomen versus thigh (p=0.60 and 0.91, respectively; Mann-Whitney test). Patients with experience gained from previous outpatient s.c. injection

therapies had less discomfort and the injections required less effort (p=0.011 and 0.022, respectively; Mann-Whitney test). Comfort/confidence with the injections and the degree of effort required showed a Spearmen's correlation coefficient of r= –0.5 (p<0.001).

Of the 144 patients completing the study, 126 estimated their comfort and effort required at the beginning and at the end of treatment (18 patients did not assess these parameters at the final interview as the injections were administered by another person). At the beginning of the therapy, 75.4% estimated their confidence with self-injecting as high (scale levels 8–10), while 32.5% reported that the injection required some effort. At the end of treatment, the corresponding values were 81.7% and 38.9%, respectively. Comfort and effort required did not change significantly over time (p=0.08 and 0.13, respectively; McNemar test). Nine (7.1%) persons stated that the injections required effort throughout treatment, resulting in complete non-compliance in one case. Ten of the 126 patients sometimes had their injections administered by another person.

A comparison of the abdomen and thigh injections sites revealed no significant associations between puncture (p=0.14, Mann-Whitney test) or injection (p=0.38, Mann-Whitney test) being unpleasant or painful and the side effects hematoma (p=0.50, chi-square test), mild injection site irritation (p=0.34, chi-square test), and site pain (p=0.24, chi-square test).

When only patients who always or sometimes self-administered the LMWH were considered (n=187), significant differences between the level of difficulty encountered in removing the needle shield were found between the different brands of syringes needle shields (p=0.037, Kruskal-Wallis test). Based on pairwise differences, the needle shield of Fragmin was rated as significantly easier to remove than those of Clexane and Fraxiparine (p=0.021 and 0.003, respectively; Mann-Whitney test).

Post-injection needle guards were only found with Fraxiparine and Fraxiforte devices. The needle guards of all syringes in the sharps collectors were correctly positioned by 22 (32.8%) of the 67 patients injecting Fraxiparine or Fraxiforte (missing data: n=5); 24 (35.8%) patients activated the safety device only partly, and 21 (31.3%) patients did not use the needle guards at all or not properly (the protective guard is only securely locked in place once a clicking sound is heard after sliding it over the needle).

The sharps collectors of 180 patients contained a total of 3,218 syringes (median 10.5, IQR 8–26; range 1–100) (Fig. 2). The pre-filled syringes had volumes of 0.2–1.0 ml and distances between the plunger and the end of the syringe barrel of 17.0–38.4 mm (including the air bubble). An overall mean residual drug volume ≥10.0% was detected for seven (3.9%) patients (median injection volume 0.6 ml). The highest overall mean residual drug volume was 17.9%, and was recorded for a patient who had injected 13 syringes of 0.8 ml.

When only those syringes with residual amounts of LMWH were considered, a median of 11.2% (IQR 8.6–17.6%) of the liquid remained in the syringe. In other words, if their syringes were not empty, 58 (59.8%) of the 97 persons affected had ≥10.0% of the total volume not injected (Fig. 3). Comparisons between these 58 patients and the remaining 122 participants showed no differences in age (p=0.61, Mann-Whitney test), sex (p=0.72, chi-square test), fine motor skills (p=0.53, chi-square test), previous outpatient s.c. injection therapies (p=0.74, chi-square test), injections administered by another person (p=0.48, chi-square test), injection volumes (p=0.53, Mann-Whitney test), the different brands (p=0.09, chi-square test), or number of used syringes as an indication of therapy duration (p=0.14, Mann-Whitney test). However, the 58 patients injected significantly less into the abdomen (p=0.021, chi-square test) and significantly more into the thigh (p=0.019, chi-square test; odds ratio 2.16, (95% confidence interval (CI) 1.04–4.51)).

Optional free-text comments provided deeper insights into the nature of the drug use problems. Handling difficulties were reported by 33 patients (15.5%); the most important of these are listed in Table 3.

A student observed that the majority of his pharmacy customers' complaints were at the beginning of treatment. In contrast, one patient's concerns increased towards the end of a 4-week treatment. Another person would have even changed from self-management to injections by another person if the therapy duration was longer than the actual 6 weeks. One patient injecting into the thigh had more side effects when injecting 0.6 than 0.4 ml.

Two patients showed restraint in injecting into the thigh; one chose the abdomen instead, and the second asked another person to administer the injection. One person noticed that hematoma generally developed more often when injecting into the abdomen.

The support offered was not always satisfying and highlights possible areas for improvement in patient care (Table 4).

Discussion

With respect to outpatient s.c. therapies, drug use problems appear to be very prevalent, diverse, and complex. They may be associated with the injection itself or with the handling of the injection-device. Notably, among the participants in our study, 85.0% experienced at least one relevant problem, with recapping being the most frequent difficulty encountered: 73.7% of the patients replaced the needle shields after injection, which is against recommended practice. At the end of the therapy, almost 40% reported that the injection required some effort, and 17.1% admitted non-compliance. Medical professionals are unable to ascertain potential patient problems in using medication at first glance. As a result, any outpatient s.c. therapy poses a challenge not only for the patients themselves and their family/friends, but also for health professionals. Therefore, adequate patient care and education are crucial and should be optimized.

In our study, 15.5% of patients had their injections performed by another person (75.8% of these by family members or friends); of these, 51.5% of patients reported that this was due to needle phobia or a fear of puncturing the skin. A review of the literature shows a 13–37% non-self-injecting rate [83, 103-105], and in 46.9–66.0% of these cases family members administered the injections [103, 105]; 75.0% of those who refuse to self-inject report that it is due to fear [103]. This fact should be considered when designing patient education programs. If injections are given by a family member, this person should be properly instructed. Consequently, physicians, hospitals, and community pharmacies should always be equipped with the latest leaflets.

There were no associations between patient characteristics and outcome measures with effort required or discomfort, with the exception of previous experience in self-injecting. A possible explanation for the absence of associations could be the heterogeneity of the study sample. Discomfort and effort required did not change notably over time. The level of comfort with the procedure was quite high in general,

with one reason probably being the fact that 41.8% of the patients already had experience of outpatient s.c. injection therapies (this patient group was significantly more confident and felt less effort was needed).

Important differences concerning difficulties with the removal of the needle shield between different LMWH brands were observed, which confirms the results of a previous investigation [106]. Only one third of patients injecting Fraxiparine or Fraxiforte applied the needle guards of all their used syringes accurately, and one third did not use them at all or used them improperly. Ironically, the danger for needle stick injuries increases when the needle guard is positioned but not locked in position, as protection is assumed but not provided. There is certainly room for improvement in this area through better patient information and education, particularly as correctly fitting the guard requires considerable force and coordination and the mechanism is poorly marked. Clexane and Arixtra have pre-filled syringes equipped with new automatic safety devices; the protective shield is triggered when the syringe is empty. In addition to preventing needle stick injuries, the Clexane and Arixtra syringes ensure that the whole amount is injected. In our study, there were no patients prescribed with Arixtra, and the new Clexane device and the new Fragmin Needle-Trap were not yet on the market in Switzerland.

Whether additional drug use problems were also mentioned by the participant when he/she was answering the questions posed during the telephone interview depended on the participant's openness for further conversation. It can be assumed that these anecdotic application problems would have been noted more frequently if they were asked for systematically. An example is the single statement of one participant about having more side effects when injecting 0.6 than 0.4 ml into the thigh, which confirms the results from another study [107]. Thus, it is likely that not all problems were revealed, and those that were may be more multifaceted than previously imagined.
Prescriptions were often incomplete with regards to therapy duration (27.7%), number of daily injections (12.7%), and injection time (73.7%). Missing written information makes patient care demanding. The probably unintentional single under- or overdoses due to a shift in the time interval of 10–12 h in comparison to the prescribed injection time occurred at a sensitive and susceptible moment after hospital discharge or at the beginning of treatment in the ambulatory setting. It can

be expected that this was a much more common occurrence than the five observed cases, as the injection time was not given by 73.7% of patients. As such time-shifts generally happen unknowingly, patients would not have mentioned it when assessing their own compliance.
Concomitant self-medication with non-steroidal analgesics did not seem to play an important role, although only 25.8% of the participants knew about potential drug interactions with LMWH. The participants also showed a lack of knowledge of potential side effects. Overall, the assistance provided was appreciated by patients, but the amount of help needs to be increased.

Two thirds of the patients injected into the thigh and one third into the abdomen. Associations with local side effects or the puncture hole and injection being painful were not significant. In additional free-text answers, however, a number of patients mentioned problems comparing the two injection sites. The literature also seems to be ambiguous on this point: a Brazilian study reported that hematomas were observed in 83.7% of patients and that the incidence of hematomas was higher if the LMWH injections were administered into the thigh [108]. In contrast, in a special series of patients following standard herniotomia, hematoma appeared in 25% of the cases when the patients injected into the abdomen and in 9% when they injected into the thigh [93]. Other investigations comparing local side effects of LMWH according to the two injection sites were not found. In a study with s.c. injections of enfuvirtide, injection site reactions were common but mild, and their incidence was higher with injections into the abdomen than into the thigh or arm [109]. Patients using a sumatriptan self-injector experienced more bleeding and local pain when injecting into the thigh compared to the gluteal area; only 15% preferred the thigh as injection site [110].

Every sixth person (17.1%) admitted to having skipped injections. In similar studies, non-compliance rates of 4.5–28.3% with different definitions of non-compliance were found [83, 103-105]. The main reason in the study of Spahn was forgetfulness (94.1%), while 13.1% of the patients discontinued early; all patients younger than 20 years were classified as unreliable and compliance was dependent on whether injections were self-administered [103]. Our study showed a wider variety of reasons for non-compliance, with the most important being forgetfulness (44.0%) and early

discontinuation (24.0%). We were unable to identify possible risk factors for self-reported non-compliance, possibly because only 25 patients actually admitted having skipped injections, or the diverse reasons for non-compliance.

Our original objective of determining patients' taking compliance by comparing the number of used syringes with the prescribed therapy duration turned out to be impossible. In 36.2% of the final interviews, the date of the last injection was not provided, and in 27.7% and 12.7% of the prescriptions, respectively, therapy duration and application frequency were not specified. In addition, terms such as "treatment until complete mobilization/international normalized ratio twice in therapeutic range/next visit with physician" did not enable the date of the last injection to be estimated reliably. Furthermore, the prescription date did not necessarily correlate with the day of discharge or start of LMWH treatment. Similarly, a patient could be fully compliant despite a delay in filling the prescription as─particularly on weekends or public holidays─syringes are often dispensed by hospitals or physicians to ensure therapeutic coverage. For various reasons, all used syringes were not discarded into the sharps collector: delayed delivery of sharps collector, injection with physician during consultation, not being at home, flights, holidays, and delivery of syringes by the hospital or physician.

The determination of the residual drug volumes enabled us to partially objectify patients' compliance: residual drug volumes were found rather sporadically, and almost half of the patients had no residual drug in any syringe. The overall mean residual drug volume was low and negligible, but the total injection volume seemed to have an influence, possibly as a result of rising tissue resistance due to the injection of higher volumes. This has a particular impact when LMWH are used for the treatment of thromboembolisms as higher volumes are administered and patients are at greater risk. If residual drug was present, however, it tended to be of pharmacological relevance. It can be expected that some of these injections were stopped early on purpose.

Patients injecting into the thigh showed a higher risk of leaving residual volumes, which may be due to the smaller area of s.c. tissue in the thigh compared to the abdomen. We therefore recommend that patients injecting high volumes or injecting into the thigh be advised to monitor closely whether the syringe is empty and be aware that they might need more force towards the end of the injection. Other risk factors for residual volumes could not be identified. Sufficient evidence was not

collected on this aspect, probably because the therapy durations were mostly short, with a median of 10.5 syringes in the sharps collectors. It has also to be taken into account that almost half of the patients (47.2%) had to inject only small volumes of ≤0.3 ml, and a minority of 9.4% injected volumes of ≥0.7 ml.

The strength of our study is the heterogeneous study population, covering a broad spectrum of drug use problems and reflecting daily life activities. Not only comparatively healthy patients participated in our study (e.g., those with a foot injury, long-distance travelers), but also seriously ill persons, such as patients with pulmonary embolism, lung transplantations, or paraplegia. However, categorization of such a study population is difficult. The community pharmacies were distributed more or less throughout Switzerland, which ensured that possible regional differences in the quality of care on the part of the physicians, hospitals, and community pharmacies were taken into account.

The main limitations of our study are the data collection by 95 students, a consent rate of only 55.5%, and a possible bias due to patient selection. Polymorbid or cumbersome pharmacy customers were less likely asked to take part in the study, whereas regular or pleasant customers were more often invited to participate. Furthermore, interested and motivated patients are more likely to participate in a study and to be more compliant, reflecting daily life in a much too positive way. Another weakness is the dropout rate of 32.4% at the final interview, setting constraints on the conclusions that could be drawn on self-reported non-compliance and the estimations of comfort or effort required in the course of the therapy duration. As no prescription duplicate was requested and data collection was anonymous, no retracing or access to medical history was possible. Therefore, the results are based on patients' self-reports only. Our determination of the residual drug volume by measuring the distance between plunger and the end of the cylindrical body was the most reliable measurement, but the approach has limitations: as the liquid had often evaporated, we were unable to recognize whether we were measuring only missing liquid or the missing liquid together with the air bubble. Thus, the results are only estimations, although they are helpful in providing an impression of the magnitude of the problem. Hence, the true mean residual drug volumes may even be smaller.

Conclusion

Low-molecular-weight heparins represent a good model for studying outpatient s.c. therapies in primary care. Among our patient cohort, 85.0% reported some relevant drug use problem, whereas no clear factors were associated with non-compliance, the injection site (beside residual drug), and discomfort or effort required (beside prior injection use). Around 4% of patients had a considerable mean residual drug volume (≥10.0%) in their syringes, with a higher risk of leaving medication when injection was into the thigh. The challenge facing not only for pharmacists but all health professionals as well as the pharmaceutical industry (design of injection-device and instruction leaflets) is to successfully contribute to a successful therapy. From a patient's point of view, injections require some effort. Therefore, it can be imagined that injection-free therapies for patients on chronic antithrombotic therapy would be appreciated.

Acknowledgments

We would like to thank the participating community pharmacies for their cooperation. We also thank the Master's students for data collection, the patients for participating in the study, Michael Mittag for his support in the statistical analysis, and Irene Vogel Kahmann, Raphaela von Grünigen, Joëlle Bader, and Paul Lavender for their valuable contributions.

Conflict of interest

This study was supported by Pfizer AG through an unrestricted Investigator-Initiated Research Grant (IIRG).

Tables and figures

Table 1 Characteristics of study sample (n_{total}=213)

Patient and clinical characteristics	*n* (%)[a]	Missing data *n* (%)
Patient characteristics		
Age (years)	54 (39–70)	2 (0.9)
Males	108 (50.7)	2 (0.9)
Education		14 (6.6)
▪ Mandatory school	24 (11.3)	
▪ Skilled worker	123 (57.7)	
▪ Technical college + university	52 (24.4)	
Previous outpatient s.c. injection therapies	89 (41.8)	1 (0.5)
Impairment in daily living due to arm, shoulder, or hand	29 (13.6)	9 (4.2)
Arthritis in arm, shoulder, or hand	32 (15.0)	20 (9.4)
Impaired vision (using glasses or contact lenses)	27 (12.7)	26 (12.2)
Medication characteristics		
Medication		0 (0.0)
▪ Fragmin (dalteparin)	99 (46.5)	
▪ Fraxiparine (nadroparin)	63 (29.6)	
▪ Clexane (enoxaparin)	33 (15.5)	
▪ Fraxiforte (nadroparin)	9 (4.2)	
▪ Sandoparin (certoparin)	9 (4.2)	
Application once daily	171 (80.3)	1 (0.5)
▪ Not specified on prescription	27 (12.7)	
Concomitant medication with an increased bleeding risk (not necessarily on the same prescription)		
▪ **Anticoagulant** (acetylsalicylic acid, phenprocoumon, acenocoumarol, clopidogrel)	68 (31.9)	4 (1.9)
- anticoagulant stopped during LMWH treatment	28/68 (41.2)	3/68 (4.4)
▪ **Prescribed analgesic**	146 (68.5)	7 (3.3)
- only paracetamol	37/146 (25.3)	0/146 (0.0)
▪ **Self-medication with analgesics**	20 (9.4)	2 (0.9)
- only paracetamol	9/20 (45.0)	0/20 (0.0)
Reason for LMWH treatment (multiple answers possible)		0 (0.0)

▪ Surgery/injury of		
- lower limb	112 (52.6)	
- hip	11 (5.2)	
- upper limb	7 (3.3)	
▪ Thrombosis, embolism	35 (16.4)	
▪ Perioperative management/bridging	16 (7.5)	
▪ Atrial fibrillation, myocardial infarction	8 (3.8)	
▪ Cancer	7 (3.3)	
▪ Pregnancy, hormone therapy	6 (2.8)	
▪ Abdominal surgery	6 (2.8)	
▪ Long-distance travel	4 (1.9)	
▪ Other	12 (5.6)	

[a] All data is presented as the number (*n*) with the percentage in parenthesis with the exception of 'Age', which is presented as the median with the interquartile range in parenthesis.

s.c. Subcutaneous; *LMWH* Low-molecular-weight heparins

Table 2 Self-reported quality of care (including patient satisfaction), self-management, drug use problems, knowledge, and non-compliance (n_{total}=213)

Parameters on patients' self-reports	*n* (%)[a]	Missing data *n* (%)
Quality of care and patient satisfaction		
Oral instruction in injection technique (previous and present treatment)		0 (0.0)
▪ None	10 (4.7)	
▪ Only by the pharmacy	8 (3.8)	
Insufficiently informed about injection site	8 (3.8)	7 (3.3)
Insufficiently informed about injection technique	14 (6.6)	9 (4.2)
Alcohol swab provided	200 (93.9)	1 (0.5)
First self-injection in the presence of a medical professional		
▪ Provided	111 (52.1)	0 (0.0)
- helpful	97/111 (87.4)	12/111 (10.8)
▪ Not provided, but desired	15/102 (14.7)	17/102 (16.7)
Delivery of leaflet		
▪ Provided	41 (19.2)	8 (3.8)
- helpful	33/41 (80.5)	3/41 (7.3)
▪ Not provided, but desired	28/164 (17.1)	22/164 (13.4)
First injection administered by the pharmacist		
▪ Provided	0 (0.0)	13 (6.1)
▪ Not provided, but desired	9/200 (4.5)	42/200 (21.0)
All injections administered by the pharmacist		
▪ Provided	0 (0.0)	12 (5.6)
▪ Not provided, but desired	8/201 (4.0)	33/201 (16.4)
Delivery of sharps collector		
▪ Provided	203 (95.3)	0 (0.0)
- helpful	135/203 (66.5)	38/203 (18.7)
▪ Not provided, but desired	0/10 (0.0)	4/10 (40.0)
Injection training into a "phantom" (injection pillow)		
▪ Provided	7 (3.3)	8 (3.8)
- helpful	6/7 (85.7)	1/7 (14.3)
▪ Not provided, but desired	10/198 (5.1)	33/198 (16.7)
Video tape		
▪ Provided	1 (0.5)	10 (4.7)

- helpful	0/1 (0.0)	0/1 (0.0)
▪ Not provided, but desired	13/202 (6.4)	33/202 (16.3)
Self-management (multiple answers possible)		
Injection site		0 (0.0)
▪ Thigh	146 (68.5)	
▪ Abdomen	80 (37.6)	
▪ Back of the upper arm	2 (0.9)	
▪ Other	2 (0.9)	
Injections administered by another person (sometimes or always)	33 (15.5)	0 (0.0)
▪ by family member/friend	25/33 (75.8)	
▪ by medical professional	9/33 (27.3)	
Reasons for not self-injecting		5/33 (15.2)
▪ needle phobia	9/33 (27.3)	
▪ fear of puncturing skin	8/33 (24.2)	
▪ severely disabled	4/33 (12.1)	
▪ family member is a medical professional	3/33 (9.1)	
▪ other	8/33 (24.2)	
Illegitimate recapping	157 (73.7)	5 (2.3)
Application problems		
Difficulties with removal of needle shield	28 (13.1)	1 (0.5)
Puncture is unpleasant/painful	105 (49.3)	3 (1.4)
Injection is unpleasant/painful	113 (53.1)	6 (2.8)
Degree of effort required to inject (scale: 1–4)	2 (1-3)	5 (2.3)
Confidence/lack of discomfort (scale: 0–10)	9 (7-10)	26 (12.2)
Side effects (multiple answers possible)	105 (49.3)	2 (0.9)
▪ Hematoma at injection site	79 (37.1)	
▪ Mild injection site irritation/burning	36 (16.9)	
▪ Hematoma in general	16 (7.5)	
▪ Site pain	15 (7.0)	
▪ Exanthema	4 (1.9)	
▪ Bleeding tendency	4 (1.9)	
▪ Induration	4 (1.9)	
▪ Epistaxis	2 (0.9)	
▪ Other	9 (4.2)	
→ no action taken by study participants	77/105 (73.3)	13/105 (12.4)

→ met criteria for reporting an adverse event to regulatory authority	1 (0.5) (arm exanthema)	0 (0.0)
Knowledge		
Discrepancy with prescribed therapy duration	9 (4.2)	4 (1.9)
▪ Not specified on prescription	59 (27.7)	
Discrepancy with prescribed daily injections	3 (1.4)	3 (1.4)
▪ Not specified on prescription	27 (12.7)	
Discrepancy with prescribed injection time	7 (3.3)	3 (1.4)
▪ Not specified on prescription	157 (73.7)	
Nescience of reason for LMWH treatment	6 (2.8)	0 (0.0)
Nescience of potential interactions with NSAR	158 (74.2)	2 (0.9)
Nescience of potential side effects	116 (54.5)	2 (0.9)
Self-reported non-compliance (assessed at final interview with *n*=144 patients)		
Difficulties with injecting the LMWH timely	15 (10.4)	2 (1.4)
Applications exceeding +/– 2 h of assigned injection time	5 (3.5)	1 (0.7)
Skipping injections (*n*=146; completion of database according to annotiations)	25 (17.1)	0 (0.0)
▪ 1 time	8/25 (32.0)	4/25 (16.0)
▪ >3 times	5/25 (20.0)	
Reason for skipping injections (multiple answers possible)		1/25 (4.0)
▪ forgotten	11/25 (44.0)	
▪ early discontinuation	6/25 (24.0)	
▪ not being at home	2/25 (8.0)	
▪ other[b]	7/25 (28.0)	

NSAR Non-steroidal anti-rheumatics

[a] All data is presented as the number (*n*) with the percentage in parenthesis with the exceptions of 'Degree of effort required to inject' and 'Confidence/lack of discomfort', which are presented as the median with the interquartile range in parenthesis

[b] Injections every 2–3 days depending on appearance of leg pain; vomiting or abdominal pain; delayed filling of the prescription; skeptical towards LMWH; news coverage about contaminated heparins; injection required too much effort (complete non-compliance); dropping a syringe leading to an insufficient number of syringes

Table 3 Handling difficulties (multiple statements per person possible)

Flap of paper backing on blister pack: Too small to remove the syringe from its packaging
Removal of needle shield: Tricky; difficulties due to single-handed removal; bending the needle; total liquid loss due to pulling the plunger rod
Needle: Too sharp; not sharp; twice blocked; bent
Air bubble: Uncertainty whether air bubble needs to be removed; annoying; no air bubble
Injection: Injection more painful with small injection angle (*n*=2); injection needs lots of force (*n*=2); uncertainty concerning the insertion length of the needle into the skin; coordination difficult regarding quick insertion of the needle vs. slow injection; high resistance when pushing the plunger rod in the beginning leading to a sudden and quick injection; needle accidentally came out of the skin during injection; liquid loss during first injection; early discontinuation due to lots of pain and problems during injection; injection by another person, because of inability to self-inject into the back of the upper arm; setting back injection time every day 15 min from 7 p.m. (injection time in hospital) to 11 p.m. (preferred injection time at home)
Recapping: Needle stick injury; needle easily penetrates the soft needle shield
Syringe: Syringe in general very small and hence difficult to handle (*n*=3); uncertainty whether total volume was injected (*n*=3); dropping the syringe before injection (*n*=2); finger flange too small (*n*=2); difficulties with positioning the needle guard of Fraxiparine

Table 4 Room for improvement in quality of care (multiple statements per person possible)

More information: On thromboembolism (*n*=4) and its prevention (*n*=2); on LMWH and side effects (*n*=2)
Improved instruction in the injection technique: Better instruction (*n*=9); increased patient involvement (*n*=8); instructions not only orally but with demonstration of the injection technique (*n*=2); self-injections during the whole hospital stay and not only on the day before hospital discharge (*n*=2); repetition of the instructions when collecting their prescription
Consistent instructions: On injection angle (*n*=3); injection site (*n*=2); skin fold; air bubble
Better leaflets: On terminology; font size; foreign languages

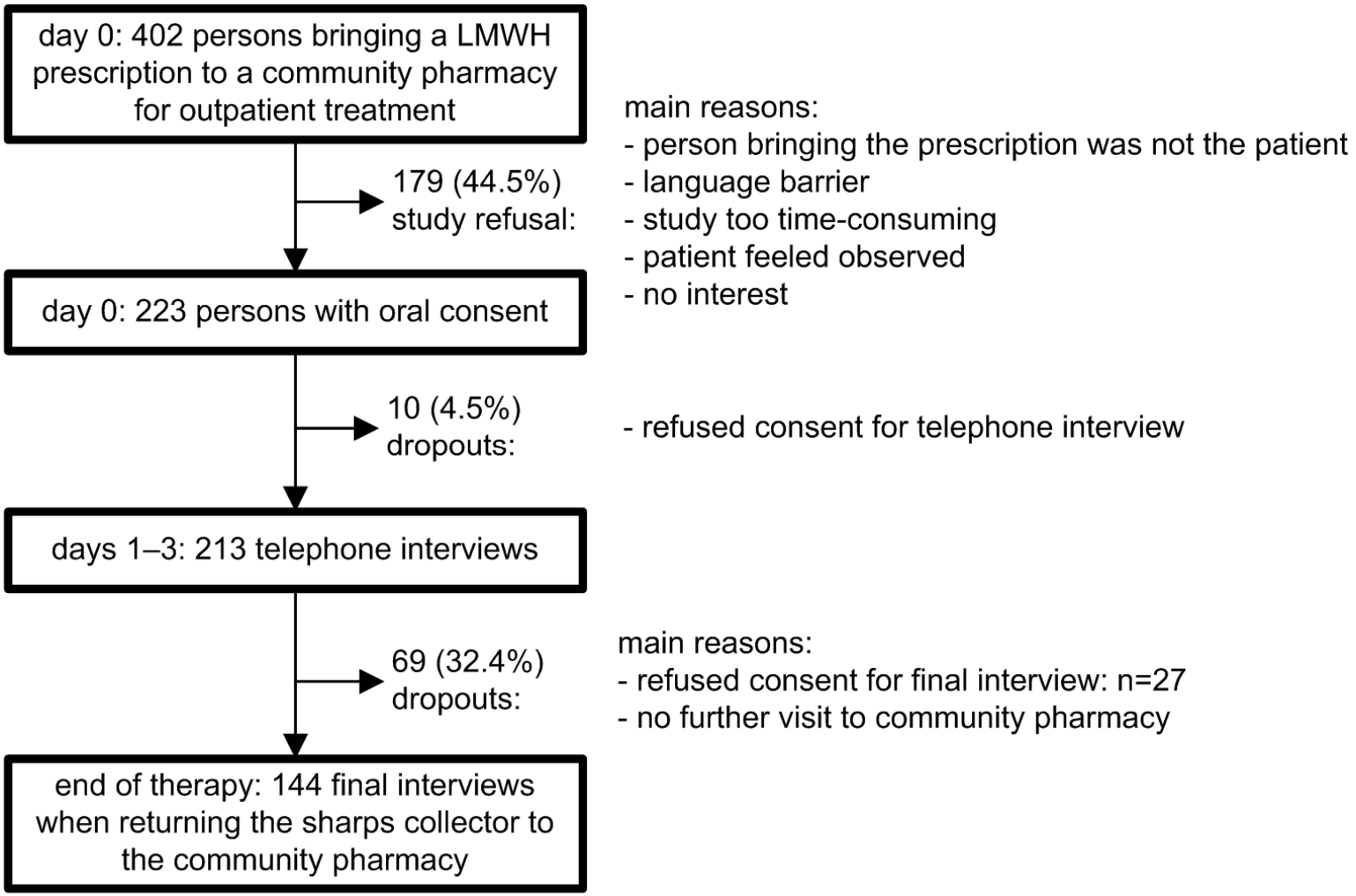


Fig. 1 Study flowchart with numbers of patients and reasons for dropout

LMWH Low-molecular-weight heparins

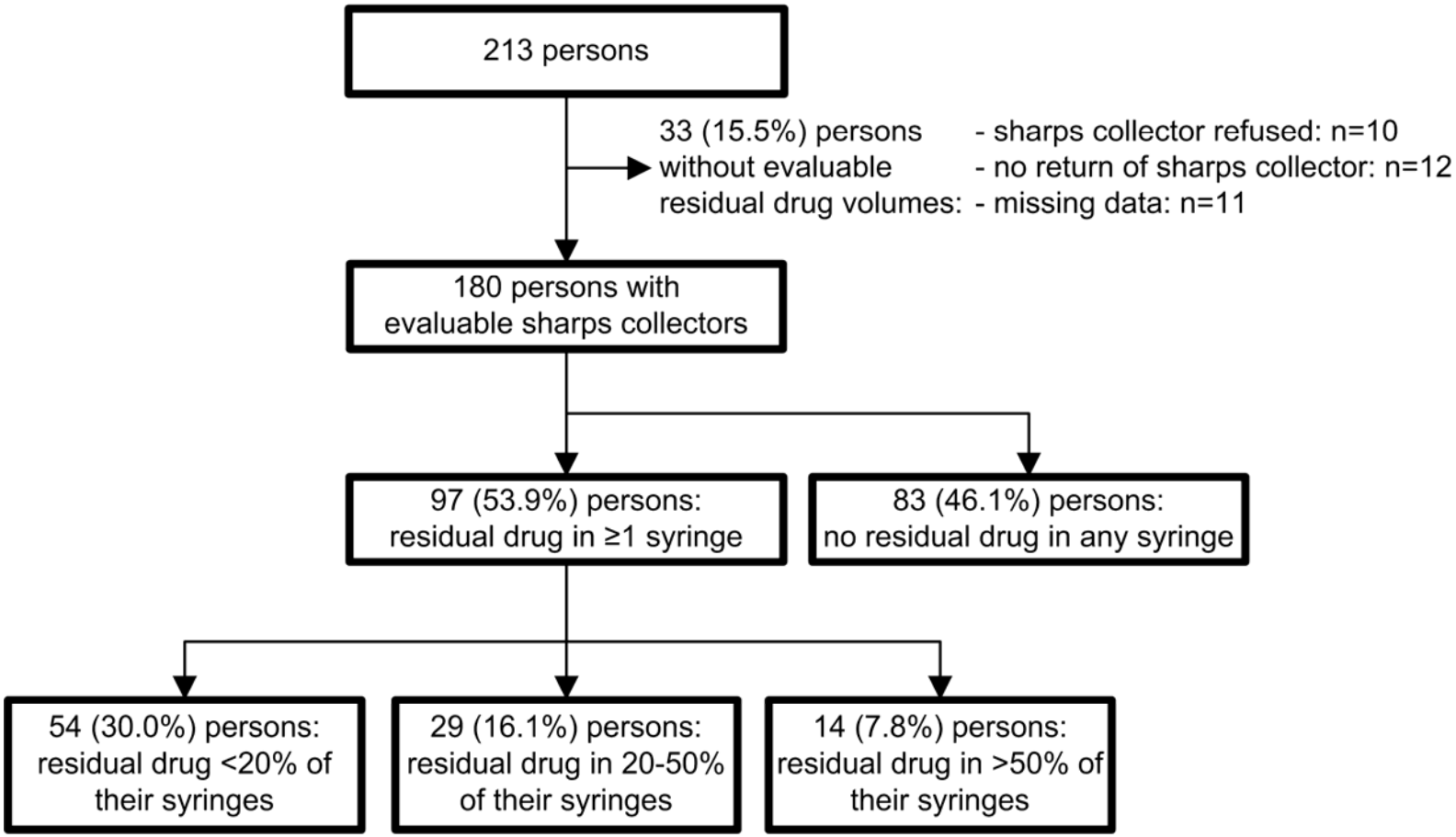


Fig. 2 Prevalence of syringes with residual drug irrespective of the volume amount

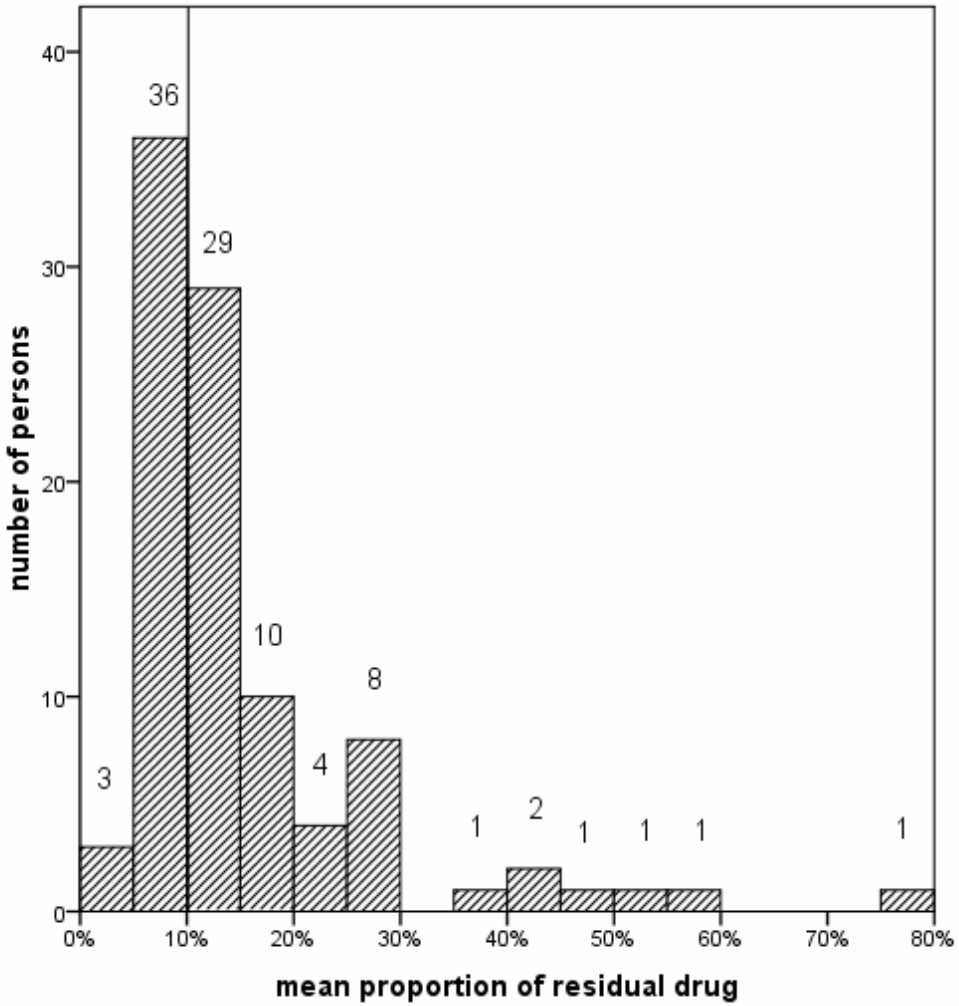


Fig. 3 Mean proportion of residual drug in used syringes still containing medication. Only those syringes with residual amounts of LMWH (97 patients, 304 syringes; range 1–16 syringes) were considered in the analysis

3 Outpatient low-molecular-weight heparin therapy

Project C:

Self-management of outpatient low-molecular-weight heparin therapy: impact of pharmaceutical care

Seraina Mengiardi[1], Dimitrios A. Tsakiris[2], Viviane Laufer-Molnar[3], Urs Kohlhaas-Styk[3], Michael Mittag[1], Stephan Krähenbühl[4], Kurt E. Hersberger[1]

[1] Pharmaceutical Care Research Group, University of Basel, Switzerland

[2] Division of Hematology, University Hospital Basel, Switzerland

[3] Clinic for Orthopedic Surgery and Traumatology, Kantonsspital Bruderholz, Switzerland

[4] Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Switzerland

Ann Pharmacother; submitted

Abstract

Background

The effectiveness of community-pharmacy-based interventions in preventing problems that arise during subcutaneous (s.c.) self-injections of low-molecular-weight heparins (LMWH) is unknown.

Objective

To develop a standard operating procedure (SOP) for community pharmacists and to compare pharmaceutical vs. standard care in both clinical and daily life settings. We hypothesized that: pharmaceutical care results in improved compliance, safety, and satisfaction, and in fewer complications; the interventions used are feasible in daily life; and the results achieved in clinical and daily life settings are comparable.

Methods

In the clinical setting (randomized controlled trial), patients were recruited sequentially in hospital wards; in the daily life setting (controlled trial), recruitment took place in community pharmacies by trained master students and pharmacists. Interventions were offered according to patient needs. Data were collected by means of a monitored self-injection at home and structured questionnaire-based telephone interviews at the beginning and the end of the LMWH treatment.

Results

The median age of the 139 patients was 54 years (interquartile range 40−65 years). Interventions resulted in improved application quality ($p<0.01$) and knowledge ($p=0.03$). Oral instructions were pivotal for improving patients' application quality. We found no significant score differences between the intervention groups in the clinical and daily life settings. Patients' baseline skills were high, with the lowest score being 0.86 (range −2.00 to +2.00). Compliance rate was high (95.8%).

Conclusions

Our SOP for pharmacist interventions was of good quality, adequate, appreciated, and feasible in daily life. Patients are capable of managing s.c. injection therapies if adequate assistance is provided.

Keywords

Low-molecular-weight heparin · Outpatients · Subcutaneous injections · Self administration · Pharmaceutical care · Community pharmacy

Introduction

The number of medications that cannot be applied orally but have to be administered subcutaneously (s.c.) is rising; such medications are used to treat a wide range of diseases, e.g. thromboembolism, diabetes, multiple sclerosis, arthritis, anemia, cancer, female infertility, hepatitis B and C, migraine, osteoporosis, and human immunodeficiency virus (HIV). Different devices are used to deliver such medication, e.g. pre-filled syringes, pens, injectors, and vials/ampules, where preparation is needed before injection. Self-injections in an outpatient setting are encouraged to strengthen patient responsibility for his/her own disease management, grant greater independence, and reduce costs.

For prophylaxis and treatment of venous thromboembolisms, the use of low-molecular-weight heparins (LMWH) is well established [3, 8, 10, 18]. Therapies are often inititated during a hospital stay or at discharge, followed by daily s.c. self-injections for a period of time varying from days to weeks or even longer. Because after discharge most patients visit a community pharmacy to fill their prescription, pharmacists play an important role in the continuity of care by assuring correct drug use over the prescribed time [45, 53]. The community pharmacist's conventional role of preparing and dispensing drugs is changing, and the provision of new pharmaceutical services is needed [45]. The influence of pharmaceutical care on asthma, elevated lipid levels, hypertension, and diabetes has been investigated [111-117], but knowledge of the effectiveness of community-pharmacy-based interventions on problems in self-administering s.c. injection therapies is lacking.

Enhancement of compliance is a multilevel challenge that includes a combination of different interventions, such as patient education with oral and written instructions, monitoring, telephone follow-up, reminder systems, and use of patient-tailored care [57, 77]. It has been reported in the literature that problems with self-administering outpatient LMWH treatments are prevalent, diverse, and may concern the injection itself or handling of the injection device [35, 106, 118]. Previous interventional studies recruited 40−214 patients, and concentrated on orthopedic patients from selected clinics or hospitals [83, 103-105]. All patients received educational programs that included instructions in the injection technique, performing their first self-injection in the presence of a medical professional, and, occasionally, written information or a

video tape. A search of the literature failed to identify studies that were controlled, examined feasibility of the interventions in daily life, or objectively assessed each patient's injection technique in everyday life after hospital discharge (e.g. direct observation technique, DOT, during a home visit).

We therefore designed a 4-arm, partly randomized, parallel, open-label, active control, phase 4, supportive care, safety study. Our aims were: (1) to develop a standard operating procedure (SOP) for the first instruction in the s.c. injection technique given by a community pharmacist and the subsequent pharmaceutical care provided during outpatient therapy; and (2) to compare intensive pharmaceutical care vs. standard care in both a clinical setting (hospital wards under study conditions) and in a daily life setting (community pharmacies following their daily routine). We hypothesized that: (1) intensive pharmaceutical care for outpatients self-injecting LMWH results in improved compliance, safety, and satisfaction, as well as in fewer complications; (2) the interventions used are feasible in the everyday routine of community pharmacies; and (3) the results achieved in clinical and daily life settings are comparable.

Methods

Setting and study population

This study comprised both clinical and daily life settings. The *clinical setting* arm (ClinS) was a *randomized controlled trial* (RCT). Patients were recruited sequentially into the intervention (ClinS-I) or control (ClinS-C) groups by the primary investigator from two orthopedic clinics (Kantonsspital Bruderholz, University Hospital Basel), from an orthopedic early rehabilitation ward of the University Hospital Basel (Felix Platter-Spital), and from an emergency department (University Hospital Basel) between June 2007 and June 2009. The primary investigator had attended a certified course for parenteral injection techniques and four specialized courses on the s.c. injection technique, including clinical training by nursing staff.

The *daily life setting* arm (DailyS) was a *controlled trial*. Patients were recruited sequentially in community pharmacies: for the control group (DailyS-C) by 65 trained students from the University of Basel during their internship between January and

May 2008 [35] and for the intervention group (DailyS-I) by trained community pharmacists between March 2008 and June 2009. We invited all 87 community pharmacies in the region to attend one of our courses, which included background information on thromboembolic diseases and heparin therapy, case analysis of LMWH prescriptions, and instructions in the s.c. injection technique, which included clinical training, presentation of the DailyS, and distribution of study material. Out of the course participants, 21 community pharmacies agreed to recruit patients for the DailyS-I arm.

We defined the following inclusion criteria: patients aged ≥18 years with a prescription for an outpatient LMWH treatment with pre-filled syringes; Fragmin (dalteparin, Pfizer AG; ClinS) or all brands of LMWH (DailyS); self-injection; prophylactic or therapeutic use; first or previous outpatient s.c. treatment; all therapy durations; no comprehension difficulties due to language.

Interventions

Our SOP comprised the following interventions, which were offered and applied according to patient need (ClinS-I, DailyS-I): delivery of a leaflet, including oral instruction; delivery of a manual for s.c. injection; delivery of a kit containing 20 alcohol swabs, cotton swabs, and plasters each; oral instruction in s.c. injection technique; injection training into a ‘phantom’ (injection pillow; PharmaDesign Inc., Warren, NJ, USA; delivered by Pfizer AG); instruction in the injection technique using a commercial video (CD-ROM or website); (first) self-injection in the presence of a pharmacist, or (first) injection administered by a pharmacist (ClinS: primary investigator; DailyS: trained community pharmacist).

The leaflet (4 pages) and the laminated manual (1 page) were created and revised regularly by reviewing package inserts, current commercial leaflets, and kits for LMWH or other medications s.c. administered, as well as patient-tailored websites of pharmaceutical companies. The leaflet contained detailed background information about: reasons for the LMWH treatment; effects, indications, injection times, therapy durations, daily injections, and potential adverse drug reactions of LMWH, as well as potential interactions with OTC medications; actions to be taken if a dose was skipped; and thrombosis and embolism, including their symptoms and actions to be taken. A step-by-step instruction in the s.c. injection technique with illustrations and

explanations completed the leaflet, along with a diary to record daily injections for self-monitoring. The manual was designed to be a quick reference card providing a brief summary of the sequential steps of the s.c. injection. Both the leaflet and manual were reviewed by a hematologist.

Data collection

In the *clinical setting* arm (RCT), patients received standard hospital care. Patient recruitment was performed by the primary investigator by regularly contacting the nurses or physicians to ask for potential study participants. The hospital staff were not involved any further in the study. If the patient met the inclusion criteria and written informed consent was obtained, a sharps collector (E-safe) for the used syringes and written patient information was delivered. The 1:1 randomisation was performed by using a research randomizer for random sampling and random assignment [119], and patients were sequentially assigned to the intervention or control group. Interventions were offered and applied according to patient need (ClinS-I), either at the patient's bedside or immediately after discharge in the 'Emergency Pharmacy Basel' – an emergency community pharmacy open only at night, weekends, and holidays – which was used as study centre during the day. Patients of the control group (ClinS-C) received standard care by filling their prescription in the community pharmacy of their choice.

In the *daily life setting* arm, routine prescription validation was performed by each community pharmacy (standard care) when a LMWH was requested. If the patient met the inclusion criteria and oral (DailyS-C) or written (DailyS-I) informed consent was obtained, the trained community pharmacists (DailyS-I) offered and applied the interventions according to each patient's needs and informed the primary investigator. All patients received at least a sharps collector (E-safe) for the used syringes and written patient information. To get their feedback and keep motivation high, the primary investigator contacted the intervention community pharmacies (DailyS-I) regularly by phone.

Data collection was identical with a former study (structured questionnaire-based interviews at the beginning and after completion of the s.c. therapy; analysis of used

syringes) [35]. At the end of the study, the final interview was performed either at the community pharmacy, when sharps collectors were returned (DailyS-C) or by phone call (ClinS; DailyS-I), and patients were asked to return their sharps collectors by mail. At a pre-arranged date and at her/his individual injection time, each patient was monitored during self-administering an s.c. injection and rated using a developed DOT-based data collection sheet. Immediately after the DOT, the injection technique was reviewed with the patient. During the DOT, the investigator would only have intervened with serious handling errors, which never was the case. Data collection was performed by the primary investigator in the ClinS and DailyS-I arm. The DailyS-C arm consisted of a subpopulation of a former study [35]: to get this subpopulation, each trained master student had to recruit one patient for whom they performed the interviews and the DOT.

The data collection was anonymized by assigning a code to each patient. The study protocol was approved by the local Ethics Committee of Basel (EKBB 95/07; ClinicalTrials.gov identifier: NCT00794560).

Outcome measures

To assess each patient's skills, we assigned points to every answer (+2=correct answer; +1; 0; -1; –2=wrong answer). For each question, we awarded at most +2 and −2 points. To minimize bias generation with the complex data transformation, we completed missing data by the mean values. A committee consisting of a hematologist, a physician working as a medical advisor for Fragmin, a nurse, two clinical pharmacists, the primary investigator, and the master student rated the importance of the questions by using a 4-point scale. Cronbach's alpha reliability coefficient (α) was used as a measure of the internal consistency and reliability of the scores (range: 0−1). The mean values on the 4-point scales (range: 1.6−3.9; α = 0.80) were converted into a weighting range between 1.0 and 2.0. This means that a question rated to be very important received twice as much emphasis as one rated to be of average importance. The scales were then computed as weighted means of the individual items (i.e. score minimum = −2.00; score maximum = +2.00). We defined different domains to group the questions and to facilitate comparisons (Table 1). The catalogue with the questions assigned to the particular domains is listed as supplementary data (Appendix Table 1).

By comparing the number of used syringes with the prescribed therapy duration, we determined levels of patient 'taking' compliance (= *syringe count*: missing syringes are used as a measure for non-compliance). If the therapy duration was not specified on the prescription or unclear (terms such as 'treatment until complete mobilization, INR twice in therapeutic range, next visit with physician'), we referred to the dates of the first and last injections. If these dates and the therapy duration were not provided, if there was an unscheduled visit with the physician/hospital, or if the sharps collectors were missing, we were unable to determine the compliance reliably and classified the patient's compliance as 'not determinable'. Patients who discontinued their s.c. treatment early due to full physical load were classified as fully compliant. If sharps collectors were not returned, patients were reminded by mail, e-mail, phone call, or text message. An internal analysis showed smaller overall mean residual drug volumes in the used syringes compared to a former study, where they were interpreted as low and negligible [35]. Thus, we did not take this parameter into further consideration.

Validation

The purposes of the validation were to screen the questionnaire for its comprehensibility and completeness, to standardize the questionnaire- and DOT-based data collection, as well as to check the primary investigator's and the data-collecting students' consistency.

Thirty-four pharmacy students serving their internship in 2007 were asked to fill in the questionnaire by answering the questions appropriate for healthy subjects. In addition, as a pilot, the full questionnaire-based interviews were performed with 4 people, during which both the primary investigator and a master student filled in the questionnaire. Discrepancies with recording were discussed and ruled out. To validate the DOT, the primary investigator and the master student observed the same 34 pharmacy students self-administering a s.c. injection (0.2 ml, 0.9% sodium chloride). Two months previously, the students had received instructions in the s.c. injection technique, including clinical training. In the same manner as described above, divergencies (of at most 20%) were identified and resolved.

To validate the monitoring and recording skills of the students recruiting for the control group of the DailyS, they were asked to analyze three videos using the DOT-

based data collection sheet. On each video, the primary investigator self-administered an s.c. injection (0.2 ml, 0.9% sodium chloride) with purposeful errors reflecting daily life situations. After recording, each video was discussed with the students. The students' accuracy improved from video 1 (mean value: 71.4%; minimum: 55.0%) to video 2 (75.2%; 60.0%) to video 3 (88.1%; 71.7%).

Statistical analysis

Data sheet processing, plausibility testing, and statistical analysis were performed in the same manner as described in a former study [35]. Because the statistical procedures used were either very straightforward, such as comparison of two sample means, or included parameters that were impossible to estimate with any confidence, such as the variance of questionnaire scores, we did not compute a power analysis. For a comparison of sample means, we have 32−40 subjects per group, so we can expect to find differences in the region of one half to one third of a standard deviation. For our aim, which is to find differences that are relevant in daily life, we believe that this is sufficient. For more complex analyses, statistical power may vary, and will typically be somewhat higher, because the more complex statistical models are better at reducing error variation. Also, we use nonparametric comparisons if possible, which are generally more stable, at a potential cost of statistical power. As a rule of thumb, statistical power of parametric tests is roughly 5% higher if data follow an exact normal distribution, but can quickly deteriorate if normal distribution is violated (even if the violation is mild). Note that for the domains, we cite the arithmetic mean and not the median, because the median does not offer a precise estimate for scales with few levels. The median almost always takes the value of a scale level, so if the scale has three levels, the median can take only three different values. Because of the way we computed our scores, different scores have a different number of levels, rendering a comparison of score medians very difficult to interpret.

Results

Of the 484 persons assessed for eligibility, 154 were included into the study and the data of 139 patients were analyzed (Fig. 1). Ten patients (16.7%) out of 60 not meeting the inclusion criteria in the ClinS arm reported needle phobia. Fourteen community pharmacies recruited 1−7 patients, 7 community pharmacies could not recruit any patients. Patient and medication characteristics and parameters on patients' self-reports are summarized in Table 2. Patients of the ClinS arm were more experienced in self-injecting than patients of the DailyS arm (p=0.04, chi-square test). Previous outpatient s.c. injection therapies had no influence on the scores (p=0.16 to p=0.90, Mann-Whitney tests), but led to a decrease in subjective effort required to administer the injection (p=0.02, Mann-Whitney test) and to an increase in confidence (p=0.04, Mann-Whitney test). In the DailyS arm, patients of the control group mentioned less adverse drug reactions than patients of the intervention group (p<0.01, chi-square test). This was confirmed by comparing the combined control (ClinS-C + DailyS-C) and intervention (ClinS-I + DailyS-I) groups (p<0.01, chi-square test). Other patient characteristics and parameters on patient's self-reports were comparable within the ClinS arm (ClinS-I vs. ClinS-C), within the DailyS arm (DailyS-I vs. DailyS-C), between the ClinS (ClinS-I + ClinS-C) and the DailyS (DailyS-I + DailyS-C), between the assembled intervention (ClinS-I + DailyS-I) and control (ClinS-C + DailyS-C) groups, and within the two intervention groups (ClinS-I vs. DailyS-I). No study participant had a thromboembolic event during the observation period (i.e. until the end of the individual LMWH treatment).

Table 3 shows the scores of the patients in the different study arms, as well as for the combined intervention (ClinS-I + DailyS-I) and control (ClinS-C + DailyS-C) groups. There was no strong correlation between the domains (Spearman's correlation coefficient of r=−0.02 to 0.2) with significance only for knowledge and application quality (DOT) (r=0.2, p=0.01). A direct correlation between 'Reality' (objectively assessed by investigators, Table 1) and 'Self-assessment' (subjectively assessed by patients themselves) was only possible for the application quality; it resulted in a low and non-significant Spearman's correlation coefficient value of r=−0.1 (p=0.20). There were no significant differences between the intervention groups of the ClinS

and DailyS (p>0.57, except for estimated assistance quality: p=0.14, Mann-Whitney test).

The application quality (DOT) was not influenced by age (r=−0.1, p=0.15), sex (p=0.63, Mann-Whitney test), previous outpatient s.c. injection therapies (p=0.22, Mann-Whitney test), first self-injection in the presence of a medical professional (p=0.38, Mann-Whitney test), fine motor skills (p=0.91, Mann-Whitney test), or the injection site (p=0.06, Mann-Whitney test; a trend towards a higher score with injections into the thigh (mean 1.17; standard deviation 0.34) than into the abdomen (mean 1.03; standard deviation 0.39) was observed). The DOT was performed 120 times at patients' homes, 3 times at the study centre, 2 times at their workplace, and 3 patients recorded their injection for DOT on a video. The observation of a self-injection was either helpful and increased confidence (n=5) or made the patient insecure and nervous (n=5). We were unable to perform 11 DOTs (7.9%) as: patients' individual therapy durations were very short and the treatment had already been terminated due to an INR in therapeutic range (n=2) or full physical load (n=2); the patient's home was too far away from study centre (n=3), it was impossible to find an appropriate date (n=2), or the patient refused the DOT (n=2).

The sharps collectors of 128 patients contained a total of 3,137 syringes (median: 18, interquartile range: 10–39.5; range: 2−93). Eleven sharps collectors were missing: Four patients lived abroad and the sharps collectors probably didn't cross the border, one person didn't want a sharps collector, and in the remaining 6 cases, the reason is unknown. In 41.0%, the therapy duration was not specified or unclear. Results of the syringe count are listed in Table 3. The compliance of 24 (17.3%) patients was not determinable; 12.9% of patients admitted skipping injections, whereas the objective syringe count detected non-compliance with 37.4% of patients (p<0.01, chi-square test). A greater than 2-hour delay to the prescribed injection time was mentioned by 15.8% patients (4.3% missing), leading to a correct 'taking' compliance (syringe count), but to a non-compliance in terms of timing; there was no difference between the combined control (ClinS-C + DailyS-C) and intervention (ClinS-I + DailyS-I) groups (p=0.17, chi-square test).

Table 4 shows the error rates of clinically relevant administration steps and the influence of the interventions upon them. We found no associations between burning

and not waiting for the alcohol to evaporate (p=0.34, chi-square test) or skin area being swabbed after injection with the alcohol swab (p=0.13, chi-square test).
Patients made use of the following compliance aids: integration of the self-injection into a daily routine (n=13), setting an alarm (n=5), and using a diary (n=3). Handling difficulties concerned the high forces needed when pushing the plunger rod in the beginning leading to a sudden and quick injection (n=4), as well as the small size of the finger flange (n=4), the thumb grip, and the syringe in general. Seven patients stated that they required much more effort in earlier LMWH treatments.

According to our SOP, the objective assistance quality in the two study arms ClinS-I and DailyS-I was patient-tailored as interventions were offered and provided only if required (Table 5). No additional care was desired. Analyzing the free-text comments of patients rating the interventions as not helpful, we worked out that these patients declared having no need of them (leaflet p<0.01; manual p<0.01; oral instructions p<0.01; injection training into a ’phantom’ p=0.01, chi-square tests). Patients of the ClinS-I received more oral instructions (93.9% vs. 70.0%; p=0.02, chi-square test) and injection training into a ’phantom’ (84.8% vs. 22.5%; p<0.01, chi-square test). On the other hand, patients of the DailyS-I assessed the leaflet to be more helpful (53.1% vs. 80.6%; p=0.02, chi-square test). Patients who received oral instructions reached higher scores in the application quality (DOT) (p=0.04, Mann-Whitney test) and self-assessed their application quality more sceptically (p=0.01, Mann-Whitney test). The delivery of a leaflet or manual and injection training into a ’phantom’ had no influence on the scores. Interventions were crucial for self-injection (n=3) and led to a reduction of anxiety (n=2) and enhancement of compliance.

Discussion

The rising prevalence of s.c. injection therapies with their potential for problems during self-administration and patient concerns provides an opportunity for community pharmacists to strengthen their role in the health-care system. We developed a feasible SOP with positive outcomes, although it lacked a strong impact due to the patients’ already high baseline skills.

Regarding the score design, Cronbach's alpha reliability coefficients between 0.58 and 0.80 (except an α = 0.03 due to a ceiling effect) are acceptable. Removing the least reliable items from the scales did not increase scale reliabilities, indicating that the reliabilities reflect the scales as a whole and not an inconsistent item quality. The number of questions per domain varied (2−27 questions). This reflects that some domains were more complex in nature, and balancing the number of questions per domain would have led to a loss of information regarding these domains, as well as to lower reliability scores.

Patients of the ClinS arm were more experienced in self-injecting than patients of the DailyS arm. As this study, as well as our previous data [35] show that patients with experience have less discomfort and the injections require less effort, there might be some bias concerning the self-assessment of the application quality. The lower prescription quality in the DailyS arm (lack of specification of number of daily injections) might be explained by the trend to more handwritten than printed prescriptions from more often general practitioners than hospitals. The high prevalence of adverse drug reactions is eye-catching. Hematoma and mild injection site irritation/burning account for the majority. They are typical adverse drug reactions of s.c. injections and might be reduced, at least to some extent, by a slow injection [32-34]. The use of alcohol swabs did not seem to have an influence on burning. Patients in the DailyS-C reported less adverse drug reactions than patients in the other study arms. This might be due to poorer reporting quality by the master students. Nevertheless, the students were skilled enough to monitor and record an s.c. self-injection after receiving instructions in the s.c. injection technique, including clinical training and the analysis of the three videos showing s.c. injections with purposeful errors. They showed a steep learning curve, which makes this tool a suitable education instrument.

We saw no relevant correlations − neither between the domains nor between 'Reality' and 'Self-assessment'. Therefore, an objective assessment of patient skills is crucial and makes the time- and cost-consuming DOT worthwhile. Overall, patient baseline skills were high, with the lowest score being 0.86 on a range of −2.00 to +2.00, making further improvement difficult. Nevertheless, through our interventions, we could increase patients' application quality and knowledge. Although there were no significant differences between the scores of the intervention groups in the clinical and daily life settings, the results of the two settings are not comparable, as in the

DailyS patients receiving interventions did not achieve better results in application quality and knowledge. A proper injection technique contributes to a safe and positive outcome. Our interventions had a positive influence on some of the clinically relevant administration steps, especially on hygiene and avoidance of needle stick injuries. Nevertheless, the contributions of the interventions resulted in no specific pattern, which might be explained by the relatively small study population.

A notable, though not intended result regards the control group's assessment of the assistance quality. Overall, the control group felt that they received a very good level of care, probably because researchers have contacted them several times (telephone interviews, home visit), inquired about their well-being, and generally showed an interest in them. This shows two things: First, that patient's assessment of assistance quality does not necessarily rely on the quality of pharmaceutical care they receive, and second that this assessment can be substantially improved by comparatively simple means, such as asking them how they are doing.

As the interventions of the SOP were not standardized, but patient-tailored, we did not focus on the time needed. The primary investigator estimated an average of 30 min was required for both recruitment and interventions, which is in line with the literature (10−45 min) [83, 105, 120]. No additional care was desired and patients had no need of the interventions if they rated them as unhelpful (e.g. previous s.c. injection therapies, medical professional, good patient care in the past). This illustrates that we provided an SOP for first instruction by a community pharmacist and subsequent pharmaceutical care during self-injection which was feasible in daily life, that the quality of our interventions was good and adequate, and that a single 2-hour course was sufficient. Patients in the ClinS received more oral instructions and injection training into a ‘phantom’. This might explain why patients in the DailyS assessed the leaflet as being more helpful. Oral instructions were the pivotal intervention of the SOP to improve the application quality. Compared to our former study investigating a heterogeneous outpatient population receiving standard care [35], patients of the two intervention groups ClinS-I and DailyS-I received more leaflets and manuals, injection training into a ‘phantom’, and (first) injection administered by or in the presence of a pharmacist. Commercial videos and patient-tailored websites were used rarely, confirming the observations of the former study [35]. High-quality videos and websites should be better promoted and might be helpful in resolving insecurities at home after the instructions.

We detected a higher objective (37.4%) than subjective (12.9%) non-compliance rate. Similar studies reported non-compliance rates of 4.5−28.3% [35, 83, 103-105, 121]. Assuming that our patients were honest, they might not have disposed all syringes in their sharps collector, they might have interpreted a 10-day course as a 10-day postoperative and not 10-day ambulatory treatment, they might have administered 40 rather than 42 syringes in a 6-week course for practical reasons (= 4 packages), or the prescription of one package (= 10 syringes) did not necessarily mean that all of them had to be injected. It illustrates that the syringe count was not very reliable, though the only way to objectively determine non-compliance. The overall compliance rate was high with an overall mean of 95.8%. Patients seem to have concerns with pre-filled syringes [35], but are aware of their need. In further research, we propose investigating the relation between concerns and needs of those injecting LMWH (pre-filled syringes) and those taking new oral direct anti-factor Xa or anti-thrombin inhibitors, as with oral medication, much lower compliance rates of about 50% are reported [59, 71]. Nevertheless, reminder systems used as a compliance aid, such as a daily text message (SMS) at the individual injection time, could be appreciated [77].

The strength of our study is the parallel implementation in community pharmacies, allowing: (1) investigation as to whether the interventions are feasible in daily life and, (2) direct comparison of the results under controlled study conditions and daily life conditions. Nevertheless, one has to be aware that experimental conditions were more strictly controlled in the ClinS arm (RCT; recruitment and data collection by one person (primary investigator); few places of recruitment (four hospital wards); one LMWH brand) than in the DailyS arm (controlled trial; recruitment and data collection by several persons (community pharmacists, master students, primary investigator); several places of recruitment (community pharmacies); all brands of LMWH). The main limitation of the study is the low overall consent rate of 31.8%. In the ClinS, the main reasons for not meeting inclusion criteria were injections administered by another person, change of hospital ward, discharge when bridging was completed (oral anticoagulants in therapeutic range), no outpatient LMWH treatment, and comprehension difficulties due to language. Additional challenges within the recruitment were the time management (patients were often already discharged, examinations were not yet done or diagnosis not clear, i.e. uncertainty whether the

patient was receiving LMWH treatment), when the informed hospital staff had days off, when patients were not in their room, or when they had their rehabilitation. One third of the community pharmacies could not recruit any patients; few LMWH prescriptions, the lack of course attendance by all pharmacists working there, and a lack of motivation might be some reasons. Also, some selection bias, observer expectation bias, and patient underreporting bias (negative things are not told) cannot totally be excluded. Rivaroxaban (Xarelto®), a new orally active antithrombotic drug, was licenced in Switzerland for thromboprophylaxis only in patients undergoing knee or hip arthroplasty in January 2009 [7, 122] and did not seem to account for a bias.

Overall, we confirmed our hypothesis that intensive pharmaceutical care resulted in more safety (objectively assessed with application quality/DOT), but we had to reject our assumptions of improved compliance (objectively assessed with syringe count), more satisfaction (subjectively assessed with assistance quality), and fewer complications (subjectively assessed with patients' self-reports on adverse drug reactions). The results of our study allow important recommendations for daily practice, which are: (1) offering each person with a prescription for an outpatient LMWH treatment a leaflet, manual, kit, sharps collector, and oral instructions in s.c. injection technique; (2) the first self-injection should occur in the presence of a medical professional to ensure proper injection technique − if not done in the hospital, we encourage the pharmacists to be present (at patient's individual injection time) [77, 118, 123]; (3) injection training into a 'phantom' and further injections in the presence of or administered by a pharmacist are very supportive tools and should be applied if the patient requires lots of effort or has discomfort; and (4) potential needle phobia [124] and handling difficulties should be kept in mind.

Conclusion

Our SOP was of good quality, adequate, appreciated, feasible in the daily life of community pharmacies, and resulted in improved application quality and knowledge, despite high baseline patient skills. The home visits with the direct observation technique were valuable in determining patient skills. Health-care professionals

should invest more time in injection training into a ‘phantom’ and delivering oral instructions, which were the pivotal interventions in improving patients’ application quality. Each patient should be offered written information, alcohol swabs, a sharps collector, oral instructions, and first self-injection in the presence of a medical professional. Patients are capable of managing s.c. injection therapies in a satisfactory way and with high compliance if adequate assistance is provided.

Acknowledgments

We would like to thank all the involved physicians and nurses from the Kantonsspital Bruderholz, University Hospital Basel and Felix Platter-Spital, especially Markus Lampert, Michael Bodmer, Roland Bingisser, Norbert Suhm, Christian Ritter, and Petra Schröder, the team of the ‘Emergency Pharmacy Basel’, and the participating community pharmacies for their effort and cooperation. We also thank the patients for participating, the students for data collection, Judith Kaiser and Raphaela von Grünigen for their assistance in developing and performing the study, as well as Joëlle Bader (data sheet processing and analysis of used syringes), Philipp Walter (technical help), and Paul Lavender (english review) for their valuable contributions.

Conflict of Interest

This study was supported by Pfizer AG through an unrestricted Investigator-Initiated Research Grant (IIRG).

Tables, figures, and Appendix

Table 1 Generation of 7 domains

Self-assessment (subjective by patients)
▪ *Application quality* (6 questions; α = 0.73)
▪ *Assistance quality* (2 questions; α = 0.80)
▪ *Compliance* (4 questions; α = 0.58)
Reality (objective by investigators)
▪ *Application quality* (DOT) (27 questions; α = 0.58)
▪ *Assistance quality*[a] (SOP)
▪ *Compliance*[b]
▪ *Knowledge* (10 questions; α = 0.03)[c]

[a] No score: interventions were done only if required.

[b] No score: assessed using syringe count.

[c] Ceiling effect: nearly all patients were very knowledgeable about the treatment itself and inconsistently ignorant about questions of recapping, drug interactions with OTC medication, and adverse drug reactions. Scale consistency is low because while patients are consistenty knowledgeable, they do not exhibit any consistent pattern regarding their (very limited) areas of ignorance.

Table 2 Characteristics of study sample (n_{total}=139)

Patient characteristics	ClinS-I (n=33) n (%)[a]	ClinS-C (n=32) n (%)	DailyS-I (n=40) n (%)	DailyS-C (n=34) n (%)	Total (n_{total}=139) n (%)	Missing data n (%)
Age (years) (range 18−84)	56 (34−60)	56 (42−66)	51 (36−65)	54 (43−67)	54 (40−65)	0 (0.0)
Male	17 (51.5)	13 (40.6)	23 (57.5)	16 (47.1)	69 (49.6)	0 (0.0)
Education						4 (2.9)
▪ Mandatory school	4 (12.1)	1 (3.1)	2 (5.0)	2 (5.9)	9 (6.5)	
▪ Skilled worker	17 (51.5)	19 (59.4)	24 (60.0)	23 (67.6)	83 (59.7)	
▪ Technical college + university	12 (36.4)	12 (37.5)	14 (35.0)	5 (14.7)	43 (30.9)	
Impairment in daily living due to arm, shoulder, or hand	3 (9.1)	8 (25.0)	10 (25.0)	5 (14.7)	26 (18.7)	2 (1.4)
Impaired vision (using glasses or contact lenses)	3 (9.1)	3 (9.4)	6 (15.0)	5 (14.7)	17 (12.2)	6 (4.3)
Medication characteristics						
Medication						0 (0.0)
▪ Fragmin (dalteparin)	33 (100.0)	32 (100.0)	22 (55.0)	14 (41.2)	101 (72.7)	
▪ Clexane (enoxaparin)			11 (27.5)	5 (14.7)	16 (11.5)	
▪ Fraxiparine (nadroparin)			2 (5.0)	12	14 (10.1)	
▪ Fraxiforte (nadroparin)			1 (2.5)	2 (5.9)	3 (2.2)	
▪ Sandoparin (certoparin)			2 (2.5)	1 (2.9)	3 (2.2)	
▪ Arixtra (fondaparinux)			2 (5.0)	0 (0.0)	2 (1.4)	
Application once daily	33 (100.0)	30 (93.8)	33 (82.5)	27 (79.4)	123 (88.5)	2 (1.4)
▪ Not specified on prescription	0 (0.0)	2 (6.2)	7 (17.5)	4 (11.8)	13 (9.4)	
Reason for LMWH treatment (multiple answers possible)						2 (1.4)

▪ Injury/orthopedic surgery	31 (93.9)	32 (100.0)	31 (77.5)	20 (58.8)	114 (82.0)	
▪ Thrombosis, embolism	2 (6.1)	0 (0.0)	3 (7.5)	3 (8.8)	8 (5.8)	
▪ Perioperative management/bridging	0 (0.0)	0 (0.0)	4	2 (5.9)	6 (4.3)	
▪ Atrial fibrillation, myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	3 (8.8)	3 (2.2)	
▪ Other	0 (0.0)	0 (0.0)	3 (7.5)	4 (11.8)	7 (5.0)	
Parameters on patients' self-reports						
Previous outpatient s.c. injection therapies	19 (57.6)	23 (71.9)	19 (47.5)	15 (44.1)	76 (54.7)	2 (1.4)
History of first self-injection in the presence of a medical professional	20 (60.6)	18 (56.3)	23 (57.5)	20 (58.8)	81 (58.3)	3 (2.2)
Injection site (multiple answers possible)						2 (1.4)
▪ Thigh	27 (81.8)	24 (75.0)	26 (65.0)	20 (58.8)	97 (69.8)	
▪ Abdomen	13 (39.4)	15 (46.9)	18 (45.0)	16 (47.1)	62 (44.6)	
Adverse drug reactions (multiple answers possible)	33 (100.0)	29 (90.6)	37 (92.5)	17 (50.0) *	116 (83.5)	2 (1.4)
▪ Hematoma at injection site	31 (93.9)	26 (81.3)	35 (87.5)	15 (44.1)	107 (77.0)	
▪ Mild injection site irritation/burning	16 (48.5)	17 (53.1)	22 (55.0)	5 (14.7)	60 (43.2)	
▪ Hematoma in general	2 (6.1)	2 (6.3)	5 (12.5)	3 (8.8)	12 (8.6)	
▪ Site pain	3 (9.1)	0 (0.0)	4 (10.0)	3 (8.8)	10 (7.2)	
▪ Induration	5 (15.2)	0 (0.0)	3 (7.5)	0 (0.0)	8 (5.8)	
▪ Exanthema	1 (3.0)	2 (6.3)	0 (0.0)	0 (0.0)	3 (2.2)	
▪ Bleeding tendency; *n*=1 met criteria for reporting an adverse event to regulatory authority (melena)	1 (3.0)	0 (0.0)	1 (2.5)	1 (2.9)	3 (2.2)	
▪ Epistaxis	0 (0.0)	1 (3.1)	1 (2.5)	0 (0.0)	2 (1.4)	
▪ Other	2 (6.1)	2 (6.3)	9 (22.5)	0 (0.0)	13 (9.4)	

Unscheduled visit with physician/hospital	6 (18.2)	3 (9.4)	5 (12.5)	0 (0.0)	14 (10.1)	1 (0.7)
▪ Exanthema; *n*=2 met criteria for reporting an adverse event to regulatory authority	1/6 (16.7)	2/3 (66.7)	0/5 (0.0)	0/0 (0.0)	3/14 (21.4)	0/14 (0.0)
Skipping injections	4 (12.1)	6 (18.8)	7 (17.5)	1 (2.9)	18 (12.9)	9 (6.5)
▪ 1 time	2/4 (50.0)	4/6 (66.7)	6/7 (85.7)	1/1 (100.0)	13/18 (72.2)	0/18 (0.0)
▪ >3 times	0/4 (0.0)	1/6 (16.7)	1/7 (14.3)	0/1 (0.0)	2/18 (11.1)	
Reason for skipping injections (multiple answers possible)						0/18 (0.0)
▪ Forgotten	2/4 (50.0)	5/6 (83.3)	5/7 (71.4)	0/1 (0.0)	12/18 (66.7)	
▪ Not being at home	1/4 (25.0)	2/6 (33.3)	1/7 (14.3)	0/1 (0.0)	4/18 (22.2)	
▪ Early discontinuation	1/4 (25.0)	0/6 (0.0)	1/7 (14.3)	0/1 (0.0)	2/18 (11.1)	
▪ Needle phobia	0/4 (0.0)	0/6 (0.0)	1/7 (14.3)	0/1 (0.0)	1/18 (5.6)	
▪ No acceptance, no need of LMWH	0/4 (0.0)	0/6 (0.0)	1/7 (14.3)	0/1 (0.0)	1/18 (5.6)	
▪ Other	2/4 (50.0)	0/6 (0.0)	1/7 (14.3)	1/1 (100.0)	4/18 (22.2)	

***** $p \leq 0.05$.

[a] All data is presented as the number (*n*) with the percentage in parenthesis, with the exception of 'Age', which is presented as the median with the interquartile range in parenthesis.

LMWH Low-molecular-weight heparins; *s.c.* Subcutaneous; *ClinS-I* Intervention group, clinical setting; *ClinS-C* Control group, clinical setting; *DailyS-I* Intervention group, daily life setting; *DailyS-C* Control group, daily life setting

Table 3 Scores of the different domains (score minimum=−2.00; score maximum=+2.00) and results from the syringe count

	ClinS-I (*n*=33)	ClinS-C (*n*=32)	*p* value (Mann-Whitney)	DailyS-I (*n*=40)	DailyS-C (*n*=34)	*p* value (Mann-Whitney)	ClinS-I + DailyS-I (*n*=73)	ClinS-C + DailyS-C (*n*=66)	*p* value (Mann-Whitney)
Domains	**Scores**, mean (standard deviation)								
Application quality (DOT)	1.25 (0.27)	0.86 (0.33)	*p*<0.01	1.20 (0.41)	1.17 (0.40)	*p*=0.80	1.22 (0.36)	1.02 (0.39)	*p*<0.01
Knowledge	1.10 (0.38)	0.95 (0.41)	*p*=0.05	1.03 (0.33)	0.94 (0.40)	*p*=0.38	1.06 (0.35)	0.95 (0.41)	*p*=0.03
Application quality, self-assessment	1.27 (0.47)	1.34 (0.41)	*p*=0.56	1.20 (0.53)	1.20 (0.38)	*p*=0.97	1.23 (0.50)	1.27 (0.40)	*p*=0.77
Compliance, self-assessment	1.43 (0.58)	1.32 (0.78)	*p*=0.93	1.35 (0.75)	1.59 (0.38)	*p*=0.47	1.38 (0.68)	1.46 (0.62)	*p*=0.68
Assistance quality, self-assessment	1.09 (0.38)	1.02 (0.44)	*p*=0.54	1.19 (0.68)	1.52 (0.62)	*p*<0.01	1.14 (0.56)	1.28 (0.59)	*p*=0.05
Compliance (syringe count)	**%**[a], mean (standard deviation)								
	94.5 (10.5)	96.2 (10.6)	*p*=0.36	95.1 (10.0)	97.5 (4.2)	*p*=0.72	94.8 (10.2)	96.8 (7.9)	*p*=0.40

[a] Overall range 48–100%.

ClinS-I Intervention group, clinical setting; *ClinS-C* Control group, clinical setting; *DailyS-I* Intervention group, daily life setting; *DailyS-C* Control group, daily life setting

Table 4 Error rates of clinically relevant administration steps and the influence of the interventions upon them

s.c. injection steps (chronological listing) Observations during the DOTs (*n*=128)	*n* (%)	Missing data *n* (%)	Intervention (ClinS-I + DailyS-I) vs. control (ClinS-C + DailyS-C) *p* value (Mann-Whitney test)
No washing or disinfection of hands right before injection	85 (66.4)	2 (1.6)	*p*=0.01 favouring intervention
Not waiting for the alcohol to evaporate (*n*=124)	58 (46.8)	2 (1.6)	*p*=0.03 favouring intervention
Difficulties to remove needle shield	12 (9.4)	0 (0.0)	*p*=0.84
Need of a new pre-filled syringe due to wrong removal of needle shield	1 (0.8)	2 (1.6)	*p*=0.29
Removal of air bubble	11 (8.6)	1 (0.8)	*p*=0.26
Not pinching a skin fold	15 (11.7)	0 (0.0)	*p*=0.84
No puncture into cleansed skin area (*n*=124)	1 (0.8)	0 (0.0)	*p*=0.14
Not inserted the full length of the needle into the skin	13 (10.2)	0 (0.0)	*p*=0.29
Not waited a second before withdrawing the needle	43 (33.6)	0 (0.0)	*p*=0.19
Skin fold released *before* withdrawing the needle (*n*=117)	12 (10.3)	1 (0.9)	*p*<0.01 favouring intervention
Recapping	57 (44.5)	0 (0.0)	*p*<0.01 favouring intervention
Syringe not disposed immediately after withdrawing the needle	45 (35.2)	0 (0.0)	*p*=0.20

ClinS-I Intervention group, clinical setting; *ClinS-C* Control group, clinical setting; *DailyS-I* Intervention group, daily life setting; *DailyS-C* Control group, daily life setting

Table 5 Patients' assessment of the received assistance quality (SOP)

	ClinS-I (*n*=33)	DailyS-I (*n*=40)	ClinS-I + DailyS-I (*n*=73)	Missing data
	SOP, *n* (%)			
Assistance quality				
▪ Delivery of leaflet - helpful	17/32 (53.1) *	29/36 (80.6)	46/68 (67.6)	0/68 (0.0)
▪ Delivery of a manual - helpful	20/32 (62.5)	24/33 (72.7)	44/65 (67.7)	0/65 (0.0)
▪ Delivery of a kit (alcohol/cotton swabs, plasters) - helpful	29/33 (87.9)	38/39 (97.4)	67/72 (93.1)	0/72 (0.0)
▪ Delivery of a sharps collector - helpful	22/33 (66.7)	26/40 (65.0)	48/73 (65.8)	21/73 (28.8)
▪ Oral instructions - helpful	22/31 (71.0)	23/28 (82.1)	45/59 (76.3)	0/59 (0.0)
▪ Injection training into a 'phantom' - helpful	21/28 (75.0)	8/9 (88.9)	29/37 (78.4)	0/37 (0.0)
▪ Commercial video tape - helpful	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
▪ (First) self-injection in the presence of a pharmacist - helpful	0/0 (0.0)	3/3 (100.0)	3/3 (100.0)	0/3 (0.0)
▪ (First) injection administered by a pharmacist - helpful	1/1 (100.0)	0/0 (0.0)	1/1 (100.0)	0/1 (0.0)

***** $p \leq 0.05$.

ClinS-I Intervention group, clinical setting; *ClinS-C* Control group, clinical setting; *DailyS-I* Intervention group, daily life setting; *DailyS-C* Control group, daily life setting

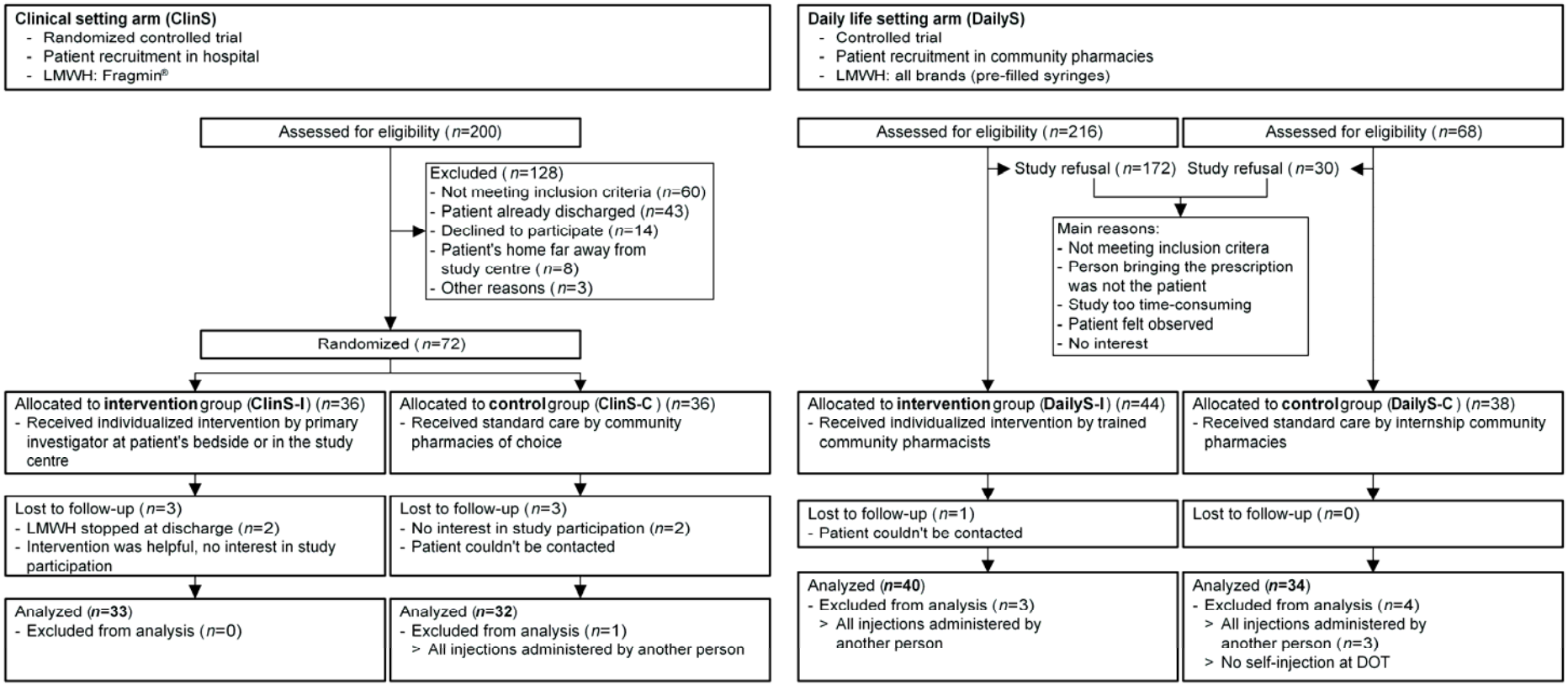


Fig. 1 Study flowchart with reasons for exclusion

LMWH Low-molecular-weight heparins

Appendix

Table 1 Questions assigned to the particular domains

Domains: Self-assessment (subjective by patients)	**Application quality** ▪ Confidence in the beginning[a] / at DOT / at the end[b]? ▪ Degree of effort required in the beginning / at the end? ▪ Difficulties with removal of needle shield in the beginning / at the end? ▪ Puncture painful in the beginning / at the end / throughout therapy? ▪ Injection painful in the beginning / at the end / throughout therapy? ▪ Self-injection or injections administered by another person in a future s.c. therapy? **Assistance quality** ▪ Sufficiently informed about injection site? ▪ Sufficiently informed about injection technique? **Compliance** ▪ Difficulties with regular application of LMWH? ▪ Degree of personal responsibility concerning compliance of LMWH? ▪ Skipped injections (and how many)? ▪ Degree of compliance concerning prescribed injection time?
Domains: Reality (objective by investigators	**Application quality (DOT)** ▪ Pre-filled syringe / alcohol swab / cotton swab / plaster / sharps collector within easy reach? ▪ Washing or disinfection of hands right before injection? ▪ Injection site? ▪ Disinfection of the skin area (e.g. by a single wipe; rubbing; no disinfection)? ▪ Waited for the alcohol to evaporate / let it dry? ▪ No contact with disinfected skin area? ▪ Difficulties to remove needle shield? ▪ Horizontal removal of the needle shield by pulling it straight off the syringe using both hands? ▪ Need of a new pre-filled syringe due to wrong removal of needle shield? ▪ Reattachment of needle shield? ▪ Removal of air bubble? ▪ Drop on the needle (e.g. shaken off; wiped off; left; no drop)? ▪ Pinched a skin fold (e.g. an inch; less than an inch; no skin fold)? ▪ Puncture into cleansed skin area? ▪ Full length of the needle inserted into the skin?

	▪ Waited a second before withdrawing the needle? ▪ Thumb grip pressed when withdrawing the needle? ▪ Needle withdrawn at the same angle that it was inserted? ▪ Skin fold released *after* withdrawing the needle? ▪ Skin area swabbed after injection (e.g. swabbing gently; rubbing; no swabbing)? ▪ Investigator's assessment of patient's confidence ▪ Syringe disposed immediately after withdrawing the needle? ▪ Recapping? **Assistance quality**[c] **Compliance**[d] **Knowledge** ▪ Consistency with prescribed therapy duration? ▪ Consistency with prescribed daily injections? ▪ Consistency with prescribed injection time? ▪ Injection site? ▪ Recapping? ▪ Reason for LMWH treatment? ▪ Potential interactions with over the counter medication? ▪ Potential adverse drug reactions? ▪ Action taken if mild injection site irritation, burning or hematoma at injection site occurred? ▪ Action taken if sudden malaise occurred?

[a] Asked for at telephone interview.

[b] Asked for at final interview.

[c] No score: interventions were carried out only if required.

[d] No score: syringe count used.

4 General discussion and conclusions

In this thesis, we evaluated the characteristics and prevalence of drug use problems and handling difficulties with pre-filled LMWH syringes and the impact of pharmaceutical care on outpatient s.c. injection therapies.

Project A is based upon the reports from patients and nurses experiencing considerable difficulties when removing the needle shields of some LMWH pre-filled syringes. The triangulation of methods ─ comprising self-assessment by a study population, simultaneous observer's assessment, and the determination by mechanical pull-off tests ─ allowed evaluations of the degree of force required to remove the cap.

The objective mechanical pull-off tests confirmed the results from the subjective self- and observer's assessments. Despite international conferences on pre-filled syringes, manufacturers seemed to be unaware of this drug use problem, as we detected significant differences between different brands and even between different lots of the same brand, and as we were unable to find studies or an ISO-norm.

Forces needed to remove the needle shields (14─30 N) were in line with the forces required to handle with other medication, packaging, or devices (4─80 N) [38-40, 44]. Nevertheless, as maximal pinch strength decrease with age [38, 42], the cap-pull-off forces for LMWH devices might be too high for some patients, leading to unintentional, complete non-compliance. Even within our young study population (median age of 29 years), 4 out of 68 persons were not able to remove all needle shields.

The take-home message for us was that handling difficulties and drug use problems with medication, packaging, or devices might occur where neither the pharmaceutical industry, nor manufacturers, researchers, or community pharmacists would expect them to happen. It outlines the importance of the pharmacists' role in recognizing and preventing handling difficulties by offering an extensive first instruction, by monitoring patients' first self-administration under daily life conditions, and by a periodic outcome evaluation.

The main objectives of **project B** were to compile a complete list of drug use problems and handling difficulties with pre-filled syringes under daily life conditions and to objectively assess the compliance of outpatients on an s.c. injection treatment. The results should highlight potential areas for improvements in patient care through specific interventions to be used for the main study (project C).

Drug use problems were either associated with the handling of the injection-device or with the injection technique. Among our study participants, 85.0% experienced at least one relevant problem, with recapping being the most frequent difficulty encountered (73.7%). Only indirect measurement methods were used to assess patient compliance. We skipped the syringe count due to poor reliability: as a result of the daily life conditions, prescriptions were often incomplete, dates of the last injection were frequently missing, and not all used syringes were discarded into the sharps collectors. We therefore determined the amounts of residual drug volumes in the used syringes, which was ─ to our knowledge ─ a new approach. However, the potential evaporation of the residual liquid limited the validity of this measurement tool. The overall mean residual drug volumes were negligible. If residual drug was present, though, it tended to be of pharmacological relevance. As far as we know, no other study has analyzed the used syringes to this extent (percentage of recapping and properly activated post-injection needle guards, determination of residual drug volumes, syringe count). Our results clearly indicate the need for further investigation of medications with relevant injection volumes (≥0.5 ml).

Apart from the residual drug, no clear factors were associated with the injection site. Thus, our study concluded that from the application point of view, the two injection sites abdomen and thigh can equally be recommended. Patients at highest risk for drug use problems, handling difficulties, and leaving residual drug volumes are those who inject high volumes into the thigh, whose treatment requires a low application frequency, and who are at high risk of being impaired in fine motor skills. Methotrexate patients, fulfilling most of these characteristics and administering a cytotoxic agent, therefore demand special care. Extensive patient education and instruction in the s.c. injection technique as well as periodic monitoring of patient self-administrations are particularly important within this population.

Based upon our experiences from projects A and B, in **project C** we aimed to develop an SOP for the first instruction in the s.c. injection technique given by a community pharmacist and the subsequent pharmaceutical care provided during outpatient therapy. To assess its effectiveness, we compared the intensive pharmaceutical care with standard care in both a clinical setting (hospital wards under study conditions) and in a daily life setting (community pharmacies following their daily routine).

With respect to our initial hypotheses, our study was not able to show an impact of pharmaceutical care on compliance, satisfaction, or complications. High baseline skills and good compliance behaviour reduced the potential for change in patients receiving interventions. Nevertheless, intensified pharmaceutical care resulted in improved safety (better s.c. injection technique) and knowledge. And, especially, we could prove the feasibility of the interventions in daily pharmacy practice. Thus, our results confirmed the conclusions of an extensive review: that overall the effectiveness of PC remains unclear [55]. High baseline compliance behaviour seems to be a common phenomenon under study conditions: a review of the effectiveness of community pharmacist's interventions showed that in 38% of the studies, a change in compliance could not be observed [67]. The same might be true for patients' baseline skills in general. Inadequate sample sizes might be the limiting factor [67].

The dynamic, patient-centered PC process can be illustrated nicely by using the example of our main study (Fig. 7). Suboptimal outcomes might have arisen from inappropriate patient behaviour (non-compliance, handling difficulties), inappropriate delivery (by the community pharmacy), or inappropriate prescribing. DRP might have comprised improper drug selection (by the GP), failure to receive the drug as intended, adverse drug reactions, or drug interactions.

The pharmaceutical industry and manufacturers could support the community pharmacists in performing PC and the patients in achieving optimal outcomes by developing improved packaging: the secondary packaging could act as sharps collector at the same time and be equipped with alcohol swabs and an Universal Serial Bus (USB) stick containing written instructions in the s.c. injection technique and a video.

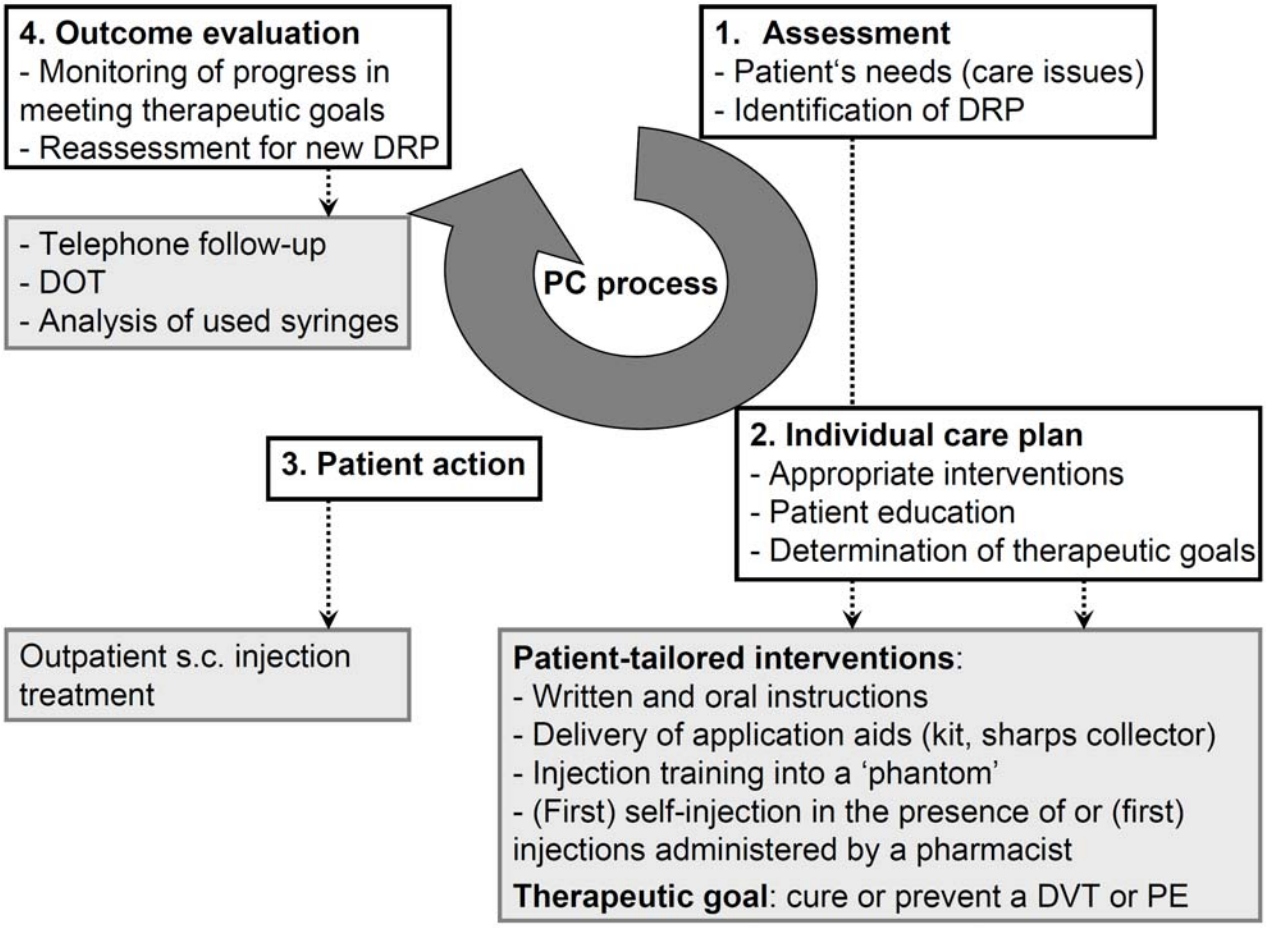


Fig. 7 The pharmaceutical care process illustrated on the example of the main study (project C)

DOT Direct observation technique; *DRP* Drug-related problems; *DVT* Deep vein thrombosis; *PC* Pharmaceutical care; *PE* Pulmonary embolism

Non-compliance was mostly unintentional comprising 'drug holidays' or wrong therapy durations, and was attributed to patient-related factors. Our strategies to improve compliance behaviour included multifaceted interventions, such as written and oral patient information, patient education, motivational interview, telephone follow-up, self-monitoring (use of diaries), close support (home visit), and involvement of relatives if needed. Although we used only indirect measurement methods to assess patient compliance behaviour (patient self-report, diaries, syringe count, residual drug volumes), we applied a multi-method approach combining self-reports and objective measures as recommended [62]. Though being the only way to objectively determine non-compliance (despite the determination of the residual drug

volumes), the syringe count also turned out to be not very reliable in this study, confirming the observations from project B.

In our main study (project C), the overall compliance rate was high with an overall mean of 95.8%. In the literature, non-compliance rates of 4.5−28.3% are found with outpatient LMWH treatments [35, 83, 103-105, 121]. Patients seem to have concerns with pre-filled syringes [35, 124], but are aware of their need. However, as poor compliance has been proved to be a worldwide phenomenon of striking magnitude with a prevalence of about 50%, it might not only be disease- and time-dependent [57-62], but also device-dependent. Patients needing to *inject* themselves with a medication might rate the necessity of the treatment higher than when swallowing 'just an additional' pill. With the rising number of new oral antithrombotic drugs on one hand and pre-filled injection systems on the other hand, we propose to investigate the following research questions in the future:

- comparison of concerns and needs [71, 72] between patients self-administering s.c. injections and patients taking oral medication on *short-term* treatments (e.g., LMWH vs. new oral direct factor Xa or thrombin inhibitors)
- comparison of concerns and needs between patients self-administering s.c. injections and patients taking oral medication on *long-term* treatments (e.g., methotrexate patients)

The transfer from the clinical setting in hospital wards under study conditions to the daily life setting in community pharmacies following their daily routine worked very well. Although under study conditions the results were slightly better, it was very encouraging that the SOP was feasible and appreciated in the daily life of community pharmacies. Our strategy of a single 2-hour training course, including theoretical and practical sessions, close support, and the provision of interventions requiring no more than 30 min might be reused for the implementation of other pharmaceutical services in the future. The method of 'learning from mistakes', which we applied to the analysis of the three videos showing s.c. injections with purposeful errors, proved to be a very suitable tool for educational purposes.

The **major challenges** of this thesis were:

- The development and validation of
  (1) an appropriate questionnaire for data collection
  (2) domains and scores as outcome measures
  (3) an appropriate tool to monitor and assess patient's s.c. injection technique in the context of a direct observation technique (DOT) during a home visit
- The standardization of data collection
- The development and performance of training courses for community pharmacists and Master's students
- The development and provision of patient-tailored interventions for outpatients on an s.c. injection therapy, such as written information material (leaflet, manual)
- The development of new methods, such as the determination of residual drug volumes in used syringes or the objective determination of forces needed to remove the needle shields from pre-filled LMWH syringes by mechanical pull-off tests
- The recruitment of an adequate number of study participants

In **conclusion** this thesis shows the following:

- The pull-off forces required to remove the needle shields of LMWH pre-filled syringes correspond roughly to the force needed to hold a narrow-neck plastic flask containing 1–3 l of water by pinching the neck between a finger and thumb. This seemed to be an unnoticed drug use problem so far.

- Drug use problems with outpatient s.c. injection therapies are very prevalent, diverse, and complex. They may be associated with the injection itself or with the handling of the injection-device. No associations with any factors studied were observed with non-compliance, the injection site (beside residual drug), and discomfort or effort required (beside prior injection use).

- The overall mean residual drug volume was negligible, but the total injection volume seemed to have an influence. If residual drug was present, however, it tended to be of pharmacological relevance. Patients injecting into the thigh showed a higher risk of leaving medication.

- From a patient's point of view, injections require some effort. Patients have concerns with pre-filled syringes, but are aware of their need. Further research should investigate whether compliance is not only disease- and time-dependent, but also device-dependent. We assume that intentional non-compliance might be lower with s.c. self-injections than with oral administration.

- The provided SOP for pharmacist interventions was of good quality, adequate, appreciated by the patients, and feasible in the daily life of community pharmacies. It resulted in improved s.c. injection technique and knowledge, despite high baseline patient skills. The home visits with the direct observation technique (DOT) were valuable in determining patient skills. Patients are capable of managing s.c. injection therapies in a satisfactory way and with high compliance if adequate assistance is provided.

- Overall, we confirmed our hypothesis that intensive pharmaceutical care for outpatients self-injecting LMWH resulted in more safety (objective assessment of the s.c. injection technique during the DOT), but we had to reject our assumptions of improved compliance, more satisfaction, and fewer complications.

- Our recommendations for daily practice are:
  (1) offering each person with a prescription for an outpatient s.c. injection treatment written information (leaflet, manual), application aids (alcohol swabs, sharps collector), and oral instructions (being the pivotal intervention in improving patients' s.c. injection technique)
  (2) the first self-injection should occur in the presence of a health-care professional to ensure proper injection technique (at patient's own individual injection time)

(3) injection training into a ‘phantom’ and further injections in the presence of or administered by a pharmacist are very supportive tools and should be applied if the patient requires lots of effort or has discomfort

(4) potential needle phobia and handling difficulties should be kept in mind

5 References

1 White RH (2003) The epidemiology of venous thromboembolism. Circulation 107 (23 Suppl 1): I4-8

2 Sandler DA, Martin JF (1989) Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? J R Soc Med 82 (4): 203-205

3 Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW (2008) Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 381S-453S

4 Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI (2008) Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 141S-159S

5 Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G (2008) Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 160S-198S

6 Patrono C, Baigent C, Hirsh J, Roth G (2008) Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 199S-233S

7 Weitz JI, Hirsh J, Samama MM (2008) New antithrombotic drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 234S-256S

8 Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, Becker RC, Ansell J (2008) The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 299S-339S

9 Warkentin TE, Greinacher A, Koster A, Lincoff AM (2008) Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 340S-380S

10 Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ (2008) Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 454S-545S

11 Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, Lip GY, Manning WJ (2008) Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 546S-592S

12 Salem DN, O'Gara PT, Madias C, Pauker SG (2008) Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 593S-629S

13 Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P (2008) Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 630S-669S

14 Harrington RA, Becker RC, Cannon CP, Gutterman D, Lincoff AM, Popma JJ, Steg G, Guyatt GH, Goodman SG (2008) Antithrombotic therapy for non-ST-segment elevation acute coronary syndromes: American College

of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 670S-707S

15 Goodman SG, Menon V, Cannon CP, Steg G, Ohman EM, Harrington RA (2008) Acute ST-segment elevation myocardial infarction: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 708S-775S

16 Becker RC, Meade TW, Berger PB, Ezekowitz M, O'Connor CM, Vorchheimer DA, Guyatt GH, Mark DB, Harrington RA (2008) The primary and secondary prevention of coronary artery disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 776S-814S

17 Sobel M, Verhaeghe R (2008) Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 815S-843S

18 Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J (2008) Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 844S-886S

19 Monagle P, Chalmers E, Chan A, DeVeber G, Kirkham F, Massicotte P, Michelson AD (2008) Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133 (6 Suppl): 887S-968S

20 Graf L, Tsakiris DA (2010) Neue Antikoagulanzien / Antithrombotika: Wo stehen wir 2010? Schweiz Med Forum 10 (45): 786-789

21 Lyman GH, Khorana AA, Falanga A, Clarke-Pearson D, Flowers C, Jahanzeb M, Kakkar A, Kuderer NM, Levine MN, Liebman H, Mendelson D, Raskob G, Somerfield MR, Thodiyil P, Trent D, Francis CW (2007)

American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 25 (34): 5490-5505

22 Bounameaux H (2009) The novel anticoagulants: entering a new era. Swiss Med Wkly 139 (5-6): 60-64

23 Garcia D, Libby E, Crowther MA (2010) The new oral anticoagulants. Blood 115 (1): 15-20

24 Documed AG (2011) Kompendium. http://www.kompendium.ch. Accessed 13 October 2011

25 pharmavista (2011) http://www.pharmavista.ch. Accessed 13 October 2011

26 Mengiardi S (2009) Neues orales Antikoagulans: Rivaroxaban (Xarelto®). i.m@il-Offizin 4

27 Gomez-Orellana I (2005) Strategies to improve oral drug bioavailability. Expert Opin Drug Deliv 2 (3): 419-433

28 http://www.pharma-kongress.de/daten/training/4_Fertigspritzen_Konferenz.pdf. Accessed 19 October 2011

29 http://www.visiongain.com/SearchResults.aspx?o=0&t=Pre-Filled+Syringes. Accessed 19 October 2011

30 VISIONGAIN (trading partner with the US Federal Government). Pre-Filled Syringes and Related Systems: World Market Outlook 2010-2025. http://www.visiongain.com. Accessed 20 October 2011

31 Commercial leaflets of Fragmin®, Clexane®, Fraxiparine®, and Arixtra® (2011)

32 Zaybak A, Khorshid L (2008) A study on the effect of the duration of subcutaneous heparin injection on bruising and pain. J Clin Nurs 17 (3): 378-385

33 Chan H (2001) Effects of injection duration on site-pain intensity and bruising associated with subcutaneous heparin. J Adv Nurs 35 (6): 882-892

34 Balci Akpinar R, Celebioglu A (2008) Effect of injection duration on bruising associated with subcutaneous heparin: a quasi-experimental within-subject design. Int J Nurs Stud 45 (6): 812-817

35 Mengiardi S, Tsakiris DA, Lampert ML, Hersberger KE (2011) Drug use problems with self-injected low-molecular-weight heparins in primary care. Eur J Clin Pharmacol 67 (2): 109-120

36 Clark CA, Mehta BH, Pruchnicki MC, Rodis JL (2006) The pharmacist's role in teaching methotrexate injection for patients with Crohn's disease. Am J Health-Syst Pharm 63: 1792-1794

37 Beckman A, Bernsten C, Parker MG, Thorslund M, Fastbom J (2005) The difficulty of opening medicine containers in old age: a population-based study. Pharm World Sci 27 (5): 393-398

38 Kircher W (2007) Anwendung von Arzneimitteln: Wie sich ergonomische und audiologische Probleme lösen lassen. http://www.pharmazeutische-zeitung.de/index.php?id=3264. Accessed 27 October 2011

39 Kircher W (2005) Anwendung von Augentropfen: Ergonomische Probleme individuell lösen. http://www.pharmazeutische-zeitung.de/index.php?id=485. Accessed 27 October 2011

40 Kircher W (2005) Tipps und Tricks, die nicht in der Packungsbeilage stehen: Hinweise für Kunden zur richtigen Handhabung verschiedener Arzneiformen. MMP 10: 351-356

41 Haefeli WE, Bertsche T, et al. (2006) Arzneimittel - Verabreichung und Einnahme. Ther Umsch 63 (6): 361-447

42 Sauer B (2010) Senioren: Medikamente schlecht im Griff. http://www.pharmazeutische-zeitung.de/index.php?id=33037. Accessed 27 October 2011

43 Arnet I, Hersberger KE (2010) Verbesserung der Compliance durch die Apotheke. Ther Umsch 67 (6): 293-301

44 Kircher W (2008) Insulinpens richtig anwenden. DAZ 25: 47-50

45 Hepler CD, Strand LM (1990) Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm 47 (3): 533-543

46 Cipolle RJ, Strand LM, Morley PC (2005) Pharmaceutical Care Practice. McGraw Hill, New York

47 Hudson SA, Mc Anaw JJ, Johnson BJ (2007) The Changing Roles Of Pharmacists In Society. IeJSME 1: 22-34

48 Hersberger KE, Arnet I (2006) Pharmaceutical Care - A New Discipline in the Curriculum: Introducing Pharmacy Students to Medication Non-Compliance. Chimia 60: 76-79

49 Becker C, Bjornson DC, Kuhle JW (2004) Pharmacist Care Plans and Documentation of Follow-up Before the Iowa Pharmaceutical Case Management Program. J Am Pharm Assoc (Wash DC) 44: 350-357

50 Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services (2011). 45th report of the WHO Expert

Committee on specifications for pharmaceutical preparations: WHO technical report series (Annex 8), No. 961. http://www.fip.org/statements. Accessed 5 November 2011

51 ESCP (European Society of Clinical Pharmacy). What is clinical pharmacy? http://www.escpweb.org/. Accessed 2 November 2011

52 Tarn DM, Heritage J, Paterniti DA, Hays RD, Kravitz RL, Wenger NS (2006) Physician communication when prescribing new medications. Arch Intern Med 166 (17): 1855-1862

53 Wiesner C (2001) Arzneimittelsicherheit in der Perihospitalphase - Eine patientenbezogene Analyse des Pharmakotherapieprozesses. Dissertation, University of Basel

54 http://www.psnc.org.uk/pages/nms.html. Accessed 5 November 2011

55 Eichenberger PM (2010) Pharmaceutical Care Practice - Drug-related Problems and Opportunities for New Services. Dissertation, University of Basel, pp 23-31

56 Haefeli WE, Arnet I (2001) Gründe für fehlende Arzneimittelwirkung. In: Documed AG (ed) Grundlagen der Arzneimitteltherapie. Basel, pp 51-57

57 Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X (2008) Interventions for enhancing medication adherence. Cochrane Database Syst Rev (2): CD000011

58 DiMatteo MR (2004) Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care 42 (3): 200-209

59 Sackett DL, Snow JC (1979) The magnitude of compliance and non compliance. In: Haynes RB, Taylor DW, Sackett DL (ed) Compliance in health care. Johns Hopkins University Press, Baltimore, pp 11–22

60 Bosworth HB, Granger BB, Mendys P, Brindis R, Burkholder R, Czajkowski SM, Daniel JG, Ekman I, Ho M, Johnson M, Kimmel SE, Liu LZ, Musaus J, Shrank WH, Whalley Buono E, Weiss K, Granger CB (2011) Medication adherence: a call for action. Am Heart J 162 (3): 412-424

61 Cushing A, Metcalfe R (2007) Optimizing medicines management: From compliance to concordance. Ther Clin Risk Manag 3 (6): 1047-1058

62 Sabaté E (2003) Adherence to long-term therapies: Evidence for action. World Health Organization. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Accessed 7 November 2011

63 Wasserfallen JB, Bourgeois R, Bula C, Yersin B, Buclin T (2003) Composition and cost of drugs stored at home by elderly patients. Ann Pharmacother 37 (5): 731-737

64 Cutler DM, Everett W (2010) Thinking outside the pillbox - medication adherence as a priority for health care reform. N Engl J Med 362 (17): 1553-1555

65 Laufs U, Rettig-Ewen V, Bohm M (2011) Strategies to improve drug adherence. Eur Heart J 32 (3): 264-268

66 Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA (2011) Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending. Health Affairs 30 (1): 91-99

67 Rickles NM, Brown TA, McGivney MS, Snyder ME, White KA (2010) Adherence: a review of education, research, practice, and policy in the United States. Pharmacy Practice 8 (1): 1-17. http://www.pharmacypractice.org/vol08/pdf/001-017.pdf. Accessed 17 November 2011

68 Schäfer-Keller P, Garzoni D, Dickenmann M, De Geest S (2010) Medikamentöse Nicht-Adhärenz - Prädiktive Faktoren und Diagnostik. Ther Umsch 67 (6): 283-288

69 Marinker M, Blenkinsopp A, Bond C, et al. (1997) From compliance to concordance: achieving shared goals in medicine taking. London: Royal Pharmaceutical Society of Great Britain

70 Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK (2008) Medication compliance and persistence: terminology and definitions. Value Health 11 (1): 44-47

71 Horne R, Weinman J (1999) Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res 47 (6): 555-567

72 Horne R (2006) Compliance, adherence, and concordance: implications for asthma treatment. Chest 130 (1 Suppl): 65S-72S

73 Jackevicius CA, Li P, Tu JV (2008) Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. Circulation 117 (8): 1028-1036

74 Lowry KP, Dudley TK, Oddone EZ, Bosworth HB (2005) Intentional and unintentional nonadherence to antihypertensive medication. Ann Pharmacother 39 (7-8): 1198-1203

75 Horne R, Hankins M, Jenkins R (2001) The Satisfaction with Information about Medicines Scale (SIMS): a new measurement tool for audit and research. Qual Health Care 10 (3): 135-140

76 Prochaska JO, DiClemente CC (1983) Stages and processes of self-change of smoking: toward an integrative model of change. J Consult Clin Psychol 51 (3): 390-395

77 Miller NH, Hill M, Kottke T, Ockene IS (1997) The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. Circulation 95 (4): 1085-1090

78 The National Collaborating Centre for Primary Care. Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009). http://www.nice.org.uk/nicemedia/live/11766/42971/42971.pdf. Accessed 9 November 2011

79 Clifford S, Barber N, Horne R (2008) Understanding different beliefs held by adherers, unintentional nonadherers, and intentional nonadherers: application of the Necessity-Concerns Framework. J Psychosom Res 64 (1): 41-46

80 Mahler C, Hermann K, Horne R, Ludt S, Haefeli WE, Szecsenyi J, Jank S (2010) Assessing reported adherence to pharmacological treatment recommendations. Translation and evaluation of the Medication Adherence Report Scale (MARS) in Germany. J Eval Clin Pract 16 (3): 574-579

81 Morisky DE, Ang A, Krousel-Wood M, Ward HJ (2008) Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich) 10 (5): 348-354

82 Horne R, Weinman J, Hankins M (1998) The Beliefs about Medicines Questionnaire (BMQ): the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health 14 (1): 1-24

83 Watts AC, Howie CR, Simpson AH (2006) Assessment of a self-administration protocol for extended subcutaneous thromboprophylaxis in lower limb arthroplasty. J Bone Joint Surg Br 88 (1): 107-110

84 Osterberg L, Blaschke T (2005) Adherence to medication. N Engl J Med 353 (5): 487-497

85 Walter P, Tsakiris DA, Romanens M, Kort W, Arnet I, Hersberger KE (2011) Fundamental progress in investigating drug resistance with electronic multidrug compliance monitoring (e-MCM). JPC 1 (2): 42-47

86 Spengler U (2010) Non Adherence - Non Response in der Transplantationsmedizin. Ther Umsch 67 (6): 317-322

87 Bangsberg DR, Perry S, Charlebois ED, Clark RA, Roberston M, Zolopa AR, Moss A (2001) Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS 15 (9): 1181-1183

88 Othieno R, Abu Affan M, Okpo E (2007) Home versus in-patient treatment for deep vein thrombosis. Cochrane Database Syst Rev (3): CD003076

89 Matsagas MI (2004) Outpatient treatment of venous thromboembolism using low molecular weight heparins. An overview. Int Angiol 23 (4): 305-316

90 Fahs PS, Kinney MR (1991) The abdomen, thigh, and arm as sites for subcutaneous sodium heparin injections. Nurs Res 40 (4): 204-207

91 Stäubli M, Suter J (2004) Die Komplikationenliste der Schweizerischen Gesellschaft für Innere Medizin. Schweiz Aerztezeitung 85 (21): 1109-1116

92 Huber AR (2005) Fragen aus der Praxis zum Thema Antikoagulation. Prim Care 5 (38): 773

93 Lemke H, Imhoff M, Lohlein D (1994) [Increased wound healing disorders in patients with inguinal hernia caused by administration of antithrombotic agents in the abdominal wall]. Chirurg 65 (8): 714-716

94 Donaldson J, Knowles CH, Clark SK, Renfrew I, Lobo MD (2007) Rectus sheath haematoma associated with low molecular weight heparin: a case series. Ann R Coll Surg Engl 89 (3): 309-312

95 Cuculi F, Gurzeler J (2006) [What is your diagnosis? Rectus sheath hematoma]. Praxis (Bern 1994) 95 (1-2): 11-12

96 Andereya S, Kalicke T, Hopf KF, Buschmeier M, Muhr G (2003) [Serious complication after subcutaneous injection of heparin for prophylaxis of thromboembolism. Case report]. Unfallchirurg 106 (2): 182-183

97 Pessina I, Bocchia M, Giansante P, Vaghi A (2003) [Hematoma of the rectus muscle of abdomen in a patient treated with nadroparin]. Recenti Prog Med 94 (7-8): 321-322

98 Luyx C, Vanpee D, Douala C, Gillet JB (2001) Acute dyspnea in a woman with swelling of the left leg treated with low molecular weight heparine. Am J Emerg Med 19 (3): 223-224

99 Morau D, Barthelet Y, Spilmann E, d'Athis F (2000) [Hematoma of the right rectus abdominis in relation to treatment with low-molecular-weight heparin]. Ann Fr Anesth Reanim 19 (1): 69-70

100 Berna JD, Zuazu I, Madrigal M, Garcia-Medina V, Fernandez C, Guirado F (2000) Conservative treatment of large rectus sheath hematoma in patients undergoing anticoagulant therapy. Abdom Imaging 25 (3): 230-234

101 Tsapatsaris NP (1991) Low-dose heparin. A cause of hematoma of rectus abdominis. Arch Intern Med 151 (3): 597-599

102 Webb KB, Hadzima S (1987) Hematoma of the rectus abdominis muscle: a complication of subcutaneous heparin therapy. South Med J 80 (7): 911-912

103 Spahn G (2002) Compliance with Self-Administration of Heparin Injections in Outpatients. Eur J Trauma 28: 104-109

104 Colwell CW, Pullido P, Hardwick ME, Morris BA (2005) Patient Compliance With Outpatient Prophylaxis: An Observational Study. Orthopedics 28 (2): 143 - 147

105 Le Gall C, Jacques E, Medjebeur C, Darques L, Briand F, Haddad J, Bleichner G (2006) Low molecular weight heparin self-injection training: assessment of feasibility, tolerance and economic analysis in emergency departments. Eur J Emerg Med 13 (5): 264-269

106 Mengiardi S, Goepfert B, Tsakiris DA, Hersberger KE (2009) Pitfalls in patient self-management of subcutaneous drug application: removal of rubber protection caps from ready-to-use syringes. Eur J Clin Pharmacol 65 (10): 1061-1062

107 Jorgensen JT, Romsing J, Rasmussen M, Moller-Sonnergaard J, Vang L, Musaeus L (1996) Pain assessment of subcutaneous injections. Ann Pharmacother 30 (7-8): 729-732

108 da Silva AA, Cassiani SH, Optiz SP (2002) [Evaluation of the technique of subcutaneous administration of heparin in the development of hematomas]. Rev Bras Enferm 55 (2): 128-133

109 Lalezari JP, Patel IH, Zhang X, Dorr A, Hawker N, Siddique Z, Kolis SJ, Kinchelow T (2003) Influence of subcutaneous injection site on the steady-state pharmacokinetics of enfuvirtide (T-20) in HIV-1-infected patients. J Clin Virol 28 (2): 217-222

110 Frid A, Hardebo JE (1997) The thigh may not be suitable as an injection site for patients self-injecting sumatriptan. Neurology 49 (2): 559-561

111 Frokjaer B, Sondergaard B, Herborg H (2004) Evidence report 3 - Follow-up on outcomes of drug therapy (Pharmaceutical Care). Pharmakon: 1-16

112 Blenkinsopp A, Hassey A (2005) Effectiveness and acceptability of community pharmacy-based interventions in type 2 diabetes: a critical review of intervention design, pharmacist and patient perspectives. Int J Pharm Practice 13: 231-240

113 Roughead EE, Semple SJ, Vitry AI (2005) Pharmaceutical care services: A systematic review of published studies, 1990 to 2003, examining effectiveness in improving patient outcomes. Int J Pharm Practice 13: 53-70

114 Machado M, Bajcar J, Guzzo GC, Einarson TR (2007) Sensitivity of patient outcomes to pharmacist interventions. Part II: Systematic review and meta-analysis in hypertension management. Ann Pharmacother 41 (11): 1770-1781

115 Machado M, Bajcar J, Guzzo GC, Einarson TR (2007) Sensitivity of patient outcomes to pharmacist interventions. Part I: systematic review and meta-analysis in diabetes management. Ann Pharmacother 41 (10): 1569-1582

116 Machado M, Nassor N, Bajcar JM, Guzzo GC, Einarson TR (2008) Sensitivity of patient outcomes to pharmacist interventions. Part III: systematic review and meta-analysis in hyperlipidemia management. Ann Pharmacother 42 (9): 1195-1207

117 Wubben DP, Vivian EM (2008) Effects of pharmacist outpatient interventions on adults with diabetes mellitus: a systematic review. Pharmacotherapy 28 (4): 421-436

118 Karch AM (2004) A needling problem. Am J Nurs 104 (4): 81-83

119 Urbaniak GC, Plous S (2011) Research Randomizer (Version 3.0) [Computer software]. http://www.randomizer.org/. Accessed May 2007

120 Harrison L, McGinnis J, Crowther M, Ginsberg J, Hirsh J (1998) Assessment of outpatient treatment of deep-vein thrombosis with low-molecular-weight heparin. Arch Intern Med 158 (18): 2001-2003

121 Deakin DE, Mishreki A, Aslam N, Docker C (2010) Patient compliance with extended low molecular weight heparin injections following hip and knee arthroplasty. Hip Int 20 (4): 555-558

122 Documed AG (2009) Kompendium: Xarelto® (Rivaroxaban). http://www.kompendium.ch/Monographie.aspx?Id=9b97842d-474d-47b6-b5d7-bb165ced277c&lang=de&MonType=fi. Accessed 29 June 2011

123 Treasure T, et al. (2010) Venous thromboembolism - reducing the risk: NICE guideline. http://www.nice.org.uk/guidance/CG92. Accessed 28 June 2011

124 Turner AP, Williams RM, Sloan AP, Haselkorn JK (2009) Injection anxiety remains a long-term barrier to medication adherence in multiple sclerosis. Rehabil Psychol 54 (1): 116-121

6 Appendix

Project A:

Project B:

Project B and C:

6.1 Data sheet for self-assessment and observer's assessment

INSTITUT FÜR KLINISCHE PHARMAZIE
Departement Pharmazie der Universität Basel

Pharmaceutical Care Research Group
Klingelbergstrasse 50, 4056 Basel

Spritzen-Vergleich

Datum: Tag ☐☐ Monat ☐☐ Jahr 2 0 0 ☐

Fragmin ®: Chargen-Nr. ☐☐☐☐☐☐☐☐ Exp.-date (mm/yy) ☐☐ / ☐☐

Fraxiparine ®: Chargen-Nr. ☐☐☐☐ Exp.-date (mm/yy) ☐☐ / ☐☐

Clexane ®: Chargen-Nr. ☐☐☐☐ Exp.-date (mm/yy) ☐☐ / ☐☐

Probanden-Code: P ☐☐ **Geschlecht:** ☐ männlich ☐ weiblich **Jahrgang:** 1 9 ☐☐

Haben Sie sich früher schon einmal Heparin spritzen müssen (Selbstinjektion)?

☐ ja ——— **Wie lange?** ☐ < 3 Tage ☐ 3 - 7 Tage ☐ > 7 Tage

☐ nein

☐ keine Angabe

Selbsteinschätzung: Visuelle Analog-Skala (VAS): Wie viel Mühe bereitet Ihnen das Abziehen der Schutzkappe von der Spitze? Stellen Sie den Schieber zwischen "keine Mühe" (100 mm) und "enorm grosse Mühe" (0 mm) ein.

Fragmin ®:

Hatte der Proband Mühe beim Abziehen der Schutzkappe von der Spritze?
☐ Proband bringt Kappe MÜHELOS weg
☐ Proband bringt Kappe nur MIT MÜHE weg
☐ Proband bringt die Kappe NICHT weg

Ging die Nadel dabei kaputt? ☐ nein ☐ ja

Skalawert VAS (0 -100mm) ☐☐☐

Wurde die Gummischutzkappe mit freien Armen in Längsrichtung der Nadel abgezogen?
☐ ja ☐ nein ☐ keine Angabe

Fraxiparine ®:

Hatte der Proband Mühe beim Abziehen der Schutzkappe von der Spritze?
☐ Proband bringt Kappe MÜHELOS weg
☐ Proband bringt Kappe nur MIT MÜHE weg
☐ Proband bringt die Kappe NICHT weg

Ging die Nadel dabei kaputt? ☐ nein ☐ ja

Skalawert VAS (0 -100mm) ☐☐☐

Wurde die Gummischutzkappe mit freien Armen in Längsrichtung der Nadel abgezogen?
☐ ja ☐ nein ☐ keine Angabe

Clexane ®:

Hatte der Proband Mühe beim Abziehen der Schutzkappe von der Spritze?
☐ Proband bringt Kappe MÜHELOS weg
☐ Proband bringt Kappe nur MIT MÜHE weg
☐ Proband bringt die Kappe NICHT weg

Ging die Nadel dabei kaputt? ☐ nein ☐ ja

Skalawert VAS (0 -100mm) ☐☐☐

Wurde die Gummischutzkappe mit freien Armen in Längsrichtung der Nadel abgezogen?
☐ ja ☐ nein ☐ keine Angabe

Bemerkungen: ☐ nein

☐ ja ———

———

8677

6.2 Mechanical pull-off tests

6.3 Local Ethics Committee approval

Beschlussmitteilung der Ethikkommission beider Basel

Die Ethikkommission beider Basel hat an ihrer Sitzung vom 17. April 2007 (in der Zusammensetzung, wie sie auf Seite 2 wiedergegeben ist) das nachstehende Forschungsprojekt eingehend begutachtet.

Titel des Forschungsprojektes Ref.Nr. EK: **95/07**

Selbstmanagement Heparintherapie - Compliance bei der Selbstinjektion von niedermolekularen Heparinen in der ambulanten Behandlung

Prüfer/in

Name, Vorname, Titel:	Hersberger, Kurt, PD Dr. sc. nat. & Tsakiris, Dimitrios, PD Dr. med.
Funktion:	Dozent Klein. Pharm., Uni Basel & Leitender Arzt, Hämostaselabor, USB
Adresse:	Pharmazentrum, Klingelbergstr. 50, 4056 Basel

Die Ethikkommission stützt ihre Beurteilung auf die Unterlagen, wie sie im beiliegenden "Antrag auf Begutachtung" vom 08. März 2007 abschliessend aufgezählt sind.

X normales Verfahren ☐ vereinfachtes Verfahren ☐ Nachbegutachtung

Die Ethikkommission kommt zu folgendem **Beschluss**:

X **A positiv**
☐ **B positiv mit Bemerkungen** (siehe Seite 2ff)
☐ **C mit Auflage** (siehe Seite 2ff)
Nachbegutachtung durch Ethikkommission notwendig ☐
schriftliche Mitteilung an Ethikkommission ausreichend ☐
☐ **D negativ (mit Begründung und Erläuterung für die Neubeurteilung)** (siehe Seite 2ff)
☐ **E Nicht-Eintreten (mit Begründung)** (siehe Seite 2ff)

Der Beschluss gilt auch für die im "Antrag auf Begutachtung" gemeldeten weiteren Prüfer/innen im Zuständigkeitsbereich der Ethikkommission.

Pro Memoria: **Pflichten des/der verantwortlichen Prüfers/in**
- Geprüfte Produkte und Vergleichsprodukte (Arzneimittel und Medizinalprodukte) müssen - zur Sicherstellung der Qualität und der Sicherheit - fachgerecht hergestellt, evaluiert und eingesetzt werden.
- Meldepflicht bei:
  a) schwerwiegenden unerwünschten Ereignissen (serious adverse events) unverzüglich
  b) neuen Erkenntnissen, die während des Versuchs verfügbar werden und die Sicherheit der Versuchspersonen sowie die Weiterführung des Versuchs beeinflussen können
  c) Änderung des Protokolls (Versuchsplans)
  d) Ende oder Abbruch der Studie
- Zwischenbericht: einmal pro Jahr
- Meldungs- oder Bewilligungspflicht von Studien bei Swissmedic bzw. anderen Bundes- oder kantonalen Behörden - sofern erforderlich (bei sponsorisierten Studien ist dies die Pflicht des Sponsors)
- Schlussbericht

Für die Ethikkommission:

Ort, Datum: Basel, 10. Mai 2007

Name(n): Prof. Dr. J. Drewe
Prof. Dr. H. Kummer

Unterschrift(en):

Ref. Nr. EK: 95/07

Zusammensetzung der Ethikkommission

Die Ethikkommission tagte in der nachfolgend erwähnten Zusammensetzung und war damit beschlussfähig (Art. 32 der Verordnung über klinische Versuche mit Heilmitteln vom 17. 10. 2001)

					am Beschluss beteiligt	
	Name, Vorname	**Berufliche Stellung / Titel**	**m**	**f**	**ja**	**nein**
Vorsitz	Prof. Dr. J. Drewe	Vizepräsident der EKBB	X	☐	X	☐
Mitglieder	Fr. PD Dr. B. Biedermann	Leitende Ärztin, Kantonsspital Bruderholz	☐	X	X	☐
	Fr. Dr. M. Hofecker	Psychiaterin, Praxis, Basel	☐	X	X	☐
	Fr. Dr. phil. S. Mendelowitsch	Fachpsychologin, Reha, Rheinfelden	☐	X	X	☐
	PD Dr. B. Meyer-Wyss	Leitender Arzt, St. Claraspital	X	☐	X	☐
	Herr S. Monteverde	Anästhesiepfleger, Bethesda-Spital, BS	X	☐	X	☐
	A. Wyss-Scholz	Röm.-kath. Pfarrei, St. Nikolaus, Reinach	X	☐	X	☐
	Fr. Dr. P. Schmid	Rechtsdienst P/S/R, US Basel	☐	X	X	☐
für Biometrie zuständiges Mitglied	Prof. Dr. J. Drewe	Leitender Arzt, Klinische Pharmakologie	☐	☐	☐	☐

Empfehlungen

Das Dekanat der Medizinischen Fakultät bietet Forschenden die Möglichkeit, Studien in einem internationalen Studienregister zu erfassen. Die EKBB empfiehlt Ihnen, sich zur Eröffnung eines User Accounts an das Dekanat (Frau C. Thoma, carolin.thoma@unibas.ch) zu wenden. Sie vermeiden damit mögliche Schwierigkeiten bei der späteren Publikation und leisten einen Beitrag zur Transparenz der wissenschaftlichen Aktivität an der Universität und weltweit.

(erweiterbar)

Auflagen

- **Die initialen Auflagen der EKBB (siehe Schreiben vom 20. April 2007) wurden erfüllt.**

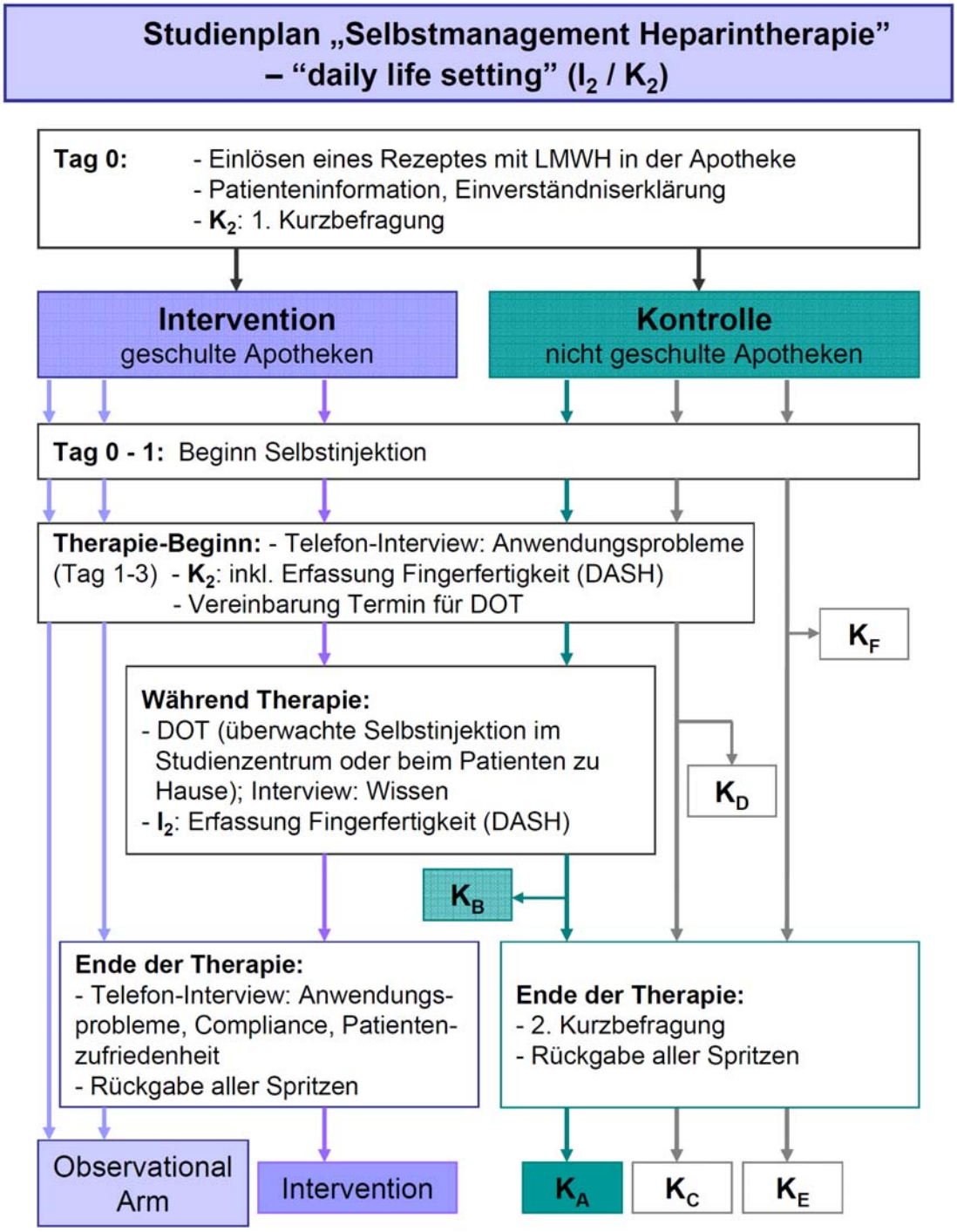
(erweiterbar)

Bemerkungen

- **Die EKBB hat die revidierte Patienteninformation und Einverständniserklärung (Version vom 26. April 2007), zustimmend zur Kenntnis genommen und genehmigt.**
- **Die EKBB bestätigt, dass sie nach GCP-ICH-Richtlinien arbeitet**

(erweiterbar)

6.4 Flowchart of the daily life setting (DailyS-I and DailyS-C)



6.5 Instructions for recruitment and data collection by trained Master's students (DailyS-C)

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

UNI BASEL

Assistenzjahr 2007/08: Institutionelle Pharmazie

Hausaufgabe „Selbstmanagement Heparintherapie"

Hintergrund und Ziel: Die Studierenden der ETH Zürich und der Universität Basel sollen im Rahmen der Institutionellen Pharmazie eine Aufgabe lösen, die sich mit der ambulanten Therapie subkutaner Selbstinjektionen am Beispiel der niedermolekularen Heparine (NMH) befasst. NMH werden therapeutisch oder zur Prävention von Thromboembolien eingesetzt. Die tägliche subkutane Injektion erfolgt (nach der Spitalentlassung) häufig zu Hause eigenständig durch den Patienten bzw. eine Drittperson. Daten zu Anwendungsproblemen und zur Compliance bei der ambulanten NMH-Therapie sind nur spärlich und von mässiger Qualität vorhanden, zeigen aber, dass die Compliance ein relevantes Problem darstellt und dass Therapieabbruch, bzw. –unterbruch häufig sind. Um die Patienten in der Apotheke zukünftig noch besser instruieren und beraten zu können, interessieren uns alle Schwierigkeiten, Probleme und Wünsche an begleitender Unterstützung vor und während der Therapie.

Aufgabe: Alle Studierenden

- sammeln die Fertigspritzen von **5** Heparin-Patienten in **e-safe-Boxen** (inkl. Kurzbefragungen bei Abgabe und Rücknahme von e-safe)
- führen mit **3** Patienten ein **Telefoninterview**
- beobachten **1** Patienten bei der Selbstinjektion (**DOT** = direct observation technique) im Rahmen eines home visits

Einschlusskriterien:	
- alle niedermolekularen Heparine (Fertigspritzen)	- Neu- oder Dauerverordnung
- prophylaktische oder therapeutische Therapie	- erwachsene Personen (≤ 18 Jahre)
- Selbstapplikation oder Injektion durch Drittperson	- genügend Deutsch-Kenntnisse

Ablauf:

- **Bei 5 Rezepten mit einem NMH:**
  Wird in der Apotheke ein Rezept mit einem NMH vorgelegt, wird dem Patienten (oder der Drittperson) der Hintergrund der Hausaufgabe erläutert. Erklärt sich die Person mit der Teilnahme einverstanden, erfolgt die normale Rezeptvalidierung in der Apotheke, die erste Kurzbefragung sowie die Abgabe einer e-safe Box (mit aufgeklebter Etikette) und eines Patientenblattes.
- **3 Telefon-Interviews (am Tag 1 – 3 nach Bezug / Beginn der NMH-Therapie):**
  Von diesen 5 Patienten wird mit 3 Personen ein Datum für ein ca. 10-minütiges Telefoninterview abgemacht, auf dem Patientenblatt vermerkt und durchgeführt.
- **1 DOT (überwachte Selbstapplikation):**
  Von diesen 5 Patienten wird mit 1 Person ein Datum für ein *home visit* / DOT abgemacht, ev. auf dem Patientenblatt vermerkt und durchgeführt.
- **Rückgabe der e-safe-Boxen:**
  Am Therapieende wird bei der Rückgabe der e-safe's die 2. Kurzbefragung durchgeführt.

Testatbedingungen: Jede/r Student/in sammelt 5 e-safe's, führt 3 Interviews durch und macht 1 DOT
Wichtig: keine persönlichen Daten (Name, Adresse, Telefonnummer, etc.) auf den Erfassungssets vermerken → Sets müssen anonymisiert sein!

Zeitplan:

17./18. Januar `08	Information und Verteilung der Aufgabe
9. Mai `08	Ende der Datenerhebungen: Die 5 e-safe-Boxen, 5 Erfassungssets und ungebrauchten, retournierten Fertigspritzen werden so rasch wie möglich abgegeben an: Seraina Mengiardi / Raphaela von Grünigen, Pharmazentrum – Kragenbau 0059, Klingelbergstr. 50, Basel

Bei Fragen oder Unklarheiten: Dr. Markus Lampert (mlampert@uhbs.ch), Irene Vogel-Kahmann (irene.vogel@bluewin.ch), PD Dr. Kurt Hersberger (kurt.hersberger@unibas.ch), Seraina Mengiardi (seraina.mengiardi@unibas.ch; Tel.: 061 267 15 29)

6.6 Patient information for the DailyS-C arm (oral informed consent)

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

UNI BASEL

PATIENTENBLATT

Erfassung von Anwendungsproblemen bei Patienten, welche sich selber zu Hause niedermolekulares Heparin spritzen

Sehr geehrte Patientin,
Sehr geehrter Patient,

Sie haben von Ihrem Arzt ein Rezept für den Bezug eines niedermolekularen Heparins in einer öffentlichen Apotheke erhalten. Sie werden sich dieses Medikament täglich selbst unter die Haut spritzen. Diese Therapie ist wichtig, sie wird aber nicht von allen Personen mit gleicher Leichtigkeit ausgeführt. Um die Patienten zukünftig in der Apotheke noch besser instruieren und beraten zu können, interessieren uns alle Ihre Schwierigkeiten, Probleme und Ihre Wünsche an begleitender Unterstützung vor und während dieser Therapie. Die Pharmazie-Studierenden der Universität Basel und ETH Zürich, welche zur Zeit ihr Praktikum in einer Apotheke absolvieren, haben deshalb verschiedene Aufgaben erhalten, um entsprechende Daten zu sammeln. Ihre Teilnahme ist freiwillig und Sie können Ihr Einverständnis zu jedem Zeitpunkt zurückziehen. Ihre Daten werden selbstverständlich anonymisiert und vertraulich behandelt.

Ablauf

- **Abgabe Entsorgungsbox:** Wenn Sie sich einverstanden erklären, wird Ihnen die/der Student/in eine gelbe Entsorgungsbox mitgeben: Bitte werfen Sie alle gebrauchten Fertigspritzen in diese Box. Anderes Verbrauchsmaterial können Sie in den normalen Hausabfall werfen (bitte nicht in die Entsorgungsbox).
- **Telefon-Interview:** 1 – 3 Tage nach dem Besuch in der Apotheke wird die/der Student/in mit Ihnen ein ca. 10-minütiges Telefoninterview führen:

Ihr Termin für das Telefoninterview: Datum: …….. Zeit: ……. Uhr

- An einem vereinbarten Termin wird die/der Student/in zu Ihnen nach Hause kommen und Ihnen bei einer Injektion zuschauen:

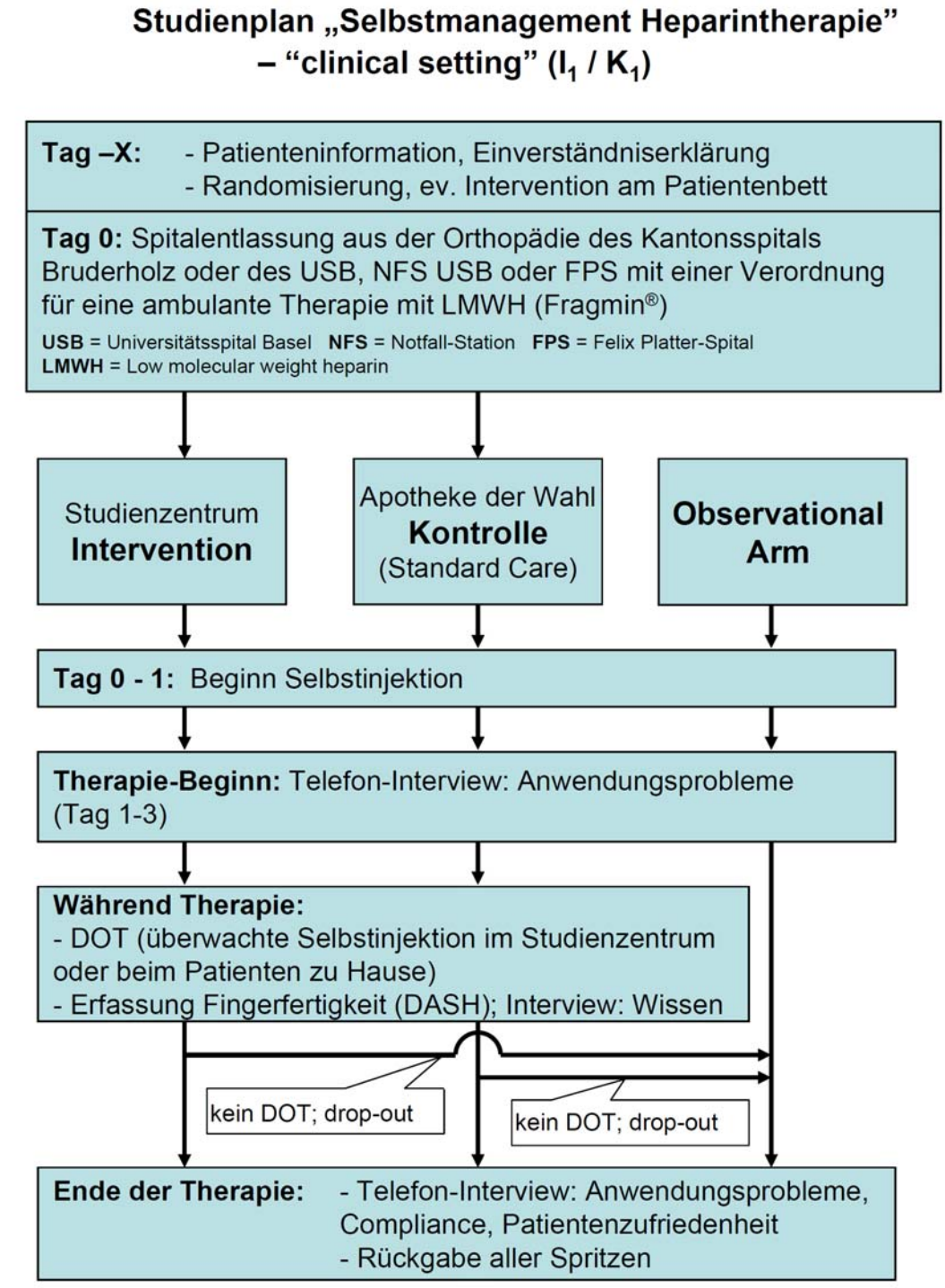
Ihr Termin für den Hausbesuch: Datum: …….. Zeit: ……. Uhr

- Sobald Sie die Therapie beendet haben, bitten wir Sie, die **Entsorgungsbox** sowie die restlichen, ungebrauchten Fertigspritzen **in Ihre Apotheke zurückzubringen**. Wir werden diese für Sie entsorgen. Bei dieser Gelegenheit wird Ihnen die/der Student/in ein letztes Mal einige wenige Fragen stellen.

--- Herzlichen Dank für Ihre Teilnahme, Ihre Bemühungen und Ihre Zeit! ---

Kontaktperson bei Fragen:	Seraina Mengiardi eidg. dipl. Apothekerin, Doktorandin Klinische Pharmazie, Universität Basel Tel.: 061 267 15 29 Mail: seraina.mengiardi@unibas.ch

6.7 Flowchart of the clinical setting (ClinS-I and ClinS-C)



K. Hersberger / S. Mengiardi 8.3.07, Inst. F. Klin. Pharmazie UNI BS

6.8 Instructions for recruitment and interventions by trained community pharmacists (DailyS-I)

Institut für Klinische Pharmazie
Pharmaceutical Care Research Group
Departement Pharmazie der Universität Basel
Klingelbergstrasse 50
4056 Basel

UNI
BASEL

Studie "Selbstmanagement Heparintherapie"
Studienarm "daily life setting" (I_2)

Erfassung von Anwendungsproblemen bei Patienten, welche sich ambulant niedermolekulares Heparin spritzen

Hintergrund und Ziel:

Ambulante s.c.-Therapien werden immer häufiger und werden bei diversen Therapien eingesetzt, z.B. zur Thromboembolieprophylaxe / -therapie, bei Multipler Sklerose, (rheumatoider) Arthritis, zur Eigenblutgewinnung oder in der Reproduktionsmedizin.
Die tägliche subkutane Injektion von niedermolekularen Heparinen (NMH) erfolgt (nach der Spitalentlassung) häufig zu Hause eigenständig durch den Patienten bzw. eine Drittperson. Daten zu Anwendungsproblemen und zur Compliance bei der ambulanten NMH-Therapie sind nur spärlich und von mässiger Qualität vorhanden, sie zeigen aber, dass die Compliance ein relevantes Problem darstellt und dass Therapieabbruch, bzw. –unterbruch häufig sind. Um die Patienten in der Apotheke zukünftig noch besser instruieren und beraten zu können, interessieren uns alle Schwierigkeiten, Probleme und Wünsche an begleitender Unterstützung vor und während der Therapie. Zudem möchten wir untersuchen, ob eine intensivierte Instruktion durch Fachpersonen zu mehr Sicherheit führt. Das Endziel der Studie ist die Implementierung einer neuen Dienstleistung in der Offizin.

Vorgehen:

1) **Einlösung eines NMH-Rezeptes** → normale Rezeptvalidierung gemäss Standard in Ihrer Apotheke

2) Durchführung der **Intervention** gemäss den individuellen Bedürfnissen des Patienten:
   - Abgabe
     - ausführliches Info-Faltblatt
     - laminierte Spritzanleitung
     - Ausrüstungspaket (Alkoholtupfer, Wattetupfer, Pflaster für 20 Tage)
     - e-safe-Entsorgungsbox
   - mündliche Instruktion zur Selbstinjektion
   - üben am Phantom
   - eigenständige Erstapplikation unter Aufsicht des Apothekers
     (*cave: abhängig von der Applikationszeit des Patienten!*)
   - ev. Erstapplikation durch Apotheker
     (*cave: abhängig von der Applikationszeit des Patienten!*)

3) **Patientenrekrutierung:**

Einschlusskriterien:	
- alle niedermolekularen Heparine (Fertigspritzen)	- Neu- oder Dauerverordnung
- prophylaktische oder therapeutische Therapie	- erwachsene Person (≥ 18 Jahre)
- Selbstapplikation (keine Drittperson)	- genügend Deutsch-Kenntnisse

- Geeigneten Patienten **Patienten-Information** zur Studie „Selbstmanagement Heparintherapie" I_2 abgegeben
- Bei Zustimmung zur Studienteilnahme: Ausfüllen von **Einverständniserklärung** (Informed Consent I_2) **mit Unterschrift → wird von der Apotheke aufbewahrt**
- Dem Patienten die **Patienten-Information** und **leere Einverständniserklärung mitgeben**

- **Vereinbarung** eines Termins für ein ca. 10-minütiges **Telefoninterview**, 1-3 Tage nach Bezug / Beginn der NMH-Therapie → auf unterschriebener Einverständniserklärung Datum, Uhrzeit und Telefon-Nummer vermerken
- Name des Patienten auf **Etikette** übertragen und Etikette auf e-safe-Entsorgungsbox kleben
- **Ausgefüllte Einverständniserklärung mit Termin und Telefon-Nummer für erstes Telefoninterview an das Studienteam faxen: 061 267 14 28 oder mailen: seraina.mengiardi@unibas.ch**

--- Ende Patientenrekrutierung ---

→ Apotheken instruieren und rekrutieren
→ gesamte Datenerfassung (Telefon-Interview etc.) erfolgt durch das Studienteam
→ gesamtes Interventionsmaterial wird vom Studienteam zur Verfügung gestellt

--- Herzlichen Dank für Ihre Bemühungen und wertvolle Unterstützung! ---

Ihre Kontaktperson:
Seraina Mengiardi
eidg. dipl. Apothekerin, Doktorandin
Klinische Pharmazie, Universität Basel
Tel.: 061 267 15 29 Fax: 061 267 14 28
e-mail: seraina.mengiardi@unibas.ch

6.9 Informed consent for the ClinsS-I, ClinS-C and DailyS-I arms

Institut für Klinische Pharmazie
Pharmaceutical Care Research Group
Departement Pharmazie der Universität Basel
Klingelbergstrasse 50
4056 Basel

Kantonsspital Bruderholz
Klinik für Orthopädische Chirurgie
und Traumatologie des
Bewegungsapparates
4101 Bruderholz

PATIENTEN-INFORMATION zur Studie "Selbstmanagement Heparintherapie"

EKBB 95/07 (Studiennummer der Ethikkommission beider Basel)

Erfassung von Anwendungsproblemen bei Patienten nach einer orthopädischen Operation, welche sich selbst zu Hause niedermolekulares Heparin spritzen

Sehr geehrte Patientin,
Sehr geehrter Patient,

Sie werden oder haben von Ihrem behandelnden Stationsarzt ein Rezept für den Bezug von Fragmin® in einer öffentlichen Apotheke erhalten. Dieses Medikament hemmt die Blutgerinnung und wird in Ihrem Fall eingesetzt, um das Auftreten von Thrombosen (Blutgerinnsel, welche die Gefässe verstopfen können) nach der Operation zu verhindern. Sie werden sich selbst Fragmin® täglich unter die Haut spritzen. Diese Therapie ist wichtig, sie wird aber nicht von allen Personen mit gleicher Leichtigkeit durchgeführt.

Ziel der Studie
Um die Patienten in der Apotheke zukünftig noch besser instruieren und beraten zu können, interessieren uns alle Ihre Schwierigkeiten, Probleme und Ihre Wünsche an begleitender Unterstützung vor und während der Therapie. Zudem möchten wir untersuchen, ob eine intensivierte Instruktion durch Fachpersonen zu mehr Sicherheit führt.

Freiwilligkeit der Teilnahme und Rücktritt
Ihre Teilnahme an der Studie ist freiwillig. Sie können Ihr Einverständnis zu jedem Zeitpunkt zurückziehen, ohne dass Sie einen bestimmten Grund dafür angeben müssen oder Nachteile für Ihre weitere Behandlung zu erwarten haben. Das gleiche gilt, wenn Sie auf die Teilnahme an dieser Studie verzichten.

Ablauf der Studie
Ihr Arzt, bzw. Ihre Ärztin oder das Pflegepersonal im Spital werden oder haben Sie bezüglich Vorbereiten der Spritzen, der Injektionstechnik und der Dosierung informiert. Wenn Sie sich einverstanden erklären, wird Ihnen mitgeteilt, in welche Gruppe Sie eingeteilt werden:

Gruppe A) erhält kurz vor der Spitalentlassung durch die Studienprüferin eine intensivierte Instruktion
Gruppe B) erfährt eine normale Spitalentlassung

Die Zuteilung in die Gruppen A oder B wird zufällig vom zentralen Steuerungskomitee der Studie getroffen. Dabei ist für Sie wichtig, dass alle Patienten die gleiche Chance haben in die eine oder andere Gruppe eingeteilt zu werden.
In jedem Fall erhalten Sie das von Ihrem Arzt verordnete Medikament. Es werden keine verschiedenen Medikamente miteinander verglichen und die Therapie bleibt bei allen Patienten wie vom Arzt verordnet.

Befragungen
Für alle Teilnehmer gilt folgendes Vorgehen:

- **Interview 1:** Wir werden Sie ca. am zweiten Tag nach Ihrer Spitalentlassung telefonisch kontaktieren und Ihnen während 5 - 10 Minuten einige Fragen zu Anwendungsproblemen mit der Heparin-Therapie stellen. Dabei haben Sie auch die Möglichkeit selbst Fragen zu stellen.
- **„vor Ort Kontrolle“:** Einige Tage später werden Sie sich an einem vereinbarten Termin bei Ihnen zu Hause in Anwesenheit der Prüferin selbst eine Injektion applizieren. Anschliessend werden wir Ihnen nochmals ein paar Fragen zur Therapie stellen. Dabei können allfällige Unsicherheiten Ihrerseits besprochen werden.
- **Interview 2:** Nach Therapieende werden wir Sie erneut telefonisch für eine Befragung von maximal 5 Minuten kontaktieren. Zudem bringen oder senden Sie alle gebrauchten Spritzen, die Sie für Ihre Therapiedauer erhalten haben, in einer Entsorgungsbox kostenlos ans Studienzentrum zurück.

Es werden zu keinem Zeitpunkt Blutproben entnommen oder Laboruntersuchungen durchgeführt.

Versicherungsschutz
Für die Therapiewahl und Dosierung ist das Kantonsspital Bruderholz verantwortlich. Bei unerwünschten Nebenwirkungen wenden Sie sich deshalb an Ihren behandelnden Arzt oder Apotheker. Für Schäden, die Sie im Rahmen dieser Studie durch die Beratung erleiden sollten, besteht bei der Rimas Insurance-Broker AG in Zusammenarbeit mit der „Zürich“ Versicherungs-Gesellschaft eine Studienversicherung durch die Universität Basel.

Vertraulichkeit der Daten
In dieser Studie werden persönliche Daten von Ihnen erfasst. Diese Daten werden anonymisiert. Sie sind nur Fachleuten zur wissenschaftlichen Auswertung zugänglich. Ebenso kann die Ethikkommission beider Basel Einsicht in die Originaldaten nehmen. Sämtliche Daten werden dabei immer strikt vertraulich behandelt. Ihr Name wird in keiner Weise in Rapporten oder Publikationen, die aus der Studie hervorgehen, veröffentlicht.

Kontaktpersonen
Falls Sie im Zusammenhang mit dieser Studie Fragen haben oder irgendwelche gesundheitliche Schwierigkeiten auftreten, so wenden Sie sich an Ihren behandelnden Arzt oder an folgende Kontaktpersonen. Diese werden Ihnen weiterhelfen:

Seraina Mengiardi
eidg. dipl. Apothekerin, Doktorandin
Tel.: 061 267 15 29
mail: seraina.mengiardi@unibas.ch

PD Dr. Kurt E. Hersberger
Offizinapotheker FPH
Tel. 061 267 14 26
mail: kurt.hersberger@unibas.ch

Dr. med. Urs Kohlhaas-Styk
Klinik für Orthopädie & Traumatologie
Kantonsspital Bruderholz
Tel.: 061 436 36 36
mail: urs.kohlhaas@ksbh.ch

Schriftliche Einverständniserklärung des Patienten zur Teilnahme an der Studie „Selbstmanagement Heparintherapie“ (EKBB 95/07)

Ich wurde von der Studienprüferin ausführlich mündlich und schriftlich über die oben beschriebene Studie informiert und habe die Patienteninformation gelesen und verstanden. Alle meine Fragen wurden mir zufriedenstellend beantwortet. Ich hatte genügend Zeit, um meine Entscheidung zu treffen.
Mit meiner Unterschrift bestätige ich meine Einwilligung zur freiwilligen Teilnahme. Ich bin mit einer eventuellen Publikation meiner anonymisierten Daten einverstanden. Ich kann meine Zustimmung jederzeit ohne Angabe von Gründen und ohne mir daraus entstehende Nachteile für meine weitere Behandlung zurückziehen. Ich bin damit einverstanden, dass wissenschaftliches Personal des Departements Pharmazie der Universität Basel, des Kantonsspitals Bruderholz und des Universitätsspitals Basel im Zusammenhang mit dieser Studie Einsicht in meine medizinischen Daten nehmen dürfen. Eine Kopie der schriftlichen Patienteninformation und der Einverständniserklärung habe ich erhalten.

vom Patienten auszufüllen:

Name des Patienten / der Patientin in Druck-schrift:	Geburtsdatum:	Geschlecht: ☐ männlich ☐ weiblich
Adresse Strasse: _____ PLZ, Ort: _____ Telefon-Nummer (Erreichbarkeit tagsüber am Tag 2): _____		
Ort, Datum:	Unterschrift des Patienten / der Patientin:	

von der Studienprüferin auszufüllen:

Patienten-Code: P _____	
Name der aufklärenden Person / Studienprüferin in Druckschrift:	
Ort, Datum:	Unterschrift der Studienprüferin:

6.10 Questionnaire for data collection

INSTITUT FÜR KLINISCHE PHARMAZIE
Departement Pharmazie der Universität Basel

Pharmaceutical Care Research Group
Klingelbergstrasse 50, 4056 Basel

Patienten-Code: P ☐☐☐ **Jahrgang:** 19☐☐ **Geschlecht:** ☐ männlich ☐ weiblich

Medikation:

Fragmin ®: ☐ ja
- ○ 2'500 I.E.
- ○ 5'000 I.E.
- ○ 7'500 I.E.
- ○ 10'000 I.E.
- ○ 12'500 I.E.
- ○ 15'000 I.E.
- ○ 18'000 I.E.
- ○ keine Angabe

☐ nein

☐ keine Angabe

andere: ☐ ja: _____

Rezept ausgestellt am: Tag ☐☐ Monat ☐☐ Jahr 200☐ **Dosierung:** ☐ 1x / die ☐ 2x / die

Datum Spitalaustritt: Tag ☐☐ Monat ☐☐ Jahr 200☐

Datum der Rezepteinlösung: Tag ☐☐ Monat ☐☐ Jahr 200☐

Therapiedauer klar: ☐ ja
- ☐☐☐ Tage
- ☐☐ OP
- bis (Datum): Tag ☐☐ Monat ☐☐ Jahr 200☐
- ○ bis zum nächsten Arzttermin
- ○ bis Ziel-INR (2x) erreicht

☐ nein

In welche Gruppe wurde der Patient eingeteilt?

☐ Kontrolle

☐ Observational Arm

☐ Intervention

Patient einverstanden, dass in seiner Apotheke um Rezeptkopie angefragt wird?
(Apotheken-Adresse auf Gesprächsvorlage) ☐ ja ☐ nein ☐ keine Angabe

Welche Interventionen wurden vom Studienteam am Tag 0 durchgeführt (Mehrfachantworten möglich)**?**

- ○ ausführliches Info-Faltblatt abgegeben
- ○ laminierte Spritzanleitung abgegeben
- ○ vollständiges Ausrüstungspaket abgegeben
- ○ mündliche Instruktion für Selbstinjektion erfolgt
- ○ am Phantom Injektionen geübt
- ○ Instruktion durch animierte Video-Sequenz
- ○ eigenständige Erstapplikation vor Ort unter Kontrolle von Studienteam
- ○ Erstapplikation durch Studienteam

Telefoninterview 1 (Tag 1 - 3)

Datum: Tag ☐☐ Monat ☐☐ Jahr 200☐

Allgemeines

1. Grösse: ☐☐☐ cm **Körpergewicht:** ☐☐☐ kg

33826

INSTITUT FÜR KLINISCHE PHARMAZIE
Departement Pharmazie der Universität Basel
Pharmaceutical Care Research Group
Klingelbergstrasse 50, 4056 Basel

2. Welches ist die höchste Ausbildung, die Sie abgeschlossen haben oder die Sie jetzt absolvieren?

☐ obligatorische Schulzeit
☐ Berufslehre / Berufsschule
☐ Matura
☐ Höhere Berufsausbildung (z.B. Meister, eidg. Diplom)
☐ Fachhochschule
☐ Universität
☐ keine Angabe

Sind Sie eine Medizinalperson oder im Gesundheitswesen tätig (z.B. Arzt, Apotheker, Pflegepersonal, Tätigkeit in Altersheim oder Spitex)**?**

☐ ja ☐ nein ☐ keine Angabe

3. Grund für Therapie:
- Operation / Verletzung an...
(Spontane Nennungen)

☐ Wirbelsäule
☐ Schultergürtel und Hals
☐ Oberarm / Ellbogen
☐ Vorderarm / Hand
☐ Becken
☐ Hüftgelenk
☐ Oberschenkel
☐ Kniegelenk (Bsp. Kreuzbandriss)
☐ Unterschenkel
☐ Fuss
☐ anderes: _____

- Therapie von...

☐ (Lungen-)Embolie
☐ tiefe Beinvenenthrombose
☐ Thrombose
☐ Myokardinfarkt
☐ keine Angabe
☐ anderes: _____

4. Wie viele Tage waren Sie im Spital?

☐ 1 Tag (= ambulant) ☐ 2-5 Tage ☐ > 5 Tage

5. Wo erhielten Sie die erste Heparin-Injektion (Erfahrung in Selbstapplikation: bei *aktueller* Therapie)**?**

☐ im Spital — **Wieviele Tage lang erhielten Sie Injektionen im Spital?** ☐☐ Tage
☐ in der Apotheke
☐ im Studienzentrum
☐ von der Spitex
☐ selber zu Hause

6. Wer hat Sie über die Anwendung des Medikamentes informiert (Erfahrung in Selbstapplikation: Bei *vorangehender und aktueller* Therapie) (Spontane Nennungen, Mehrfachantworten möglich)**?**

☐ Arzt
☐ Pflegepersonal im Spital
☐ Arztgehilfin
☐ Apotheke
☐ Studienteam
☐ Spitex
☐ niemand
☐ andere: _____

33826

INSTITUT FÜR KLINISCHE PHARMAZIE
Departement Pharmazie der Universität Basel
Pharmaceutical Care Research Group
Klingelbergstrasse 50, 4056 Basel

7. Wie viele Selbstapplikationen sind im Spital erfolgt (Erfahrung in Selbstapplikation: bei *aktueller* Therapie)**?**
☐ 1 ☐ > 1 ☐ keine

8. Erfolgte die erste Selbstapplikation unter Aufsicht / Anleitung einer Fachperson? (Erfahrung in Selbstapplikation: Bei *vorangehender* oder *aktueller* Therapie)

☐ ja — **Unter wessen Aufsicht?** (Spontane Nennungen)**:**
○ Arzt / Pflege ○ Apotheke ○ Studienteam ○ andere Fachperson ○ keine Ahnung
War Ihnen dies hilfreich? ○ ja ○ nein ○ keine Ahnung

☐ nein

9. Haben Sie sich früher schon einmal Heparin spritzen müssen oder haben Sie Erfahrungen in der Selbstapplikation von anderen s.c.-Therapien (*exklusiv* Insuline)**?**

☐ ja
○ immer Selbstapplikation
☐ nein
○ teils Selbstapplikation, teils Applikation durch Drittperson
○ immer Applikation durch Drittperson
○ keine Angabe

Heparin-Therapie

10. Wie viele Tage müssen Sie die Heparin-Therapie insgesamt anwenden?

verordnet: ☐☐☐ Tage
☐ bis zum nächsten Arzttermin ☐ nicht klar definiert im Rezept ☐ bis zur vollständigen Mobilisation ☐ k. A.

Anzahl Tage: ☐☐☐ Anzahl Packungen: ☐☐

☐ bis zum nächsten Arzttermin ☐ nicht klar definiert im Rezept ☐ bis zur vollständigen Mobilisation ☐ k. A.

Stimmt die Antwort überein mit der Verordnung? ☐ ja ☐ nein ☐ keine oder unklare Verordnung

11. Wieviel mal pro Tag spritzen Sie sich das Heparin?

verordnet: ☐ 1x pro Tag ☐ 2x pro Tag ☐ nicht klar definiert im Rezept

☐ 1x pro Tag ☐ 2x pro Tag

Stimmt die Antwort überein mit der Verordnung? ☐ ja ☐ nein ☐ keine oder unklare Verordnung

12. Wann spritzen Sie jeweils?

verordnet: ☐☐☐☐ Uhr ☐ nicht klar definiert im Rezept

zwischen ☐☐:☐☐ Uhr und ☐☐:☐☐ Uhr

Stimmt die Antwort überein mit der Verordnung? ☐ ja ☐ nein ☐ keine oder unklare Verordnung

33826

INSTITUT FÜR KLINISCHE PHARMAZIE
Departement Pharmazie der Universität Basel
Pharmaceutical Care Research Group
Klingelbergstrasse 50, 4056 Basel

13. Wo spritzen Sie jeweils (Mehrfachantworten möglich)**?**

☐ Oberschenkel ☐ Bauch ☐ Oberarm ☐ anderes: _____

14. Erhielten Sie genügend Informationen darüber, *WO* Sie sich spritzen müssen?

☐ ja, sehr umfassend ☐ ja, genügend ☐ nein, eher zu knapp ☐ nein, zu wenig ☐ keine Angabe

15. Erhielten Sie genügend Informationen darüber, *WIE* Sie sich spritzen müssen (Technik allgemein)**?**

☐ ja, sehr umfassend ☐ ja, genügend ☐ nein, eher zu knapp ☐ nein, zu wenig ☐ keine Angabe

Anwendung

16. Kostet Sie der Einstich viel Überwindung?

☐ nein, überhaupt nicht ☐ nein, eher nicht ☐ ja, manchmal schon ☐ ja, erheblich ☐ keine Angabe

17. Haben Sie Schwierigkeiten beim Abziehen der Schutzkappe von der Nadel?

☐ nein, überhaupt nicht ☐ nein, eher nicht ☐ ja, manchmal schon ☐ ja, erheblich ☐ keine Angabe

18. Wie beurteilen Sie allfällige Schmerzen *beim Einstich*?

☐ keine Schmerzen ☐ ein wenig unangenehm ☐ leichte Schmerzen ☐ starke Schmerzen ☐ keine Angabe

19. Wie beurteilen Sie allfällige Schmerzen *beim Spritzen*?

☐ keine Schmerzen ☐ ein wenig unangenehm ☐ leichte Schmerzen ☐ starke Schmerzen ☐ keine Angabe

20. Haben Sie andere Schwierigkeiten beim Spritzen?

☐ nein ☐ ja —— **Welche?** _____

21. Wie sicher fühlen Sie sich beim Spritzen, ausgedrückt auf einer Skala von 0 bis 10
(0=sehr unsicher, 10=sehr sicher)**?**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

22. Wie entsorgen Sie die Spritzen (Spontane Nennungen, Mehrfachantworten möglich)**?**

Mit oder ohne Gummischutzkappe?
☐ lose (ohne Gummischutzkappe)
☐ mit Gummischutzkappe

Wo?
☐ in die gelbe Entsorgungsbox
☐ zurück in die Apotheke bringen
☐ in der Originalverpackung in den Kehricht
☐ ohne Originalverpackung in den Kehricht
☐ in einer Pet-Flasche in den Kehricht
☐ andere: _____

Kommentare: ☐ ja: —— _____
☐ nein _____

Termin für DOT:

Ort: ☐ Notfallapotheke Basel ☐ beim Patienten zu Hause

33826

Version 31.01.08 **INSTITUT FÜR KLINISCHE PHARMAZIE** Pharmaceutical Care Research Group
Copyright © **Departement Pharmazie der Universität Basel** Klingelbergstrasse 50, 4056 Basel

DOT (direct observation technique)

Datum: Tag Monat Jahr 2 0 0

Vorbereitungen

23. Wurde alles griffbereit gelegt (Mehrfachantworten möglich)**?**

Fertigspritze:	☐ ja	☐ nein	☐ keine Angabe
Alkoholtupfer:	☐ ja	☐ nein	☐ keine Angabe
Tupfer:	☐ ja	☐ nein	☐ keine Angabe
Pflaster:	☐ ja	☐ nein	☐ keine Angabe
gelbe Entsorgungsbox:	☐ ja	☐ nein	☐ keine Angabe

24. Hände waschen oder desinfizieren ☐ ja ☐ nein ☐ keine Angabe

Wurden die Hände wirklich unmittelbar vor der Injektion desinfiziert oder gewaschen?

☐ ja ☐ nein ☐ Hände nicht gewaschen / desinfiziert ☐ keine Angabe

25. Ort der Applikation ☐ Oberschenkel ☐ Bauch ☐ Oberarm ☐ anderes: _____

Desinfektion

26. Wurde die Hautstelle desinfiziert?
- ☐ ja, durch einmaliges Wischen
- ☐ nicht korrekt (reibend, mehrmaliges Wischen...)
- ☐ nein
- ☐ keine Angabe

27. Wurde gewartet, bis die desinfizierte Stelle trocken war (ca. 30 sec., Hautpartie nicht mehr glänzend)?

☐ ja ☐ nein ☐ keine Angabe ☐ keine Desinfektion

28. Blieb die desinfizierte Stelle frei? ☐ ja ☐ nein ☐ keine Angabe ☐ keine Desinfektion

Injektion

29. Hatte der Patient Mühe beim Abziehen der Gummischutzkappe?
- ☐ nein, Patient bringt Kappe mühelos weg
- ☐ ja, Patient bringt Kappe nur mit Mühe weg
- ☐ ja, Patient bringt die Kappe NICHTweg
- ☐ keine Angabe

30. Korrekte Entfernung der Gummischutzkappe

Wurde die Gummischutzkappe mit freien Armen in Längsrichtung der Nadel abgezogen?	☐ nein	☐ ja	☐ keine A.
Ging die Nadel kaputt (neue Spritze nötig)?	☐ nein	☐ ja	☐ keine A.
Wurde die Gummischutzkappe nach dem Entfernen wieder aufgesetzt?	☐ nein	☐ ja	☐ keine A.

31. Luftbläschen in der Spritze
- ☐ das Luftbläschen wurde NICHT entfernt (korrekt)
- ☐ das Luftbläschen wurde fälschlicherweise aus der Spritze entfernt
- ☐ keine Angabe

32. Wurde ein allfälliger Tropfen vorsichtig abgeschüttelt und NICHT abgestreift?

☐ ja ☐ nein ☐ es gab keinen Tropfen ☐ weder abgeschüttelt noch abgestreift ☐ keine Angabe

33. Wurde eine genügend grosse (ca. 2 cm dick) Hautfalte gemacht?

☐ ja ☐ nein, nicht genügend dick ☐ nein, gar keine Hautfalte ☐ keine Angabe

34. Wurde wirklich in die desinfizierte Stelle injiziert? ☐ ja ☐ nein ☐ keine Angabe ☐ keine Desinfektion

35. Wie war der Injektionswinkel? ☐ 45° (schräg) ☐ 90° (senkrecht) ☐ keine Angabe

33826

Version 31.01.08 **INSTITUT FÜR KLINISCHE PHARMAZIE** Pharmaceutical Care Research Group
Copyright © **Departement Pharmazie der Universität Basel** Klingelbergstrasse 50, 4056 Basel

36. Wurde die Nadel vollständig in die Haut eingestochen? ☐ ja ☐ nein ☐ keine Angabe

37. Wurde nach dem Injizieren mindestens 1 sec. gewartet, bevor die Spritze herausgezogen wurde?
☐ ja ☐ nein ☐ keine Angabe

38. Blieb der Kolben der Spritze beim Herausziehen gedrückt?
☐ ja ☐ nein, der Kolben wurde losgelassen ☐ keine Angabe

39. Wurde die Spritze im gleichen Winkel herausgezogen, wie gespritzt wurde? ☐ ja ☐ nein ☐ keine A.

40. Wurde die Hautfalte erst losgelassen, als die Spritze wieder draussen war?
☐ ja ☐ nein ☐ keine Hautfalte gemacht ☐ keine Angabe

41. Wurde die Injektionsstelle richtig abgetupft nach der Injektion?
☐ ja, durch leichtes Tupfen ☐ nein, zu starkes Tupfen bzw. Reiben ☐ kein Tupfen ☐ keine Angabe

42. Wie sicher wirkte der / die Patient / in bei der Injektion?
☐ sehr sicher
☐ einigermassen sicher
☐ unsicher
☐ keine Angabe

Selbsteinschätzung: Visuelle Analog-Skala (VAS): Wie sicher fühlten Sie sich bei der Injektion? Stellen Sie den Schieber zwischen "sehr sicher" und "enorm unsicher" ein.

Skalawert VAS (0-100mm) ☐☐☐

Entsorgung

43. Wurde die gebrauchte Spritze *sofort* nach dem Herausziehen entsorgt? ☐ ja ☐ nein ☐ keine Angabe

44. Wie wurde die gebrauchte Spritze entsorgt?

Mit oder ohne Gummischutzkappe?
☐ lose (ohne Gummischutzkappe)
☐ mit Gummischutzkappe
☐ keine Angabe

Wo?
☐ in die gelbe Entsorgungsbox
☐ in der Originalverpackung in den Kehricht
☐ ohne Originalverpackung in den Kehricht
☐ in einer Pet-Flasche in den Kehricht
☐ andere: _____

Allfällige Interventionen während DOT
bei Nummern: ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

33826

Version 31.01.08 **INSTITUT FÜR KLINISCHE PHARMAZIE** Pharmaceutical Care Research Group
Copyright © **Departement Pharmazie der Universität Basel** Klingelbergstrasse 50, 4056 Basel

Adaptierter DASH

Anhand einiger Fragen möchten wir herausfinden, wie gut Sie mit Ihren Händen alltägliche Tätigkeiten durchführen können. Dies ist wichtig für uns, um festzustellen, ob Sie bei der Selbstinjektion gewisse Einschränkungen haben.

Bitte schätzen Sie Ihre Fähigkeiten ein, folgende Tätigkeiten auszuführen, indem Sie das entsprechende Kästchen ankreuzen.

Haben Sie irgendwelche Schwierigkeiten, Schmerzen, Verletzungen oder Erkrankungen im Arm-, Schulter- oder Handbereich, welche Sie bei der Ausführung von alltäglichen Tätigkeiten einschränken?

☐ ja ——— --> alle Fragen einzeln durchgehen
☐ nein ——— --> weiter bei Frage16 ("Allgemeines")
☐ keine Angabe

	keine Schwierig-keiten	wenig Schwierig-keiten	merkliche Schwierig-keiten	erhebliche Schwierig-keiten	nicht möglich
1. Ein Marmeladen-, Honig-, Einmachglas schliessen und wieder öffnen	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Schreiben	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Schlüssel umdrehen	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Messer benutzen, um Lebensmittel zu schneiden	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Nagel einschlagen	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Ein Streichholz anzünden	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Freizeitaktivitäten, die wenig körperliche Anstrengung verlangen (Spielkarten austeilen, stricken, Nadel einfädeln)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Reissverschluss einfädeln	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. Hemd / Bluse zuknöpfen	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	überhaupt nicht	**kaum**	**merklich**	**deutlich**	**extrem**
10. Sind Sie durchallfällige Schulter-, Arm- oder Handprobleme in Ihrer Arbeit oder anderen täglichen Aktivitäten eingeschränkt?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

33826

Version 31.01.08 **INSTITUT FÜR KLINISCHE PHARMAZIE** Pharmaceutical Care Research Group
Copyright © **Departement Pharmazie der Universität Basel** Klingelbergstrasse 50, 4056 Basel

Bitte schätzen Sie die Schwere der folgenden Symptome ein, indem Sie das entsprechende Kästchen ankreuzen.

	keine	wenig	merkliche	erhebliche	extrem
11. Schmerzen in Schulter, Arm, Hand	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. Schmerzen in Schulter, Arm, Hand, nachdem Sie eine bestimmte Tätigkeit ausgeführt haben	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. Kribbeln (Nadelstiche) in Schulter, Arm, Hand	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Schwächegefühl in Schulter, Arm, Hand	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. Steifheit in Schulter, Arm, Hand	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Allgemeines:

16. Haben Sie Arthrose / Arthritis an Schulter, Arm, Hand?	☐ nein	☐ ja	☐ keine Angabe
17. Haben Sie Gicht an Schulter, Arm, Hand?	☐ nein	☐ ja	☐ keine Angabe
18. Hatten Sie in der Vergangenheit eine Handverletzung, die Sie immer noch einschränkt?	☐ nein	☐ ja	☐ keine Angabe
19. Sind Sie Brillen- oder Kontaktlinsenträger (inkl. Lesebrille)?	☐ nein	☐ ja	☐ keine Angabe

20. Schätzen Sie Ihre Sehfähigkeit (mit Brille oder Kontaktlinsen) ein. ☐ normal ☐ beeinträchtigt ☐ ernsthaft behindert ☐ keine Angabe

Zeichnen Sie bitte die unten stehenden 7 Buchstaben möglichst präzise nach.

Anzahl Übertretungen: ☐☐☐

33826

Version 31.01.08 **INSTITUT FÜR KLINISCHE PHARMAZIE** Pharmaceutical Care Research Group
Copyright © **Departement Pharmazie der Universität Basel** Klingelbergstrasse 50, 4056 Basel

Interview beim DOT

Wissen

45. Wissen Sie, warum Sie Heparin spritzen müssen (Spontane Nennungen, Mehrfachantworten möglich)**?**

☐ zur Blutverdünnung
☐ Prophylaxe / Therapie von Herzinfarkt
☐ Prophylaxe/Therapie von Thrombose/Blutgerinnsel
☐ Behandlung einer Thrombose
☐ Propyhlaxe/Therapie von (Lungen-)Embolie
☐ lange Reise / Fliegen
☐ Bettlägrigkeit, d.h. vorwiegend liegend
☐ Thrombophilie
☐ eingeschränkt mobil (z.B. Krücken)
☐ anderes: _____
☐ wegen Operation / postoperativ
☐ keine Ahnung

46. Haben Sie noch andere *vom Arzt verschriebene* Medikamente, während der Heparin-Therapie oder als Dauermedikation?

- **Blutverdünnung?** (ASS (Asprin Cardio®, Tiatral®, Thrombace®), Plavix®, OAK (Marcoumar®, Sintrom®))

☐ ja ☐ nein ☐ keine Angabe

Blutverdünnung während Heparin-Therapie abgesetzt? ☐ ja ☐ nein ☐ keine Blutverdünnung ☐ k. A.

- **Schmerzmittel?** ☐ ja _____ **Welche(s) Schmerzmittel?** _____
☐ nein _____
☐ keine Angabe _____

- junge Patientinnen: **hormonelle Verhütung?** ☐ ja ☐ nein ☐ k. A.

- ältere Patientinnen: **Hormonersatztherapie?** ☐ ja ☐ nein ☐ keine Angabe

- alle Patienten: **Insulin?** ☐ ja ☐ nein ☐ keine Angabe

47. Welche *selbstgekauften* Medikamente nehmen Sie während der Therapie sonst noch ein (Mehrfachantworten möglich)**?**

☐ keine
☐ Schmerzmittel _____ **Wie oft nehmen Sie Schmerzmittel ein?**
☐ andere:
_____ ○ regelmässig (> 1x / Woche)
_____ ○ sporadisch
_____ ○ abgesetzt
○ keine Angabe

Welche(s) Schmerzmittel?
_____
_____
_____

48. Kennen Sie *selbstgekaufte* Medikamente, welche Sie während der Heparin-Therapie nicht einnehmen sollten (Spontane Nennungen, Mehrfachantworten möglich)**?**

☐ Schmerzmittel (ASS, NSAR) ☐ Erkältungsmittel ☐ keine Ahnung ☐ andere: _____
_____

33826

INSTITUT FÜR KLINISCHE PHARMAZIE
Departement Pharmazie der Universität Basel
Pharmaceutical Care Research Group
Klingelbergstrasse 50, 4056 Basel

49. Kennen Sie mögliche Nebenwirkungen der Heparin-Therapie (Mehrfachantworten möglich)**?**

☐ Blutungen an der Einstichstelle (blaue Flecken), kleine Hämatome
☐ lokale Irritationen an der Einstichstelle (es beisst oder brennt)
☐ Schmerzen an der Einstichstelle
☐ Hämatome, exkl.derjenigen an der Einstichstelle (Druckstellen, schneller blaue Flecken)
☐ erhöhte Blutungsneigung
☐ innere Blutungen
☐ Hautausschlag / Allergie
☐ Anzeichen einer anaphylaktischen Reaktion (z.B. Fieber, Erytheme, Asthma, Kollaps,...)
☐ andere: _____
☐ keine Ahnung

Heparin-Therapie

50. Haben Sie Nebenwirkungen? (spontane Nennungen)

☐ nein ☐ ja —— **Welche** (Mehrfachantworten möglich)**?**

○ Blutungen an der Einstichstelle (blaue Flecken), kleine Hämatome
○ lokale Irritationen an der Einstichstelle (es beisst oder brennt)
○ Schmerzen an der Einstichstelle
○ Hämatome, exkl.derjenigen an der Einstichstelle (Druckstellen, schneller blaue Flecken)
○ erhöhte Blutungsneigung
○ innere Blutungen *
○ Hautausschlag / Allergie *
○ Anzeichen einer anaphylaktischen Reaktion (z.B.Fieber, Erytheme, Asthma, Kollaps...) *
○ andere: * _____

Was haben Sie dagegen unternommen (Spontane Nennungen, Mehrfachantworten möglich)**?**
Telefon an / Besuch bei:

○ Arzt	○ Studienteam
○ Spital	○ nichts
○ Notfallstation	○ keine Angabe
○ Apotheke	○ anderes: _____

UAW mit Meldepflicht: ☐ ja * --> Meldeformular der Swissmedic ausfüllen (Pharmakovigilance)!

51. Was würden Sie tun, wenn Sie blaue Flecken bekommen würden oder wenn es um die Einstichstelle beisst oder juckt (Spontane Nennungen, Mehrfachantworten möglich)**?**
Telefon an / Besuch bei:

☐ Arzt	☐ Studienteam
☐ Spital	☐ nichts
☐ Notfallstation	☐ keine Angabe
☐ Apotheke	☐ anderes: _____

52. Was würden Sie bei plötzlichem Unwohlsein tun (Spontane Nennungen, Mehrfachantworten möglich)**?**
Telefon an / Besuch bei:

☐ Arzt	☐ Studienteam
☐ Spital	☐ nichts
☐ Notfallstation	☐ keine Angabe
☐ Apotheke	☐ anderes: _____

33826

INSTITUT FÜR KLINISCHE PHARMAZIE
Departement Pharmazie der Universität Basel
Pharmaceutical Care Research Group
Klingelbergstrasse 50, 4056 Basel

Betreuung

nur Kontroll-Gruppe und Observational Arm fragen:

53. Was hat Ihnen Ihr Apotheker beim Bezug der Spritzen mitgegeben?

Alkoholtupfer:	☐ ja	☐ nein	☐ angeboten, aber kein Bedarf
Watten-Tupfer:	☐ ja	☐ nein	☐ angeboten, aber kein Bedarf
Pflaster:	☐ ja	☐ nein	☐ angeboten, aber kein Bedarf
Entsorgungsbox:	☐ ja	☐ nein	☐ angeboten, aber kein Bedarf

nur Kontroll-Gruppe und Observational Arm fragen:

54. Hat Ihnen das Spital / Ihr Arzt ein Infoblatt / Broschüre zur Spritz-Technik mitgegeben?

☐ ja ☐ nein ☐ angeboten, aber kein Bedarf

Hat Ihnen Ihr Apotheker beim Bezug der Spritzen ein Infoblatt / Broschüre zur Spritz-Technik mitgegeben?

☐ ja ☐ nein ☐ angeboten, aber kein Bedarf

nur Kontroll-Gruppe und Observational Arm fragen:

55. Welche der folgenden Unterstützungen haben Sie erhalten?

Firmenbroschüre von Pfizer AG:	☐ ja	War es Ihnen hilfreich?	○ ja	○ nein	○ keine Angabe
	☐ nein	Hätten Sie es gewünscht?	○ ja	○ nein	○ keine Angabe
Erste Selbstinjektion unter Aufsicht:	☐ ja	War es Ihnen hilfreich?	○ ja	○ nein	○ keine Angabe
	☐ nein	Hätten Sie es gewünscht?	○ ja	○ nein	○ keine Angabe
Erstinjektion nach Spitalentlassung durch Drittperson:	☐ ja	War es Ihnen hilfreich?	○ ja	○ nein	○ keine Angabe
	☐ nein	Hätten Sie es gewünscht?	○ ja	○ nein	○ keine Angabe

nur Interventions-Gruppe fragen:

56. Welche Interventionen wurden vom Studienteam am Tag 0 durchgeführt (Mehrfachantworten möglich)**?**	**War es Ihnen hilfreich?** sehr hilfreich	hilfreich	nicht nötig
☐ ausführliches Info-Faltblatt abgegeben	○	○	○
☐ laminierte Spritzanleitung abgegeben	○	○	○
☐ vollständiges Ausrüstungspaket abgegeben	○	○	○
☐ mündliche Instruktion für Selbstinjektion erfolgt	○	○	○
☐ am Phantom Injektionen geübt	○	○	○
☐ Instruktion durch animierte Video-Sequenz	○	○	○
☐ Erstapplikation unter Aufsicht von Studienteam	○	○	○
☐ Entsorgungsbox	○	○	○
☐ Erstapplikation durch Studienteam	○	○	○

57. Welche weiteren Unterstützungen hätten Sie sich gewünscht / Kommentare?

33826

Version 31.01.08 **INSTITUT FÜR KLINISCHE PHARMAZIE** Pharmaceutical Care Research Group
Copyright © **Departement Pharmazie der Universität Basel** Klingelbergstrasse 50, 4056 Basel

Telefoninterview 2

Datum: Tag ☐☐ Monat ☐☐ Jahr 2 0 0 ☐

Heparin-Therapie

58. Mussten Sie während der Therapiezeit *unvorhergesehen* ins Spital oder zum Arzt?

☐ nein ☐ ja — **Weshalb?** ——— ○ Thrombose / Embolie *
○ Blutung *
○ andere: ———

Wann war Ihre letzte Injektion?

Datum: Tag ☐☐ Monat ☐☐ Jahr 2 0 0 ☐

59. Hatten Sie Nebenwirkungen?

☐ nein ☐ ja — **Welche** (Mehrfachantworten möglich)**?**

○ Blutungen an der Einstichstelle (blaue Flecken), kleine Hämatome
○ lokale Irritationen an der Einstichstelle (es beisst oder brennt)
○ Schmerzen an der Einstichstelle
○ Hämatome, exkl.derjenigen an der Einstichstelle (Druckstellen, schneller blaue Flecken)
○ erhöhte Blutungsneigung
○ innere Blutungen *
○ Hautausschlag / Allergie *
○ Anzeichen einer anaphylaktischen Reaktion (z.B.Fieber, Erytheme, Asthma, Kollaps...) *
○ andere: * ———

Was haben Sie dagegen unternommen (Spontane Nennungen, Mehrfachantworten möglich)**?**
Telefon an / Besuch bei:

○ Arzt ○ Studienteam
○ Spital ○ nichts
○ Notfallstation ○ keine Angabe
○ Apotheke ○ anderes: ———

UAW mit Meldepflicht: ☐ ja * --> Meldeformular der Swissmedic ausfüllen (Pharmakovigilance)!

60. Wie gut fühlten Sie sich auf einer Skala von 0 bis 10 bzgl. der Heparin-Therapie betreut
(0=sehr schlecht, 10=sehr gut)**?**

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Anwendung

61. Kostete Sie der Einstich viel Überwindung?

☐ nein

☐ ja, aber nur anfangs ——— **Während wievieler Tage?** ○ < 2 Tage ○ 2-5 Tage ○ > 5 Tage

☐ ja, aber nur zeitweise ——— **Während wievieler Tage?** ○ < 2 Tage ○ 2-5 Tage ○ > 5 Tage

☐ ja, während der ganzen Therapiedauer

62. Haben Sie Schwierigkeiten beim Abziehen der Schutzkappe von der Nadel?

☐ nein, überhaupt nicht ☐ nein, eher nicht ☐ ja, manchmal schon ☐ ja, erheblich ☐ keine Angabe

63. Wie beurteilen Sie allfällige Schmerzen *beim Einstich*? ☐ nie ☐ manchmal ☐ immer ☐ k. A.

☐ keine Schmerzen ☐ ein wenig unangenehm ☐ leichte Schmerzen ☐ starke Schmerzen ☐ keine Angabe

64. Wie beurteilen Sie allfällige Schmerzen *beim Spritzen*? ☐ nie ☐ manchmal ☐ immer ☐ k. A.

☐ keine Schmerzen ☐ ein wenig unangenehm ☐ leichte Schmerzen ☐ starke Schmerzen ☐ keine Angabe

33826

Version 31.01.08 **INSTITUT FÜR KLINISCHE PHARMAZIE** Pharmaceutical Care Research Group
Copyright © **Departement Pharmazie der Universität Basel** Klingelbergstrasse 50, 4056 Basel

65. Wie sicher fühlten Sie sich beim Spritzen, ausgedrückt auf einer Skala von 0 bis 10 (0=sehr unsicher, 10=sehr sicher)?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

66. Hatten Sie andere Schwierigkeiten beim Spritzen?

☐ nein, keine

☐ ja, aber nur anfangs — **Während wievieler Tage?** ○ < 2 Tage ○ 2-5 Tage ○ > 5 Tage

☐ ja, aber nur zeitweise — **Während wievieler Tage?** ○ < 2 Tage ○ 2-5 Tage ○ > 5 Tage

☐ ja, während der ganzen Therapiedauer

Welche (nur solche, die bis hierhin noch nicht erwähnt wurden) / Kommentare ?

Compliance

67. War es schwierig, das Medikament regelmässig anzuwenden?

☐ nein, gar nicht ☐ nein, meistens nicht ☐ ja, teilweise ☐ ja, meistens ☐ keine Angabe

68. Wie hoch schätzen Sie Ihre Eigenverantwortung für das vorschriftsgemässe Spritzen ein (Pünktlichkeit, Regelmässigkeit,...)?

☐ sehr hoch ☐ hoch ☐ mittel ☐ tief ☐ keine Angabe

69. Ist es während der gesamten Therapiedauer einmal vorgekommen, dass Sie nicht gespritzt haben?

☐ nein ☐ ja — **Wie oft?** ☐ 1 mal ☐ 2 mal ☐ 3 mal ☐ > 3 mal

Grund (Mehrfachantworten möglich):

☐ vergessen
☐ keine Akzeptanz (nicht wichtig, bringt nichts)
☐ frühzeitiger Therapieabbruch
☐ Angst vor dem Spritzen
☐ andere:

Haben Sie sich immer selber gespritzt?

☐ ja — Injektion durch wen? ○ Fachperson ○ Familienmitglied / Freunde ○ keine Angabe

☐ nein — Wie oft? ○ 1 x ○ 2 x ○ > 2 x ○ immer ○ keine Angabe

☐ keine Angabe — Grund? ○ Angst vor Spritzen ○ Angst vor Einstich ○ anderes:

70. Wie streng haben Sie sich an die Dosierung "alle 12 bzw. 24 Stunden" gehalten?

☐ +/- 15 Minuten ☐ +/- 2 Stunden

☐ +/- 30 Minuten ☐ +/- 3 Stunden

☐ +/- 1 Stunde ☐ > 3 Stunden

71. Würden Sie sich bei einer erneuten Heparin-Therapie noch einmal für die Selbstinjektion entscheiden oder würden Sie die Injektion durch fremde Hilfe bevorzugen?

☐ ja, wieder Selbstinjektion

☐ nein, lieber durch eine andere Person — **Warum?**

☐ keine Angabe

33826

6.11 Leaflet: patient information on low-molecular-weight heparin treatment

Institut für Klinische Pharmazie
Pharmaceutical Care Research Group
Departement Pharmazie der Universität Basel
Klingelbergstr. 50, 4056 Basel

UNI BASEL

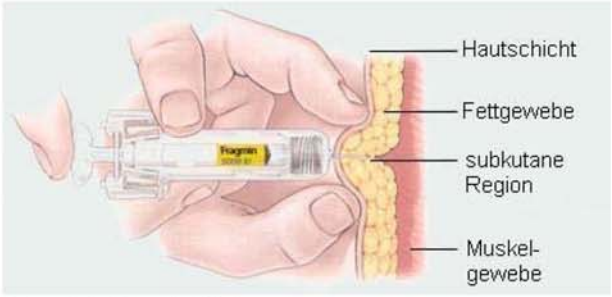
Kantonsspital Bruderholz
Klinik für Orthopädische Chirurgie
und Traumatologie des
Bewegungsapparates
4101 Bruderholz

ORTHO TRAUMA Bruderholz

PATIENTEN-INFORMATION über die Heparintherapie

Sehr geehrte Patientin, sehr geehrter Patient,

Ihre Ärztin, bzw. Ihr Arzt hat Ihnen ein Medikament (Fragmin®) verschrieben, welches Sie sich zur Blutverdünnung während einiger Tage selbständig zu Hause subkutan spritzen werden. Diese Injektionstechnik wird subkutan (lateinisch, s.c., sub = unter, cutan = Haut) genannt, da die Injektion in das Fettgewebe unter der Haut erfolgt (siehe Abbildung).



Fragmin® ist ein Medikament, das die Blutgerinnung hemmt. Der Wirkstoff von Fragmin® ist Dalteparin-Natrium, ein niedermolekulares Heparin. Es wird eingesetzt, um das Auftreten von Thrombosen zu verhindern (z.B. nach einer Operation oder Verletzung) oder um Thrombosen zu behandeln. Thrombosen sind Blutgerinnsel, welche die Gefässe verstopfen und somit die normale Blutzirkulation behindern können: Schmerzen und Schwellungen an den Beinen (beide Beine in gleicher Höhe unterschiedlich dick), Spannungsgefühl, Überwärmung, bläuliche Verfärbung der Haut oder verstärkt sichtbare Venen z.B. können auf eine tiefe Beinvenenthrombose hinweisen und erfordern einen sofortigen Arztbesuch. Seltener können die Blutgerinnsel über den Kreislauf in die Lungen gelangen und dort eine gefürchtete Lungenembolie verursachen (Thrombose der Lungengefässe).
Damit Sie möglichst sicher vor einer Thrombose geschützt sind, ist es wichtig, dass Sie Fragmin® regelmässig und möglichst immer zur gleichen Tageszeit (Zeitfenster +/- 2h) spritzen. Halten Sie sich an die von Ihrer Ärztin bzw. Ihrem Arzt festgelegte Dosierung und Behandlungsdauer. Auch wenn das Ziel der Therapie die Verhinderung von Thrombosen ist, kann dies trotz idealen Umständen nicht ausgeschlossen werden. Für die Therapiewahl und Dosierung ist Ihre Ärztin, bzw. Ihr Arzt verantwortlich. Bei unerwünschten Nebenwirkungen wenden Sie sich deshalb an Ihren behandelnden Arzt oder Apotheker.
Wenn Sie einmal eine Spritze vergessen haben, nehmen Sie am darauf folgenden Tag keine doppelte Dosis, um die vergessene Spritze auszugleichen. Spritzen Sie sich sofort eine normale Dosis, sobald die vergessene Injektion bemerkt wurde. Fahren Sie danach im verschobenen, aber gewohnten 12- bzw. 24-Stunden-Rhythmus fort und informieren Sie Ihren Arzt darüber.

Folgende Nebenwirkungen können bei der Anwendung von Fragmin® auftreten: an der Einstichstelle können blaue Flecken (Blutergüsse), leichte Schmerzen, Brennen oder Verhärtungen auftreten, die meist harmlos sind. Hohe Dosierungen können Blutungen, sogenannte Hämatome verursachen. In seltenen Fällen sind Hautausschläge und andere allergische Reaktionen (z.B. Juckreiz, Fieber) möglich.

Bei gleichzeitiger Einnahme von Medikamenten, welche die Blutgerinnung beeinflussen, kann die Blutverdünnung der niedermolekularen Heparine verstärkt werden. Dies betrifft sowohl selbstgekaufte Medikamente wie z.B. Aspirin® oder ähnliche Arzneimittel zur Behandlung von Fieber, Schmerzen und Entzündungen als auch «Blutverdünnungsmittel» (orale Antikoagulantien). Vermeiden Sie die Einnahme selbst gekaufter Medikamente oder fragen Sie zuvor in Ihrer Apotheke oder bei Ihrem Arzt nach.

Spritztechnik

Bitte befolgen Sie sowohl die Firmenbroschüre „Anleitung zur Selbstinjektion von Fragmin®“ (von Pfizer AG) als auch die nachfolgenden Tipps für die Selbstinjektion.

TIPPS für die Selbstinjektion von Fragmin® für Patienten / innen

1. Alles griffbereit legen

Legen Sie folgendes Zubehör griffbereit:

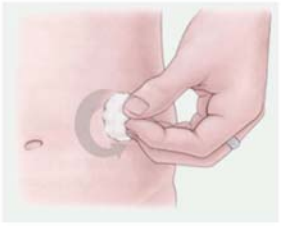
Fertigspritze	Alkoholtupfer	Wattetupfer	evt. Pflaster	Entsorgungsbox

Ziehen Sie den Schutzfilm von der Verpackung ab und entnehmen Sie vorsichtig die Fertigspritze. Injizieren Sie im Sitzen oder Liegen, nicht im Stehen.

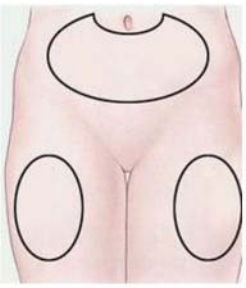
2. Hände waschen

Bevor Sie mit der Selbstinjektion beginnen, sollten Sie sich gründlich die Hände waschen.

3. Desinfizieren



Wählen Sie eine Injektionsstelle aus, die Ihnen bei der Instruktion empfohlen wurde, vorzugsweise auf der Vorderseite des Oberschenkels. Um Hautreizungen zu vermeiden, wechseln Sie täglich die Injektionsstelle. Halten Sie einen Sicherheitsabstand von 5 cm zum Knie oder zur Leiste ein. Die Injektionsstelle sollte der operierten / verletzten Region nicht zu nahe kommen. Es reicht völlig aus, die Einstichstelle durch *einmaliges* Wischen mit dem Alkoholtupfer zu desinfizieren. Merken Sie sich die desinfizierte Stelle. Lassen Sie das Desinfektionsmittel ca. 30 Sekunden trocknen (bis das Hautareal nicht mehr glänzt). Dadurch vermeiden Sie, dass beim Einstich Alkohol unter die Haut gelangt und ein zusätzliches Brennen entsteht. Achten Sie darauf, dass die desinfizierte Stelle frei bleibt und nicht mit Kleidungsstücken in Berührung kommt.



4. Gummischutzkappe vorsichtig entfernen

Es ist wichtig, dass Sie die Gummischutzkappe vorsichtig entfernen, damit die Nadel dabei nicht beschädigt wird. Am besten wird die Gummischutzkappe horizontal mit freien Armen in Längsrichtung der Nadel durch gleichzeitiges Drehen und Ziehen entfernt. Ist die Schutzkappe einmal entfernt, sollte sie nicht mehr auf die Nadel aufgesetzt werden, da dadurch der Schliff der Nadel beschädigt werden könnte und Verletzungsgefahr besteht. Ebenso sollten Sie die sterile Nadel nicht berühren.

5. Luftbläschen nicht entfernen

Das in der Spritze vorhandene kleine Luftbläschen sollte nicht entfernt werden. Es dient der vollständigen Entleerung der Spritze. Klopfen Sie leicht an der Spritze, sodass die Luftblase zum Kolben hochsteigt.
Falls sich an der Nadelspitze ein Tropfen gebildet hat, soll dieser vorsichtig abgeschüttelt, nicht abgestreift werden.

6. Einstechen der Nadel

Das Medikament soll ins Fettgewebe unterhalb der Haut gespritzt werden. Deshalb ist es zu empfehlen, Fragmin® in eine Hautfalte zu spritzen: Schieben Sie die desinfizierte Haut mit Daumen und Zeigefinger der einen Hand zu einer ca. 2 cm dicken Falte zusammen, ohne fest zu drücken. Die Spritze wird mit Daumen und Mittelfinger der anderen Hand gehalten. Die Nadel wird senkrecht, *zügig* und *vollständig* (bis zum Anschlag) in die Hautfalte eingestochen. (Bei sehr schlanken oder sehr muskulösen Patienten kann ein flacherer Injektionswinkel (45°), bei sehr korpulenten Personen eine Injektion ohne Hautfalte in Erwägung gezogen werden.)
Bei starken Schmerzen während des Einstichs haben Sie einen Hautnerv oder ein Blutgefäss getroffen. Ziehen Sie die Spritze heraus und stechen Sie die Nadel in eine andere, vorerst desinfizierte Stelle ein.

7. Injizieren

Beginnen Sie erst zu injizieren, wenn die Nadel vollständig in der Hautfalte versenkt wurde. Spritzen Sie sich die gesamte Flüssigkeit durch *langsames* Hinunterdrücken des Kolbens mit dem Zeigefinger unter die Haut. Das Injizieren des Medikamentes kann ein Brennen verursachen. Dies ist nicht ungewöhnlich, kann aber durch langsameres Spritzen gedämpft werden. Spritzen Sie also nur so schnell, dass Sie dabei keine zu starken Schmerzen empfinden. Drücken Sie den Kolben bis zum Anschlag hinunter und warten Sie dann mindestens eine Sekunde ab, bevor Sie die Nadel wieder herausziehen. Nur so haben Sie die Gewissheit, dass die gesamte Flüssigkeit verabreicht wurde.

8. Herausziehen der Nadel

Ziehen Sie die Nadel vorsichtig und gerade (gleicher Winkel wie beim Einstich) aus der Hautfalte heraus und lassen Sie den Kolben dabei nach unten gedrückt. Erst jetzt sollten Sie die Hautfalte loslassen.

9. Richtige Abfallentsorgung

Entsorgen Sie die gebrauchte Spritze *umgehend* in die dafür geeignete gelbe Entsorgungsbox. Die Gummischutzkappe sollte dabei *nicht* wieder aufgesetzt werden. Dadurch verhindern Sie unnötige Stichverletzungen und Infektionsgefahren für Drittpersonen und Sie selber. Die Box mit den gebrauchten Spritzen werden wir für Sie entsorgen. Anderes Verbrauchsmaterial wie benutzte Tupfer, Gummischutzkappen etc. können Sie in den normalen Hausabfall werfen (bitte nicht in die Entsorgungsbox).

10. Tupfen

Drücken Sie mit einem sauberen Wattetupfer leicht auf die Injektionsstelle, um allfällige Bluttröpfchen zu beseitigen. Bitte reiben Sie nicht, da dies die Injektionsstelle reizen und Blutergüsse fördern könnte. Ein Pflaster kann bei Bedarf auf die Einstichstelle geklebt werden.

11. Tagebuch führen

Kreuzen Sie zu Ihrer Selbstkontrolle nach durchgeführter Verabreichung den entsprechenden Wochentag an.

Mo	Di	Mi	Do	Fr	Sa	So
Mo	Di	Mi	Do	Fr	Sa	So
Mo	Di	Mi	Do	Fr	Sa	So
Mo	Di	Mi	Do	Fr	Sa	So
Mo	Di	Mi	Do	Fr	Sa	So
Mo	Di	Mi	Do	Fr	Sa	So
Mo	Di	Mi	Do	Fr	Sa	So

Ihre Zeit zum Spritzen

morgens: _____ Uhr abends: _____ Uhr

Dauer der Therapie

bis: _____

Lesen Sie auch die Packungsbeilage von Fragmin®. Bei Fragen wenden Sie sich bitte an Ihren Arzt oder Apotheker.

Referenzen:

Packungsbeilage von Fragmin®, Pfizer AG
Anleitung zur Selbstinjektion von Fragmin®, Pfizer AG
www.fragmin.com
www.thromboseprophylaxe.de

Kontaktperson: Seraina Mengiardi, eidg. dipl. Apothekerin, Doktorandin
Klinische Pharmazie, Universität Basel
Tel.: 061 267 15 29
e-mail: seraina.mengiardi@unibas.ch

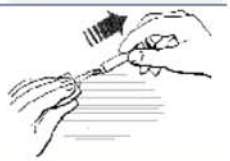
6.12 Manual: summary of the subcutaneous injection steps

Anleitung zur s.c.-Selbstinjektion

1. gesamtes Material griffbereit hinlegen
2. Hände waschen

3. Einstichstelle desinfizieren

4. Gummischutzkappe in Längsrichtung entfernen



5. - Luftbläschen NICHT entfernen
   - allfälliger Tropfen abschütteln, nicht abstreifen

6. Injektion:
   - Hautfalte bilden
   - Nadel senkrecht, zügig und vollständig in Hautfalte einführen
   - gesamte Flüssigkeit langsam und vollständig injizieren
   - Nadel vorsichtig herausziehen
   - Hautfalte loslassen

7. Spritze sofort und ohne Gummischutzkappe entsorgen

8. bei Bedarf Injektionsstelle leicht tupfen und Pflaster verwenden

Curriculum vitae

Personal data

Name	Seraina Mengiardi
Date of Birth	23 October 1980
Place of Origin	Ardez and Chur (GR)
E-Mail	seraina.mengiardi@ksbh.ch

Education and Professional Life

November 2011	Postgraduate degree in Clinical Pharmacy „Fähigkeitsausweis FPH in klinischer Pharmazie“
Since February 2011	Employed as pharmacist-IT for the development of a computerized physician order entry (CPOE) system at the Kantonsspital Bruderholz
July 2008 – June 2011	Postgraduate course in Clinical Pharmacy „Fähigkeitsausweis FPH in klinischer Pharmazie“, at the Kantonsspital Bruderholz. Supervisor: Dr. phil. II Markus L. Lampert
May 2006 – December 2011	PhD thesis at the Pharmaceutical Care Research Group, Department of Pharmaceutical Sciences at the University of Basel. Supervisors: Prof. Dr. sc. nat. Kurt E. Hersberger, Prof. Dr. med. Dr. pharm. Stephan Krähenbühl Thesis topic: *Outpatient Subcutaneous Injection Therapy – Drug Use Problems with Low-Molecular-Weight Heparins and Impact of Pharmaceutical Care*
May 2006 – January 2011	Employed as deputy pharmacist at the “TopPharm Apotheke Hersberger” in Basel
May 2006 – May 2010	Assistant in university courses on Pharmaceutical Care Author in the framework of i.m@il-Offizin, a drug information service for community pharmacies

May 2006 – December 2008	Head of the editorial board of i.m@il-Offizin
December 2005 – April 2006	Employed as deputy pharmacist at the “Montana Apotheke” in Arosa during the winter season 2005/06
September 2005	Swiss federal diploma in pharmacy
	MSc in Pharmaceutical Sciences
November 2004 – August 2005	Practical year at the "Barfüsser-Apotheke" in Basel
May 2004 – September 2004	Master thesis on Molecular Pharmacy, Department of Pharmaceutical Sciences at the University of Basel.
	Supervisor: Prof. Dr. Beat Ernst
	Thesis topic:
	Multimedia-based and didactical processing of pharmaceutical topics for e-testing
October 2000 – September 2005	Studies in pharmacy at the University of Basel
June 2000	Matura, main subject Latin (type B)
August 1993 – June 2000	High school at the Bündner Kantonsschule in Chur (GR)
August 1987 – June 1993	Basic education in Chur (GR)

Additional Courses

2011	2. Kongress für Arzneimittelinformation, Köln (Germany), 14 – 15 January
2008	ESCP Congress: European Symposium on Clinical Pharmacy, Dubrovnik (Croatia), 22 – 24 October
	ESPACOMP Congress: European Symposium for Patient Adherence, Compliance, and Persistence, Basel (Switzerland), 5 September
	FIP Congress: Symposium of the International Pharmaceutical Federation, Basel (Switzerland), 31 August – 4 September
2007	ESCP Congress: European Symposium on Clinical Pharmacy, Istanbul (Turkey), 25 – 27 October
2006	ESCP Congress: European Symposium on Clinical Pharmacy, Vienna (Austria), 18 – 21 October

Publications

Mengiardi S, Tsakiris DA, Laufer-Molnar V, Kohlhaas-Styk U, Mittag M, Krähenbühl S, Hersberger KE. Self-Management of Outpatient Low-Molecular-Weight Heparin Therapy: Impact of Pharmaceutical Care. Ann Pharmacother; submitted

Mengiardi S, Tsakiris DA, Lampert ML, Hersberger KE. Drug use problems with self-injected low-molecular-weight heparins in primary care. Eur J Clin Pharmacol 2011;67:109-20

Mengiardi S, Goepfert B, Tsakiris DA, Hersberger KE. Pitfalls in patient self-management of subcutaneous drug application: removal of rubber protection caps from ready-to-use syringes. Eur J Clin Pharmacol 2009;65:1061-2

Schlatter C, Mengiardi S. Unerwünschte Arzneimittel-Wirkungen erkennen und melden. i.m@il-Offizin 2009;16

Mengiardi S. Neues orales Antikoagulans: Rivaroxaban (Xarelto®). i.m@il-Offizin 2009;4

Mengiardi S. Reisethrombose. i.m@il-Offizin 2008;8

Mengiardi S. Management der oralen Antikoagulation. i.m@il-Offizin 2008;1

Mengiardi S. Konjunktivitis. i.m@il-Offizin 2007;16

Mengiardi S. Pfefferminzöl bei Colon irritabile. i.m@il-Offizin 2007;10

Mengiardi S. Vareniclin (Champix®). i.m@il-Offizin 2007;4

Mengiardi S. Endokarditisprophylaxe. i.m@il-Offizin 2006;18

Oral presentations and workshops

Mengiardi S. Workshop C: Self-management of thromboembolism prophylaxis. Anticoagulation: Tightrope walk between haemorrhage and coagulation, Advanced Study Centre, Bruderholz (Switzerland), 14 September 2010

Mengiardi S. Workshop III: Case analysis “Polypharmacy”. Clinical pharmacy in geriatrics, Advanced Study Centre, Bruderholz (Switzerland), 25 September 2009

Egger S, Mengiardi S, Eichenberger P. Workshop I: Inappropriate medications in the elderly: Evaluation of different instruments. Clinical pharmacy in geriatrics, Advanced Study Centre, Bruderholz (Switzerland), 24 September 2009

Mengiardi S. Case presentation “Self-management of heparin therapy: Compliance with self-injected low-molecular-weight heparins in ambulatory care”. Video

conference “GSK Academy for hospital pharmacists”, University Hospital Basel (Switzerland), 14 March 2007

Mengiardi S, Lampert ML, Vogel Kahmann I, **Hersberger KE**. Evaluation of patient knowledge regarding oral anticoagulants. 35th ESCP Symposium on Clinical Pharmacy, Vienna (Austria), 18 – 21 October 2006

Posters and poster presentations

Mengiardi S, Tsakiris DA, Lampert ML, Hersberger KE. Problems with Self-injecting Low-Molecular-Weight Heparins in Primary Care. 39th ESCP Symposium on Clinical Pharmacy, Lyon (France), 21 – 23 October 2010 → **Award for Best Poster Presentation**

Mengiardi S, Göpfert B, Tsakiris DA, Hersberger KE. Pitfalls in patient self-management of subcutaneous drug application: removal of rubber protection caps from ready-to-use syringes. 37th ESCP Symposium on Clinical Pharmacy, Dubrovnik (Croatia), 22 – 24 October 2008

Hersberger KE, Bodenmann T, Mengiardi S, Eichenberger P, Zemp Stutz E, Frey Tirri B. Emergency contraception: change of user's profile 2003-2006. 36th ESCP Symposium on Clinical Pharmacy, Istanbul (Turkey), 25 – 27 October 2007

Lectures

Mengiardi S. Anticoaluation and clinical training of the subcutaneous injection technique. AGFAM ABS for pharmacy technicians, Brugg (Switzerland), 29 November 2011

Mengiardi S. Anticoaluation and clinical training of the subcutaneous injection technique. AGFAM ABS for pharmacy technicians, Brugg (Switzerland), 25 October 2011

Mengiardi S. Outpatient thromboembolism prophylaxis: Problems and room for improvement. Anticoagulation: Tightrope walk between haemorrhage and coagulation, Advanced Study Centre, Bruderholz (Switzerland), 15 September 2010

Mengiardi S. Urinary tract infection. Course “Infectiology for master students”, University of Basel (Switzerland), 28 May 2010

Mengiardi S, Hersberger KE. Clinical training for pharmacists – heparin therapy, University of Basel (Switzerland), 2 and 3 February 2009

Mengiardi S, Tsakiris DA, Hersberger KE. Clinical training for pharmacists – heparin therapy, University of Basel (Switzerland), 15 April 2008

Mengiardi S, Tsakiris DA, Hersberger KE. Pharmaceutical Care and heparin therapy. Education and training courses FPH at the Swiss Tropical Institute, Swiss Tropical and Public Health Institute Basel (Switzerland), 21 February 2008

Other contributions

Goepfert B, Mengiardi S. Computer animation of the ideal needle shield removal forces from pre-filled syringes. 550th anniversary of the University of Basel festivities (Wissen und Gesellschaft, Wissen mobil, Fest der Wissenschaften), Basel (Switzerland), 2010

During my PhD thesis I followed courses of the following lecturers:

Arnet I, Bircher A, Bodmer M, Bruppacher R, Dieterle T, Drewe J, Fuhr P, Grünig HM, Haschke M, Heininger U, Hersberger KE, Hess C, Jeanneret C, Jehle A, Krähenbühl S, Kränzlin ME, Krapf R, Kressig RW, Lampert ML, Langewitz W, Leuppi J, Liechti ME, Mayr M, Meier C, Meier CR, Mühlebach S, Müller C, Odermatt A, Pauli-Magnus C, Rätz Bravo A, Rickenbacher P, Rüegg S, Scholer A, Seiler WO, Tarr P, Tichelli A, Tsakiris DA, Walker U, Widmer A, Zeller A, Zulewski H