Original Research Article

Comparison of Complication Rates in Hip Fractures with or without Pre-existing Anticoagulation

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Abstract: According to current guidelines surgical treatment of hip fractures has to be initiated within 48h. This often poses a challenge, as the main focus group are elderly patients with numerous comorbities and frequently medical anticoagulation. The aim of this study was to assess the complication rate in hip fractures, anticoagulated with phenprocumon in comparison to patients without anticoagulation. A total of 534 consecutive patients, treated in 2011, with diagnosed hip fractures were studied with 74% being female. Age distribution was 79.9 ± 12.6, range (24.7 to 104.9). In addition to medical anticoagulation, we evaluated the time to surgery, length of stay, several blood values over multiple time points and the mobilization as well as systemic and local complications. Out of 534 patients included in the study, 210 (39.3%) were on medical anticoagulation. Patients who received phenprocumon reversal with vitamin K, had the longest time to surgery (3.7 days) as well as the longest length of stay (19.5 days) while patients who received phenprocumon reversal with human prothrombin complex (PPSBP) had the shortest time to surgery (0.1) and the shortest length of stay (11.3 days). Furthermore patients who received phenprocumon reversal with vitamin K had the highest rate of mortality with 9.8%.Preoperative length of stay appeared as a significant predictor for respiratory infections, wound infections, and urinary tract infections, in a multivariate model test. Phenprocumon reversal with PPSBP appears to be superior to phenprocumon reversal with vitamin K in regard of postoperative infections and the mortality rate. An analysis of a bigger cohort over a longer period of time should be conducted.
Keywords: hip fracture, mortality, elderly patients, phenprocumon, reversal of anticoagulation

INTRODUCTION

Proximal femoral fractures are representing a major cause of morbidity and mortality in the elderly [1, 2]. They have a high impact on public health because of the related morbidity, risk of nursing-home admission and increased healthcare costs [3-5]. The expected demographic changes resulting from rapidly ageing population in Western countries have led to prediction of a huge increase in the worldwide incidence of hip fracture [3, 6]. Women make up at least 70% of all patients with a proximal femoral fracture [7,8].

Outcome of surgical treatment is superior to that of conservative treatment for hip fractures[9]. It has been shown that surgical treatment of these fractures within the first 48 hours decreases the morbidity and mortality rates in this group [10-13]. Complications of recumbency include pneumonia, pressure sores, muscle wasting, and urinary tract infections [14, 15]. In recent years, phenprocumon has been used increasingly as a preventive measure of thromboembolic events [13, 16, 17]. Approximately 1 to 1.5% of the population takes phenprocumon as a prophylaxis against thrombosis

[18,19]. This has led to a growing number of hip fracture patients who are treated with phenprocumon at presentation in the emergency room, resulting in high level of international normalized ratio (INR) [13, 20].

Current recommendations state that unless there is a very high risk of thromboembolism, anticoagulation should be temporarily discontinued in preparation for surgery [18, 21]. Patients with an INR of greater than 1.5 are considered at higher risk for intra- or postoperative bleeding [1-5, 18, 21-27]. However, delaying surgery because of a high INR can also lead to increased complications and health costs [18].

Phenprocumon and other coumarin anticoagulants act by inhibiting the synthesis of functional vitamin K-dependent coagulation factors II, VII, IX and X[28-30]. Normal INR in patients receiving phenprocumon can be achieved by various methods: "watch and wait", oral or intravenous vitamin K, or fresh frozen plasma administration [13, 20, 31-33]. Studies have shown that it may take up to 4 days for INR to reach acceptable levels for surgery [20]. After

revising the current literature, there is a lack of guidelines for reversal of anticoagulation in patients with a hip fracture [34, 35].

The purpose of our study, was to assess the relationship between patients under phenprocumon anticoagulation and complications caused by hip fractures in elderly patients at a level I Trauma Centre with a control group of patients without anticoagulation.

MATERIAL AND METHODS

A total of 534 consecutive patients with a diagnosed fracture of the proximal femur admitted to Dep. Trauma Surgery, Medical University Vienna, in 2011 have been considered for inclusion. Data collection was performed prospectively and statistical evaluation was performed retrospectively, approved by local IRB. Patients were identified from surgical records and Hospital In-patient Enquiry System. Data were retrieved from our database. Laboratory findings at admission were retrieved from the database of Institute of Central Laboratory, General Hospital Vienna. Patients were classified in femoral neck-, per trochanteric-, sub trochanteric- and pertrochetsubtrochanteric fractures, according to Garden and AO classification [36, 37].

Study population was divided into the following subgroups: no anticoagulation, phenprocumon + Vit. K, phenprocumon + PPSBP, and other anticoagulation.Phenprocumon was administered as Marcoumar® (Hoffmann La Roche AG, Basel, CH), and ashuman prothrombin complex (PPSBP), Beriplex® (CLS Behring Inc., PA, USA) was used in the entire study population. Patients not managed operatively were excluded from the study. Other exclusion criteria were pathological fractures and revision surgery. The primary outcome measured was the complication rate in patients with hip fractures with or without pre-existing anticoagulant therapy.

STATISTICAL METHODS

The primary endpoint is the incidence of complications. Secondary endpoints include length of stay, blood values within the framework of stay and mobilization.

The primary endpoint was based on crosstabs, on the one hand by means of chi-square goodness of fit test for nominal scaled data (frequencies), and the other part by means of model checking with binary logistic regression for metric and dichotomous predictors were examined. The binary logistic regression allows the prediction to what extent predictors (presence of pre-existing anticoagulant medication, comorbidities, fracture type, type of surgical rehabilitation, but also patient's age, sex, blood values at admission) are able to predict the occurrence of complications.

The statistical analysis of secondary endpoints was performed by means of parameter-free U-test according to Mann and

Whitney or Kruskal-Wallis rank means of analysis of variance. For the comparison of blood values assuming the normal distribution assumption were parametric methods such as the t-test for independent samples or two-factor analysis of variance method used, which also interactions (interactions) can be tested for significance between the factors.

In addition, the respective descriptive statistical parameters (mean, standard deviation, minimum, maximum, range, median) are calculated for the characterization and description of the parameters of interest in the various patient groups.

RESULTS

We enrolled 534consecutive patients with a mean age of 77.6 (range 24.7 to 101.9). 74% of who were female, and 26% were male. Follow up was 15.2 ± 08.7 days (range 2 to 99).Study population was divided into the following sub-groups: no anticoagulation (n=324), phenprocumon + Vit. K (n=41), phenprocumon + PPSBP (n=7), other anticoagulation (n=162). A total number of 22 patients (4.1%) died within observation time. Table 1 deals with general study population data and laboratory values.

In our study population n=534, a total of 534 fractures were observed. Fractures were divided due to the following: femoral neck (n=252, 47%), per trochanteric (n=228, 43%), subtrochanteric (n=23, 4%), per trochanteric and subtrochanteric (n=31, 6%). All surgical procedures were performed by different attendings. Table 2 deals with the details regarding sub-group and surgical procedures.

Laboratory parameters used for statistical analysis: haemoglobin (Hb), haematocrit (Hct), normotest, international normalized ratio (INR), leukocytes (Leu), creatinine (Crea), creatine kinase (CK-MB), glucose (Gluc), and c-reactive protein (CRP). Comorbidities were subdivided as following: heart failure, hypertension, renal failure, diabetes mellitus, hyperlipidaemia, thyroid function test, organ transplantation, cancer, chronic heart disease, chronic obstructive pulmonary disease, osteoporosis, and dementia.

Complications were subdivided as following: fever, anaemia, respiratory tract infection, urinary tract infection, wound infection, and death. Table 3 and 4 deals with the variables according to the complications.

Table-1: General patients characteristivs

	No anticoagulation				Warfarin + Vit. K				Warfarin + Beriplex®				Other anticoagulation			
	n	**M**	**SD**	**Md**	**n**	**M**	**SD**	**Md**	**n**	**M**	**SD**	**Md**	**n**	**M**	**SD**	**Md**
Total patients & Age	324	77.6	14.4	81.9	41	82.9	7.4	84.7	7	81.4	10.2	85.7	162	83.7	8.0	85.6
Gender																
Male	81				13				2				43			
Female	243				28				5				119			
Hospital stay																
Days	324	14.7	9.3	13.0	41	19.5	8.1	18.0	7	11.3	4.4	11.0	162	15.5	7.3	14.0
Laboratory values At admission																
Hb	324	12.47	1.73	**12.60**	41	12.42	1.97	**12.50**	7	14.07	0.99	**13.90**	161	12.29	1.67	**12.40**
Hct	324	37.22	4.86	**37.70**	41	38.06	5.62	**38.20**	7	41.91	2.50	**41.40**	161	37.02	4.69	**37.10**
Normotest	324	99.60	21.87	**98**	41	26.07	8.89	**27.00**	7	41.29	21.20	**29.00**	162	96.88	22.02	**96.00**
INR	45	1.14	0.15	**1.10**	40	3.27	1.37	**2.95**	5	2.48	0.98	**2.90**	27	1.18	0.15	**1.20**
CRP	323	1.93	3.77	**0.46**	41	2.39	4.61	**0.54**	7	0.76	0.83	**0.26**	162	1.42	2.39	**0.41**
Before surgery																
Hb	322	12.38	1.72	**12.50**	36	11.21	1.56	**11.20**	7	14.07	0.99	**13.90**	160	12.08	1.75	**12.20**
Hkt	322	36.91	4.94	**37.50**	36	34.19	4.86	**33.55**	7	41.91	2.50	**41.40**	160	36.28	5.03	**36.55**
Normotest	320	98.58	21.65	**97.00**	41	69.39	19.00	**71.00**	7	41.29	21.20	**29.00**	159	95.03	21.93	**94.00**
INR	55	1.16	0.14	**1.20**	35	1.45	0.28	**1.40**	5	2.48	0.98	**2.90**	31	1.21	0.14	**1.20**
CRP	323	2.67	4.34	**0.61**	37	9.89	4.25	**10.32**	7	0.76	0.83	**0.26**	160	2.84	4.24	**0.99**
After surgery																
Hb	321	10.13	1.42	**10.20**	41	10.24	1.38	**10.00**	7	11.84	2.01	**11.40**	159	10.20	1.30	**10.20**
Hkt	321	29.92	4.22	**30.10**	41	30.98	4.54	**29.80**	7	35.01	5.84	**33.60**	159	30.17	3.94	**30.80**
Normotest	311	85.41	18.24	**84.00**	39	73.77	17.20	**74.00**	7	52.57	14.93	**51.00**	156	83.16	20.48	**81.00**
INR	92	1.18	0.15	**1.20**	23	1.26	0.16	**1.20**	5	1.48	0.30	**1.30**	185	1.21	0.16	**1.20**
CRP	320	9.21	5.51	**8.91**	41	12.58	5.72	**12.48**	6	4.32	5.45	**2.23**	161	9.90	5.49	**9.86**
Before discharge																
Hb	321	10.62	1.31	**10.50**	41	10.66	1.32	**10.70**	7	11.36	0.95	**10.80**	159	10.71	1.13	**10.60**
Hkt	321	31.71	3.58	**31.80**	41	32.92	4.27	**33.30**	7	33.80	2.87	**32.70**	159	32.19	3.32	**32.00**
Normotest	305	105.05	22.79	**104.00**	39	73.90	28.68	**73.00**	7	77.29	34.75	**91.00**	151	102.44	23.28	**103.00**
INR	66	1.15	0.48	**1.10**	18	1.58	0.57	**1.50**	4	1.38	0.69	**1.10**	39	1.12	0.16	**1.10**
CRP	320	4.20	4.05	**2.79**	41	5.56	5.35	**4.23**	7	3.17	4.68	**1.25**	161	4.19	3.91	**2.87**
Mobilisation grade																
After surgery	319	**3.92**	0.81		41	**4.29**	0.64		7	**3.93**	0.59		160	**4.20**	0.69	
At discharge	319	**2.68**	1.14		41	**3.07**	1.14		7	**3.11**	0.67		160	**3.21**	1.12	

Hb= hemoglobin, Hct= Hematocrit, INR= International normalized ratio, CRP= C-reaktive protein, M= Median, SD= Standard deviation, Md=mean difference

Patients who received phenprocumon reversal with vitamin K, had the longest time to surgery (3.7 days) as well as the longest length of stay (19.5 days) and the highest CRP levels at all times, while patients who received phenprocumon reversal with PPSBP had the shortest time to surgery (0.1) and the shortest length of stay (11.3 days) as well as the lowest CRP values.

Furthermore, with 14.6%, patients who received phenprocumon reversal with vitamin K had the highest rate of respiratory infections and with 9.8% the highest rate of mortality, whilst patients on medical anticoagulation with other drugs with 8.0% had the highest proportion of wound infections. Table 5 deals with the significant predictors for complications.

Table-2: Fractures and surgery

	DHS	DCS	Gamma Nail	long Gamma Nail	IM	PFN	HEP	TEP	SCREW	TOTAL	%
Femoral neck	69	0	3	0	0	3	141	14	22	252	47
Pertroch.	7	0	94	3	2	120	0	0	2	228	43
Subtroch.	0	0	3	11	1	8	0	0	0	23	4
Pertroch. + Subtroch.	0	1	6	12	0	12	0	0	0	31	6
Total	76	1	106	26	3	143	141	14	24	534	100

DHS=Dynamic hip screw, DCS= Dynamic condylar screw, IM= Intramedullary nail, PFN= Proximal femur nail, HEP= Hemi arthroplasty, TEP= Total arthroplasty

Table-3: Variables according to complications

Tab.3(a): Variables according to fever			
	B(Regr. Koeff.)	Wald (df)	p	Exp(B)
Hospital stay	.047	8.63	.003	1.05
CRP	.095	4.02	.045	1.10

Table-3b: Variables according to anemia			
	B(Regr. Koeff.)	Wald (df)	p	Exp(B)
Age	.052	15.87(1)	<.001	1.05
Gender	.619	4.53(1)	.033	1.86
Hospital stay	.048	7.08(1)	.008	1.05
Fx type		26.39(9)	.002	
Surgery		23.15(8)	.003	
Hct	-.225	7.28(1)	.007	.80
Normotest	.012	5.12(1)	.024	1.01

Tab.3c: Variables according to respiratory infect			
	B(Regr. Koeff.)	Wald (df)	p	Exp(B)
Group		13.39(3)	.004	
Age	.072	6.36(1)	.012	1.08
Days till surgery	-.373	4.60(1)	.032	.69
Hospital stay	.048	8.03(1)	.005	1.05
Normotest	.027	6.17(1)	.013	1.03
CRP	.136	6.57(1)	.010	1.15

Tab.3d: Variables according to urinary infect			
	B(Regr. Koeff.)	Wald (df=1)	p	Exp(B)
Age	.037	7.07	.008	1.04
Days till surgery	.235	9.63	.002	1.27

Tab.3e: Variables according to wound infect			
	B(Regr. Koeff.)	Wald (df)	p	Exp(B)
Group		8.24(3)	.041	
Days till surgery	-.744	5.04(1)	.025	.48
Hospital stay	.108	19.64(1)	<.001	1.11
Hb	1.01	5.33(1)	.021	2.74
Hct	-.425	7.38(1)	.007	.65
CRP	.209	5.48(1)	.019	1.23
Cronic coronary disease	1.67	3.83(1)	.050	5.30

Tab.3f: Variables according to death			
	B(Regr. Koeff.)	Wald (df)	p	Exp(B)
Age	.118	7.27	.007	1.13
CRP	.207	8.61	.003	1.23
Diabetes	1.36	4.06	.044	3.90

Hb= hemoglobin, Hct= Hematocrit, CRP= C-reaktive protein;

Table-4: Complications

Complications	No anticoagulation		Phenprocumon + Vit. K		Phenprocumon + PPSBP		Other anticoagulation		Total	
	n	%	n	%	n	%	n	%	n	%
Fever	17	5.2	3	7.3	0	0.0	15	9.3	35	6.6
Anaemia	134	41.4	14	34.1	1	14.3	70	43.2	219	41.0
Respiratory infect	15	4.6	6	14.6	0	0.0	18	11.1	39	7.3
Urinary infect	77	23.8	15	36.6	3	42.9	44	27.2	139	26.0
Wound infect	7	2.2	1	2.4	0	0.0	13	8.0	21	3.9
Death	7	2.2	4	9.8	0.	0.0	11	6.8	22	4.1

Table-5: Significant predictors for complications

Predictors	Fever	Anemia	Pulmonary infect	Urinary infect	Wound infect	Death
Sub-groups			**		*	
Age		**	*	**		**
Gender		*				
Days till surgery			*	**	*	
Hospital stay	**	**	**		**	
Fracture type		**				
Surgery		**				
Hb					*	
Hct		**			**	
Leukocytes						
Normotest		*	*			
Creatinine						
CRP	*		*		*	**
Urinary tract infection						
Hypertonia						
Renal failure						*
Diabetes mellitus						*
Hyperlipidemia						
Tyroid function test						
Organ transplantation						
Cancer						
Chronic heart disease					*	
Cronic obstructive pulmonary disease						
Osteoporose						
Dementia						
Variant R^2 according to Nagelkerke	25.1%	41.7%	32.9%	21.8%	48.1%	42.4%

Hb= hemoglobin, Hct= Hematocrit, CRP= C-reaktive protein;

DISCUSSION

Proximal femoral fractures represent a surgical challenge, not only because of the complexity of the fracture morphology, but also because of the high perioperative risk, most multi-morbid patients are associated with [39-44]. Despite the availability of rapid-acting drugs to antagonize the anticoagulation effects, due to missing clear directives for implementation, clinical usage can be seen as limited [21, 34, 35].

The average age of all patients studied at the time of fracture was 79.9 years, which is comparable to the literature indicating an average age of 80.8 years, with men already in a slightly younger age (74.2 years) compared to women (82.0 years) [45, 46]. In our study population 4.1% died within observation time, representing a lower number than 6% reported by Schulze et al. in the literature [47].

Proximal femoral fractures are more common in women. In our patients, the ratio was 74.0% female to 26.0% male, compared to Geiger et al. publishing a ratio 82.3% to 17.7%,women to men. Existing higher prevalence in women is explained in the literature by the frequent occurrence of osteoporosis [45, 48-54].

Medial femoral neck fracture sets with 45.1% of cases, the most common fracture (compared with 40.6% reported in the literature), followed by the

intertrochanteric fractures with 42.7% (compared with 44.0%), the per trochanteric and sub trochanteric fractures with 5.8%, the sub trochanteric fractures with 4.3% and the lateral femoral neck fracture with 2.1% of cases [45, 55].

Patients have, depending on their anticoagulant medication and antagonizing procedure, both a different preoperative length of stay as well as a total different length of stay. Preoperative length of stay in the phenprocumon + vitamin K group scored the highest average value of 3.7 days, while the phenprocumon + PPSBP patients with 0.1 days show the least time. The length of stay was in the phenprocumon + vitamin K group with 19.5 days (Md = 18.0) the longest, while in the phenprocumon + PPSBP group, 11.3 days (Md = 11.0) show again the shortest duration. In contrast a preoperative length of stay with 0.9 days (Md=1.5) and a total length of stay with 14.7 (Md=13.0) was observed in the subgroup without anticoagulation.

This is remarkable, because the length of stay within the multivariate model testing was identified as the most significant predictor variable thus for the occurrence of complications in this study. In particular, the length of stay is in a strong correlation with the occurrence of fever, bleeding, anaemia, respiratory infections and wound infections. However, it should be noted that the length of stay on the practical relevance for the prediction of complications is put into perspective, because they can be described in comparison with the other predictors as retrospective variable.

Preoperative length of stay, also a retrospective variable, can be easily influenced by the possibility of a quick reversal of the anticoagulant medication than the entire length of stay and thus has a higher clinical relevance. Our data demonstrate a shorter preoperative duration of stay, represent a positive predictive value for lower complication rates and better outcomes, as published in several studies [56, 57]. Preoperative length of stay appeared as a significant predictor for respiratory infections, wound infections, and urinary tract infections, in a multivariate model test.

The blood parameters, showed decreased haemoglobin level as a predictor of wound infections, a decreased haematocrit value for bleeding anaemia and wound infections, an increased value of Normotest value for bleeding anaemia, and respiratory infections. CRP value increased fastest in the phenprocumon + vitamin K, and additional attime points for pre-operative and post-operative time, and showed higher values compared to all other groups. The lowest levels were observed in the phenprocumon + PPSBPgroup. In particular, the CRP value is closely related to the occurrence of fever, respiratory infections, wound infections and significantly in death. Levels of leukocytesin the phenprocumon + PPSBP group was at all times above the values of all the other groups.

The degree of mobilization was set in relationship to that before the accident, but did not show significant differences between the groups.

The comorbidities gathered in the course of data collection were also tested for differences in distribution as a function of the groups. Significant differences were associated with heart failure (14.6% most often in phenprocumon + vitamin K), coronary heart disease (28.6% most often in the phenprocumon + PPSBP group), diabetes mellitus (24.4% most common in the phenprocumon + vitamin K group) and dementia (23.5% most often in the other anticoagulation group). This contrasts with the overall most frequently occurring comorbid hypertension (total of 42.3% of all patients in the sample). For the occurrence of respiratory complications, a significant distribution difference between the groups could be found, with 14.6% in the phenprocumon + vitamin K group, the largest share.

A significant distribution difference could also be observed for the occurrence of wound infections, with 8.0%, the largest share was found in the group of patients treated with other anticoagulant drugs. The in-hospital mortality for proximal femoral fractures in our patients was 4.1%, compared to the literature with 3.2 [58]. The phenprocumon + vitamin K group showed with 9.8% the highest percentage of deceased patients.

LIMITATIONS OF THIS STUDY
The main limitations of our study were the small number of patients and the unequal distribution between the subgroups. A critical reader may see the surgical procedures performed by different surgeons as a lack of quality.

CONCLUSION
In our study, we could demonstrate that phenprocumon reversal with PPSBP appears to be superior to phenprocumon reversal with vitamin K in regard of postoperative infections and the mortality rate. An analysis of a bigger cohort over a longer period of time should be conducted.

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REFERENCES
1. Bhaskar D, Parker MJ; Haematological indices as surrogate markers of factors affecting mortality after hip fracture. Injury, 2011; 42(2):178-82.
2. O`Daly BJ, Walsh JC, Quinlan JF, Falk GA,

Stapleton R, Quinlan WR, O´Rourke SK; Serum albumin and total lymphocyte count as predictors of outcome in hip fractures. Clin Nutr., 2010; 29(1):89-93.

3. Mann E, Icks A, Meyer G; Discrepancies in national incidence trends for hip fracture: why does Austria have such a high incidence? WKW, 2010; 122:126-8.

4. Wiktorowicz ME, Goeree R, Papaioannou A; Economic implications of hip fracture: health service use, institutional care and cost in Canada. Osteoporos Int., 2001; 12:271-8.

5. Cumming RG, Klineberg R, Katelaris A; Cohort study of risk of institutionalization after hip fracture. Aust N Z J Public Health, 1996; 20(6):579-582.

6. Meunier PJ; Prevention of hip fractures. Am J Med., 1993; 95:75S-8S.

7. Jacobsen SJ, Goldberg J, Miles TP, Brody JA, Stiers W, Rimm AA; Hip fracture incidence among the old and very old: a population-based study of745,435 cases. Am J Public Health, 1990; 80(7):871-3.

8. Endres HG, Dascj B, Lungenhausen M, Maier C, Smektala R, Trampisch HJ, Pientka L; Patients with femoral or distal forearm fracture in Germany: a prospective observational study on health care situation and outcome. BMC, 2006; 6:87-100.

9. Beloosesky Y, Hendel D, Hershkovitz A, Skribnic G, Grinblat J; Outcome of medically unstable elderly patients admitted to a geriatric ward after hipfracture. Aging(Milano), 2001; 13(2):78-84.

10. Rogers FB, Shackford SR, Keller MS; Early fixation reduces morbidity and mortality in elderly patients with hip fractures from low impact falls. J Trauma, 1995; 261-5.

11. Bottle A, Aylin P; mortality associated with delay in operation after hip fracture: observational study. BMJ 2006;332:947-51.

12. Zuckerman JD, Skovron ML, Kovai KJ, Aharonoff G, Frankel VH; Postoperative complications and mortality associated with operative delay in older patients who have fracture of the hip. B Bone Joint Surg Am., 1995; 77:1551-6.

13. Tal A, Rubin G, Rozen N; Treatment with vitamin K in hip fractures patients receiving warfarin. IMAJ, 2013; 15416-9.

14. Ashouri F, Al-Jundi W, Patel A, Mangwani J; Management of warfarin anticoagulation in patients with fractured neck of femur. ISRN Hematology, 2011.

15. Al-Rashid M, Parker MJ. Anticoagulation management in hip fracture patients on warfarin. Injury 2005;36(11):1311-5.

16. Cannegieter SC, Rosendaal FR, Wintzen AR, Van der Meer JM, Vandebroucke JP, Briet E; Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med., 1995; 333:11-17.

17. AzarAJ, Cannegieter SC, Deckers JW; Optimal intensity of oral anticoagulant therapy after myocardial infarction. J Am CollCardiol., 1996; 27:1349-55.

18. Tharmarajah P, Pusey J, Keeling D, Willet K; Efficacy of warfarin reversal in orthopaedic trauma surgery patients. J Orthop Trauma, 2007; 21(1):26-30.

19. Salamat A, Seaton J, Watson HG; Impact of introducing guidelines on anticoagulant reversal. Transfus Med., 2005; 15:99-105.

20. White RH, McKittrik T, Hutchinson R, Twitchell J; Temporary discontinuation of warfarin therapy: changes in the international normalized ratio. Ann Intern Med., 1995; 122:40-2.

21. Baglin TP, Keeling DM, Watson HG; Guidelines on oral anticoagulation(warfarin): third edition: 2005 update. Br J Haematol., 2006; 132:277-85.

22. Bhatia m, Talawadekar G, Parihar S, Smith A; An audit of the role of vitamin K in the reversal of international normalized ratio (INR) in patients undergoing surgery for hip fracture. Annn R Coll Surg Engl., 2010; 92:473-6.

23. Gogna A, Arnu S. Oral anticoagulation in clinical practice. J Indian Acadclin Med., 2005; 6:53-66.

24. Francis CW, Marder VJ, Evarts CM; Two-step warfarin therapy: prevention of postoperative venous thrombosis without excessive bleeding. JAMA, 1983; 249:374-8.

25. Carrel TP, Klingenmann W, Mohacsi PJ; Perioperative bleeding and thromboembolic risk during non-cardiac surgery in patients with mechanical prosthetic heart valves: an institutional review. J Heart Valve Dis., 1999; 8:392-8.

26. Gallus AS, Baker RI, Chong BH; Consensus guidelines for warfarin therapy: recommendations from the Australasian Society of thrombosis and haemostasis. Med J Aust., 2000; 172:600-5.

27. Sandset PM, Abildgaard U; Perioperative management of oral anticoagulant therapy. Thromb Res., 2002; 108:1-2.

28. Baker RI, Coughlin PB, Gallus AS, Harper PL, Salem HH, Wood EW; warfarin reversal: consensus guidelines, on behalf of the Australasian society of thrombosis and haemostasis. MJA, 2004; 181:492-7.

29. Boots Healthcare Australia; Coumadin. Australian product information. Sydney: Boots Healthcare Australia Pty Ltd., 26 July 2000.

30. Majerus PW, Broze GJ, Miletich JP; Anticoagulant thrombolytic, and antiplatelet drugs. In: Hardman JG, Limbird LE, editors. Goodman and Gilman´s the pharmacological basis of therapeutics. 9thed. New York: McGra-Hill, 1996; 1347-351.

31. Weibert RT, Le DT, Kaysar SR, Rapaport SI; Correction of excessive anticoagulation with low-dose oral vitamin K1. Ann Intern Med., 1997; 126:959-62.

32. Whitling AM, Bussey HI, Lyons RM; Comparing different routes and doses of vitamin K for reversing excessive anticoagulation. Arch Intern

Med., 1998; 158:2136-40.

33. Ahmed I, Kahn MA, Nayak V, Mohsen A; An evidence-based warfarin management protocol reduces surgical delay in hip fracture patients. J of orthopaedics and traumatology: official journal of the Italian Society of Orthopaedics and Traumatology, 2014; 15(1):21-7.

34. Starks I, Cooke S, Docker C, Raine A; Warfarinized patients with proximal femoral fractures: survey of UK clinical practice. European Journal of Trauma and Emergency Surgery, 2009; 35(3):287-290.

35. Verma R, Tayton E, Birch B. Does oral vitamin K given in A%E help expedite surgery in fracture neck of femur patients on warfarin for atrial fibrillation. Injury Extra, 2008; 39(5):177-8.

36. Garden RS; Reduction and fixation of subcapital fractures of the femur. Orthop Clin North Am., 1974; 4:683-712.

37. Marsh JL, Slongo TF, Agel J, Broderick JS, Creevey W, DeCoster TA; Fracture and dislocation classification compendium – 2007: Orthopedic Trauma Association classification, database and outcomes committee. J Orthop Trauma, 2007; 21:1-133.

38. Ulmar B, Simon S, Eschler A, Mittlmeier T; Subtrochantäre Femurfrakturen. Der Unfallchirurg, 2013; 116(12):1097-114

39. Hung WW, Morrison RS; Hip fracture: a complex illness among complex patients. Annals of internal medicine, 2011; 155(4):267-8.

40. Perez JV, Warwick DJ, Case CP, Bannister GC; Death after proximal femoral fracture- an autopsy study. Injury, 1995; 26(4):237-40.

41. Rosen SF, Clagett GP; Prevention of venous thromboembolism. Curr Opin Haematol., 1999; 6(5):285-90.

42. Landefeld CS, Cook EF, Flatley M, Weisberg M, Goldman L; Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. American Journal of Medicine, 1987; 82(4):703-13.

43. Travis S, wary R, Harrison K; Perioperative anticoagulation control. Br j Surg., 1989; 76:1107-8.

44. British Committee for Standards in Haematology. Guidelines on oral anticoagulation.3rdedn. Br J Haematol., 1998;101:374-87.

45. Geiger F, Schreiner K, Schneider S, Pauschert R, Thomsen M; Die proximale Femurfraktur des älteren Patienten. Orthopäde, 2006; 35(6):651-8.

46. Elffors L, Gullberg B, Alexander E; Methodology of medos-multicenter study of hip fracture incidence : validity and relevance consideration. Bone, 1993; 14:45-9.

47. Schulze RU, Grams A, Smektala R; Guideline compliance in hip fracture: results of an external quality-assurance program in North Rhine Westphalia: 2003-2005. Unfallchirurg, 2008; 111(2):65-70.

48. Hinton RY, Smith GS; The association of age, race and sex with the location of proximal femoral fractures in the elderly. J Bone Joint Surg Am., 1993; 75:752-9.

49. Aitkin JM; Relevance of osteoporosis in women with fracture of the femoral neck. Br Med J Clin Res., 1984; 288:597-601.

50. Pientka L; Proximale Femurfrakturen (Osteoporose) und geriatrische Rehabilitation. Bundesgesundheitsbl - Gesundheitsforsch – Gesundheitsschutz, 2004; 47(6):547-53.

51. Gage BF, Birman-Deych E, Radford MJ, Nilasena DS, Binder EF; Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. Archives of internal medicine, 2006; 166(2):241-6.

52. Sato Y, Honda Y, Jun I; Long-term oral anticoagulation therapy and the risk of hip fracture in patients with previous hemispheric infarction and nonrheumatic atrial fibrillation. Cerebrovascular diseases, 2010; 29(1):73-8.

53. Woo C, Chang LL, Ewing SK, Bauer DC; Osteoporotic Fractures in Men Study G. Single-point assessment of warfarin use and risk of osteoporosis in elderly men. Journal of the American Geriatrics Society, 2008; 56(7):1171-6.

54. Rezaieyazdi Z, Falsoleiman H, Khajehdaluee M, Saghafi M, Mokhtari-Amirmajdi E; Reduced bone density in patients on long-term warfarin. International journal of rheumatic diseases, 2009; 12(2):130-5.

55. Arbes S, Widhalm H, Vécsei V; Hüftgelenksnahe Femurfrakturen. JATROS Unfallchirurgie & Sporttraumatologie, 2010; 5(2):6-9.

56. Smektala R, Endres HG, Dasch B, Maier C, Trampisch HJ, Bonnaire F; The effect of time-to-surgery on outcome in elderly patients with proximal femoral fractures. BMC musculoskeletal disorders, 2008; 9:171.

57. Simunovic N, Devereaux PJ, Sprague S, Guyatt GH, Schemitsch E, Debeer J; Effect of early surgery after hip fracture on mortality and complications: systematic review and meta-analysis. CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne, 2010; 182(15):1609-16.

58. BQS Institut für Qualität und Patientensicherheit. Qualitätsindikator "Hüftgelenknahe Femurfrakturen 2007; Online verfügbar unter: http://www.bqs-qualitaetsindikatoren.de [Recherchedatum: 14.07.2014].