

# Are pharmacological properties of anticoagulants reflected in pharmaceutical pricing and reimbursement policy? Out-patient treatment of venous thromboembolism and utilization of anticoagulants in Poland

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**Abstract. – OBJECTIVES:** Pharmacotherapy with vitamin K antagonists (VKA) and low-molecular-weight heparins (LMWH) is a major cost driver in the treatment of venous thromboembolism (VTE). Major representatives of anticoagulants in Europe include: acenocoumarol and warfarin (VKA), enoxaparin, dalteparin, nadroparin, rivaroxan, parnaparin and bemiparin (LMWH). Aim of this report is to measure and critically assess the utilization of anticoagulants and other resources used in the out-patient treatment of VTE in Poland. To confront the findings with available scientific evidence on pharmacological and clinical properties of anticoagulants.

**MATERIALS AND METHODS:** The perspectives of the National Health Fund (NHF) and the patients were adopted, descriptive statistics methods were used. The data were gathered at the NHF and the clinic specialized in treatment of coagulation disorders.

**RESULTS:** Non-pharmacological costs of treatment were for the NHF 1.6 times higher with VKA than with LMWH. Daily cost of pharmacotherapy with LMWH turned out higher than with VKA (234 times for the NHF, 42 times per patient). Within both LMWH and VKA the reimbursement due for the daily doses of a particular medication altered in the manner inversely proportional to the level of patient co-payment. Utilization of long-marketed and cheap VKA was dominated by LMWH, when assessed both through the monetary measures and by the actual volume of sales. Pharmaceutical reimbursement policy favored the more expensive equivalents among VKA and LMWH, whereas in the financial terms the patients were far better off when remaining on a more expensive alternative.

**CONCLUSIONS:** The pharmaceutical pricing and reimbursement policy of the state should be more closely related to the pharmacological properties of anticoagulants.

*Key Words:*

Anticoagulants, Pharmaceutical pricing and reimbursement, Therapeutic equivalence, Therapeutic indications, Venous thromboembolism.

## Introduction

Venous thromboembolism (VTE), a major health disorder, embraces the two inter-related diseases: deep vein thrombosis (DVT) and pulmonary embolism (PE), both treated with long-term anticoagulation typically offered within out-patient care. Pharmacotherapy is deemed a dominant cost driver in the VTE treatment of out-patients, making use of the two major groups of anticoagulants, i.e. vitamin K antagonists (VKA) and low molecular weight heparins (LMWH). In line with the results of the recently published systematic review and metaanalysis, comparing LMWH with VKA in treating VTE in terms of overall efficacy and safety, the main differences between the two groups of anticoagulants consist in appreciably more advantageous effects of LMWH in preventing deep vein thrombosis in the cancer patients and protecting against minor bleedings in the non-cancer ones<sup>1</sup>.

Acenocoumarol and warfarin (representatives of VKA), the derivatives of 4-hydroxycoumarin, are administered orally. Acenocoumarol has been used in many European countries for many years, whereas warfarin is a relatively new arrival. Unlike in continental Europe, application of warfarin is common place in the USA and the UK. Hence, most of the VTE research has been related to it. Formulations of LMWH (administered subcutaneously), like enoxaparin, dalteparin, nadroparin, reviparin, parnaparin and bemiparin are commercially available on the European market. Only the first three, however, remain in common use in Poland, and are much more expensive than VKA. In many countries LMWH are utilized only in the first phase (hospital-based) of the VTE treatment. They are recommended for the VTE treatment only, i.e. in special groups of out-patients like pregnant women and cancer patients. In Poland, however, both LMWH and VKA are subject to statutory reimbursement by the National Health Fund (NHF).

The present study aimed to critically assess the utilization of major resources applied in the VTE treatment, as well as the costs of statutorily reimbursed anticoagulants used in the out-patient clinics. We also intended to have their findings on the differences in the actual patterns of utilization of comparable anticoagulants confronted with the available data on their pharmacological and clinical properties.

## Materials and Methods

Identification and breakdowns of specific costs into categories, embracing both pharmacological and non-pharmacological components of the VTE treatment on the out-patient basis, as well as a detailed assessment of the utilization of anticoagulants, were carried out, whilst respectively adopting the perspectives of the NHF and that of the patients. Two alternative modalities of pharmacological treatment were assessed, including all marketed formulations of LMWH and VKA. Applicable tariffs (i.e. endorsed rates) for financing public health care services by the NHF in 2009, regulating the actual contracting of specialist out-patient care services and the reimbursement for specific medications, were applied accordingly<sup>2-5</sup>.

Information on acenocoumarol dosage patterns, frequency of out-patient care visits and practice of the VTE treatment in the out-patient

setting was gathered at the internal medicine clinic specialized in the treatment of coagulation disorders (in the present study referred to as the CCD - Clinic of Coagulation Disorders), Krakow (full medical records spanning 2003-2007). The guidelines for the VTE treatment were also given due consideration, with a view to identifying and assessing the recommended patterns for dosage and treatment with LMWH and VKA<sup>6</sup>. The WHO methodology for calculating the Defined Daily Doses (DDD) of the medications was applied in relevant analyses.

In order to access information on the consumption of antithrombotic drugs in Poland detailed data on the consumption of medications and attendant reimbursements for 2009, as obtained from the NHF at its regional division – the Silesian Voivodeship Division, were scrutinized. The well-established history of pharmaceutical reimbursement monitoring, overall level of technological advancement and a high number of the insured (12.2% of the country's population) actually vindicated the selection of this region of Poland, as well as made it possible to have the findings effectively extrapolated onto the entire country, allowing for a narrow margin of error.

An abundance of marketed preparations of anticoagulants is directly correlated with the complexity of the attendant computations of the actual costs of treatment. Prices of medications differ not only with regard to their names, but also in relation to the number of drug units (e.g. tablets, pre-filled syringes) in a particular package. Furthermore, prices or the limits of reimbursement due may change over time. Prices of identical units of medications with identical INN (international non-proprietary name), trade name and form may also differ depending on the size of a particular package (number of doses). Bearing the above in mind, the actual utilization of all 57 identified combinations of medications, forms, doses and quantities of units within a package was converted into the units of utilization relevant for a particular substance (mg, g, anti-Xa unit), and then also expressed in terms of total value and the reimbursement due.

## Results

### *Utilization and Costs of Out-Patient Services in the VTE Treatment*

Patients' records, obtained from the CCD, were scrutinized to assess the number of out-pa-

tient consultations during the VTE treatment. A set of 141 patients was randomly selected from the group of 353 patients with DVT or/and PE. Due to thrombophilia or neoplasm (associated with the need of sustained treatment) or incompleteness of the records, 109 out of them were excluded. Among the 32 patients who proved eligible for the data extraction there were 17 women (53%) and 15 men (47%), aged 32-82 years (median 66). DVT was diagnosed in 19 patients (59%), PE in 17 (53%), and both diseases concurrently – in 4 (13%). Complete data from a full-year treatment were taken into consideration in the case of 30 patients, whereas from a half-year – in just two. Mean monthly number of visits was 0.804; whereas mean half-a-year number of visits – 4.823 (minimum = 2; maximum = 10).

Treatment with LMWH is associated with the less frequent monitoring than in the case of VKA. Based on applicable regulations on a maximum allowable amount of medicines prescribed during a single out-patient visit, a working assumption was made that the treatment with LMWH required three visits during a half-year treatment. All visits were categorized as “specialist consultations”, with four accounting points assigned, priced at PLN 8.20 each, so overall NHF rate totaled PLN 32.80 (the currency exchange rates EUR/PLN in 2009 ranged from 3.96 to 4.90). Hence the cost of out-patient visits during a half-year period of VTE treatment with LMWH amounted to PLN 98.40, whereas with VKA – to PLN 158.19.

As opposed to the LMWH treatment, frequent measurements of prothrombin time, usually expressed as international normalized ratio (INR), are required during the VKA therapy. The attendant testing costs are not borne as the extra costs by the NHF, as they are actually included within the price of a specialist consultation itself. Nevertheless, using the available data, the frequency of INR testing was also calculated, resulting in the average of 4.79 tests per patient, per half a year.

### **Dosage of LMWH and VKA – Guidelines Versus the Actual Utilization Data**

The main source of information for establishing the dosage of VKA was the CCD. Additionally, expert opinions offered by clinicians, and the real-life data were duly compared with the VTE treatment guidelines and the DDD system. All patients at the CCD were on acenocoumarol. Daily dosage records of 32 patients were scrutinized to calculate the average daily dose of acenocoumarol per patient (ca. 2.96 mg). Average daily dosage of VKA, according to the VTE treatment guidelines, was established as 5.0 mg for acenocoumarol and 7.5 mg for warfarin, although it referred to the initial treatment only, as any further dosage remains subject to individual adjustment. Those doses proved compatible with the DDD values for both medications. They were significantly different, though, from the doses actually applied in the group of patients under review and also from the opinions offered by the three consulted clinical experts. Eventually, it was determined that the real-life data would be applied in the analysis. This proved feasible in the case of acenocoumarol only, though not warfarin (no prescriptions). Average daily dose of warfarin (approximately 4.43 mg) was calculated, based on the proportion of acenocoumarol to warfarin dosage, as recommended in the initial VTE treatment by pertinent guidelines (5.0:7.5)<sup>6</sup>. It was found to be consistent with DDD.

In order to calculate the doses of LMWH, the VTE treatment guidelines were consulted (Table I). Substantial differences were noted between the values of daily doses, as recommended by the treatment guidelines, and those established by the WHO, resulting from different therapeutic indications (own calculations related to the VTE treatment, whereas DDD to VTE prevention in the patients with moderate risk factors).

The DDD values served yet another purpose, i.e. the assessment of the actual proportion of patients within either the VKA or the LMWH

**Table I.** Doses and dosage of LMWH – own calculations and DDD.

LMWH	Calculation	Dose based on a calculation (c)	DDD (d)	c/d
Enoxaparin	1.5 mg/kg/day × 70 kg of body mass	105 mg	2,000 anti-Xa IU equivalent to 20 mg	5.25
Nadroparin	171 anti-Xa IU/kg/day × 70 kg	11,970 anti-Xa IU	2,850 anti-Xa IU	4.20
Dalteparin	200 anti-Xa IU/kg/day × 70 kg	14,000 anti-Xa IU	2,500 anti-Xa IU	5.60

group, administered a particular formulation. Overall number of measurement units of a particular medication consumed in 2009 was divided by the appropriate value of DDD, thus yielding the total number of DDD consumed annually. The prevalence of particular formulations within LMWH and VKA is illustrated in Figure 1.

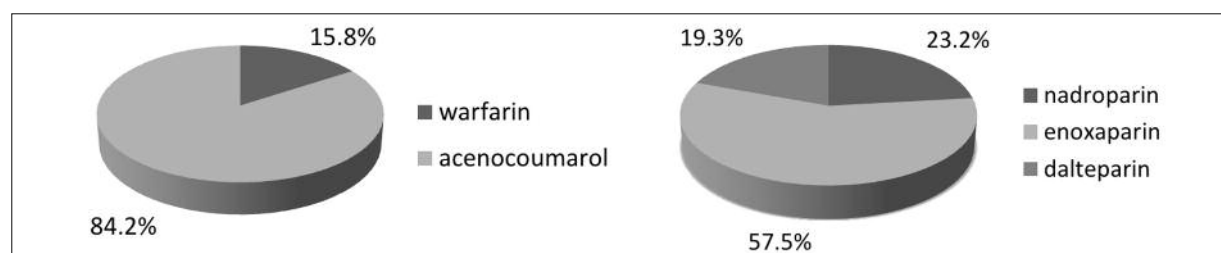
### **Costs of Anticoagulants in the Out-Patient Treatment of VTE**

Total reimbursement for the medications under review (both LMWH and VKA) amounted to PLN 52,336,994.87 and their total value (including reimbursement plus patients' co-payment) to PLN 56,198,907.29 (837,991 packages). The LMWH medications accounted for the lion share, i.e. 97% of total value, 98% of the reimbursement due, and 85% of the volume expressed as the number of packages. The ratio of the reimbursement due to the total value was 94% for LMWH and 73% for VKA, respectively, automatically translating into a proportionally larger NHF share in the reimbursement due for the LMWH group. The analysis of respective medication subgroups revealed that acenocoumarol preparations equaled 68.33% of the reimbursement value, and 73.58% of total VKA value. Within the LMWH group the largest share was claimed by enoxaparin (57.31% of the reimbursement value and 57.06% of the total value), then by nadroparin (22.35% and 22.92%), and dalteparin (20.34% and 20.02%). Having had the total consumption of all antithrombotic medications duly recalculated into DDD, it was possible to establish that LMWH corresponded to 62% of the total volume, whereas VKA to 38%. It seems quite likely that the respective percentage shares in the daily doses could be different in the VTE treatment, if this indication was assessed in isolation, considering that (as shown above) the actual dosage of a particular LMWH in this indication was 4.2-5.6 times higher than DDD, and the dosage of acenocoumarol was 1.7 times lower than DDD. Daily cost of VTE pharmacotherapy

with LMWH turned out higher than with VKA (234 times for the NHF, 42 times per patient). A patient treated with VKA co-paid ca. PLN 1.20/month, whereas the one on LMWH – ca. PLN 50.40/month.

Within both groups of LMWH and VKA the reimbursement due for the daily doses of a particular medication altered in the manner inversely proportional to the level of patient co-payment. Application of warfarin instead of acenocoumarol proved by 147% more expensive for the NHF, whilst cheaper for the patients by 25%. Application of enoxaparin instead of nadroparin was by 29% more expensive for the NHF, although cheaper for the patients by 15%. Application of dalteparin instead of nadroparin proved even more expensive for the NHF (by 46%), whereas cheaper for the patients (by 23%). From an individual patient's point of view, it was appreciably less expensive to be prescribed the most costly medicine, within both LMWH and VKA groups. In this particular case a nominal co-payment was the lowest one out of all available options (details in Tables II and III).

The intriguing nature of the interrelationship governing the patients' co-payment, the reimbursement due by the NHF, and the respective prices of specific LMWH and VKA medications, as addressed in the present paper, boasts clear potential for achieving substantial economies in the expenditure borne by a public payer through the introduction of specific changes in the actual patterns of issuing prescriptions by the physicians, as well as in the rules governing pharmaceutical reimbursement. Before any specific plans are adopted, with a view to making the reimbursement policy more cost-effective and rational through promoting the administration of the appreciably less costly LMWH and VKA medications, it would be prudent, however, to verify whether it would be viable in terms of vital pharmacological and clinical constraints to introduce a patient intra-group swap as a practical solution.



**Figure 1.** Utilization of medications (in DDD) within the VKA (*left*) and the LMWH (*right*) groups.

**Table II.** Data on the administration of LMWH and VKA, and the attendant costs of antithrombotic treatment.

Groups of medicines (INN)	Denomination of utilization unit (dosing)	Reimbursement per one utilization unit (PLN)	Patient co-payment to one	Value of one utilization unit (PLN)*	Daily dosing in VTE treatment (utilization units)	Daily value per one patient (PLN)*
Warfarin	mg	0.0514	0.0075	0.0589	4.4339	0.261
Acenocoumarol	mg	0.0313	0.0150	0.0462	2.9559	0.137
Nadroparin	anti-Xa IU	0.0017	0.0002	0.0019	11,970	22.421
Enoxaparin	g	252.51	15.69	268.21	0.105	28.162
Dalteparin	anti-Xa IU	0.0021	0.0001	0.0022	14,000	31.304

\*Value is expressed as the total of the reimbursement due (NHF) and the patients' co-payment.

## Discussion

The present study demonstrated that there were significant differences in the utilization of healthcare resources during the antithrombotic treatment of outpatients, depending on whether they had received LMWH or VKA. An out-patient VTE treatment with VKA resulted in pertinent NHF costs (excluding pharmaceuticals) being 1.6 times higher, as compared to LMWH. The range of differences was much wider when the costs of pharmacological treatment were assessed, since VTE treatment with LMWH turned out 234 times higher for the NHF than with VKA, whereas for the patients – 42 times higher. Patient co-payment contributions to VKA were negligible, whereas with regard to LMWH, despite being much higher, seemed to be very much on a par with a variety of other pharmacological treatment regimens in Poland.

Some rather unexpected associations were encountered between the level of reimbursement due and the patients' co-payment, when the LMWH and VKA preparations were assessed separately, i.e. as two discrete groups. Assuming that various medications representing either

LMWH or VKA might well be treated as the therapeutic alternatives, despite being not identical in character, this seems to be unwarranted from the NHF's point of view. It would therefore stand to reason that a less expensive treatment alternative, both among LMWH and VKA, was given a clear preference, or at least treated on a par with the more expensive and clinically or pharmacologically no more effective alternatives. Treating more expensive options preferentially, even if inadvertently so, does not seem to be reasonably justified in terms of nationwide pharmaceutical policy. When expressed in DDD, acenocoumarols were used over five times more intensively than the higher-priced warfarin formulations. Among the LMWH formulations, the most expensive dalteparins were used almost three times less eagerly than the most popular and medium-priced enoxaparins, but the cheapest nadroparins were used almost 2.5 times less often than enoxaparins. Utilization of old and cheap VKA in Poland was dominated by LMWH, when assessed through the monetary measures, as well as by the actual volume of sales. These findings might well offer a certain insight into what must actually have prompted

**Table III.** Differences in the NHF reimbursement due and the patients' co-payment in the antithrombotic treatment.

Names (INN) of medicines (name of the cheapest equivalent – in italics)	Daily reimbursement per one patient (PLN)	Daily co-payment of one patient (PLN)	Difference for the NHF in relation to the cheapest equivalent (in groups: VKA and LMWH)	Difference for a patient in relation to the cheapest equivalent (in groups: VKA and LMWH)
Acenocoumarol	0.092	0.044	n.a.	n.a.
Warfarin	0.228	0.033	147%	-25%
Nadroparin	20.490	1.931	n.a.	n.a.
Enoxaparin	26.514	1.648	29%	-15%
Dalteparin	29.820	1.484	46%	-23%

the specific marketing activities undertaken by some pharmaceutical companies. At the time no sufficiently robust response was launched by Polish public health authorities to have their marketing endeavors effectively cushioned, with a view to maintaining the rationalization drive in the national pharmaceutical policy.

Warfarin has longer half-life than acenocoumarol (36h compared to 10h), which theoretically speaking should result in more stable anti-coagulation. The study that focused on comparing both medicines within the same group of 103 patients treated for various indications, who had initially commenced the oral anticoagulation treatment with acenocoumarol, continuing it for six months, and then changed over to warfarin for the following six months, concluded that the differences between the two medications were of no clinical significance<sup>7</sup>. Similarly, a study of 120 patients on the preventive anticoagulation course due to atrial fibrillation, treated with acenocoumarol, and another 120 with warfarin, who continued treatment for a minimum of 1 year, revealed that the patients treated with acenocoumarol exhibited a higher risk of presenting with an INR  $\geq 6$ , although no statistically significant differences were observed in the therapeutic stability<sup>8</sup>. A comparative one-year clinical study, aimed at evaluating the differences in the quality of treatment between warfarin and acenocoumarol in the patients with non-valvular atrial fibrillation, revealed that both medications had shown similar quality of individual anticoagulation control, although acenocoumarol had shown significantly better anticoagulation stability with the therapeutic INR values, covering significantly longer time of treatment<sup>9</sup>. The SPORTIF-III substudy aimed to compare acenocoumarol with warfarin in the same group of 74 patients with chronic atrial fibrillation, who started off with warfarin, continued for three months, and then changed over to acenocoumarol for the following three months. Anticoagulation effect stability was superior for acenocoumarol, as compared to warfarin<sup>10</sup>.

Pharmacological and therapeutic similarities encountered between acenocoumarol and warfarin might well be attributable to the fact that both compounds are the coumarin derivatives, boast the same mechanism of action, the same route of administration (oral), are available in similar pharmaceutical forms (tablets) and belong to the same ATC code group (B01AA), this

being clearly related to the shared similarities in their chemical structure. They are commonly described in the same monographs in pharmacology handbooks and other monographic sources with cross references to their safety and efficacy profile<sup>1</sup>. Furthermore, the more costly VKA in Poland is warfarin – an older compound, whereas cheaper acenocoumarol represents a newer coumarin derivative, developed as the warfarin successor with the improved therapeutic properties. Interchangeability of warfarin and acenocoumarol may be considered safe and effective not only thanks to the similarities between those two compounds, but also due to the fact that the indications officially approved for the acenocoumarol products in Poland (both original and generic) fully cover all indications of warfarin. The cheaper acenocoumarol seems to be fully utilizable in all clinical indications endorsed (and reimbursed) to the same extent, as the more expensive warfarin<sup>12,13</sup>.

Similarly to VKA, different representatives of LMWH are not identical, either. They differ from each other with regard to average molecular weight, length of their polysaccharide chains and pharmacological properties, due to different manufacturing methods. Dosage of LMWH is different and specific for each medicine, also depending on individual body weight. Biochemical differences influence variations of *in vivo* action, especially with regard to the ability of binding with serum proteins and cellular surfaces, pharmacokinetic properties, bioavailability and serum half-time<sup>14</sup>. Being interchangeable at clinically optimized/approved dosage, they are not interchangeable at the equivalent anti-Xa dosage and even at the optimized dosage, as each medication's clinical profile may actually be different<sup>15</sup>. Despite a large database of pre-clinical studies on the differences between various LMWH, only limited clinical data is currently available. These pharmacokinetic and pharmacodynamic differences become increasingly apparent, as the application of LMWH in therapeutic uses (where higher doses are used) develops. There are also important differences in non-anticoagulant actions of various LMWH, like their ability to interact with the growth factors. Current scientific evidence shows that each LMWH is rather individual in character<sup>16</sup>. They boast different and quite unique pharmacokinetic and pharmacodynamic profiles, and therefore should be prescribed only for those indications and only at such specific dosage that had been investigated,

and for which they had actually proven to be effective<sup>17</sup>. When the officially endorsed indications for the use of enoxaparin, nadroparin and dalteparin are concerned, it is evident that all main indications of LMWH, also generating a majority of the reimbursement costs, are identical in the case of all three of them<sup>12,13</sup>. Altering their respective shares in the reimbursed medications market, to be achieved through an appropriate modification of the prescribing patterns, can have no negative clinical consequences, as long as the medications are used in line with their common indications.

To justify such a conclusion it should be duly noted that all the compounds called “LMWHs” originate from the so called standard or unfractionated heparin, being a mixture of polysaccharide chains of an irregular sequence. Regardless of this approximate composition, UH boasts entries in all key pharmacopoeias, whereas a number of pharmaceutical companies the world over manufacture the products of UH for parenteral use. LMWH were discovered by fractionation and/or depolymerisation of UH. This process facilitates the manufacturing of heparin with more stable, uniform and controllable action. Although LMWH differ in the manufacturing specifications, molecular weight and the degree of sulfation; their action, overall safety and efficacy profile, as well as the actual potential for clinical use, generally remain very much on a par<sup>18</sup>. This gives sufficient grounds to approach any preferences for a specific LMMH with caution. There is definitely a room for flexibility of choice of LMWH without incurring any significant risks to the patients<sup>11,19,20</sup>.

The recently published European draft guidelines on biosimilar LMWHs somehow attenuated the myths about the non-reproducibility and exceptionality of each individual LMWH. This actually paves the way for a relatively uncomplicated development of fully interchangeable, biosimilar versions of the existing LMWHs. The innovativeness and uniqueness of those guidelines rest upon acknowledging the non-availability of clinical comparative studies on the new product and its originator (i.e. by far the best scenario from an applicant's point of view). It is postulated therefore that non-clinical *in vivo* studies and the quality comparative studies be accepted as a viable source of information instead of the clinical studies, as routinely required by the majority of guidelines on other biosimilar medicinal products<sup>21,22</sup>.

## Conclusions

Indications for use, resulting both from official medication registration documents and clinical practice, may be regarded as uniform for all medicines within VKA, as well as LMWH. Acenocoumarol and warfarin may well be deemed viable therapeutic equivalents among VKA, similarly to enoxaparin, dalteparin and nadroparin among LMWH. As demonstrated by the present study, pharmaceutical reimbursement policy in Poland clearly used to favor the more expensive equivalents, whereas in the financial terms the patients were far better off, when remaining on a more expensive alternative. This observation still begs a plausible enough explanation, which in turn gives rise to some fundamental questions as to an overall shape of nationwide pharmaceutical policy. Should these differences among the representatives of VKA and LMWH be reflected in the actual pricing and the reimbursement due, and if so, in what way precisely? Having a cost-minimization strategy incorporated into the reimbursement policy regarding the respective groups of medicines would favorably impact overall NHF expenditure without actually jeopardizing any clinical benefits.

Widespread use of LMWH in Poland most likely goes far beyond pregnant women, cancer patients, or those who find it hard to secure stable coagulation parameters with the aid of VKA, as indicated by clinical guidelines. This is so despite the fact that LMWH prove far more expensive both for the patients and the NHF, and that their clinical superiority over VKA is negligible, except for strictly selected populations.

Surprisingly enough, within recent years warfarin has quickly gained popularity against a much more long-term popularity of acenocoumarol; its higher price and clinical performance hardly justifying such an impressive marketing success. Admittedly, marketing activities pursued by the pharmaceutical industry seem to hold considerable sway over the statutorily reimbursed medicines market in Poland.

The pharmaceutical pricing and reimbursement policy in Poland has undergone very substantial changes around the turn of 2011 and 2012 due to the implementation of a new pharmaceutical reimbursement law<sup>23</sup>. The findings of the present study should therefore soon be up for a confrontation with specific material evidence, as readily supplied by the new circumstances under the recently introduced public health policy

regulations. The reforms of health care system should be carefully monitored for the actual impact they are likely to exert on the rationalization of public health policy and expenditure. The pharmacological knowledge should be better reflected in the pharmaceutical pricing and reimbursement policy – not only in Poland but in the other countries of the European Union as well.

### Statement of interests

Authors' declaration of personal interests: Rafal Nizankowski has served as a speaker and a consultant for Glaxo-SmithKline, Pfizer and Sanofi Aventis. Other authors declare that they have no competing interests.

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