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# Drug Therapy Problems and Associated Factors in Patients on Anticoagulant Therapy at Kenyatta National Hospital, Kenya.

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**Achieving the goals of therapy with anticoagulants can be complicated by drug therapy problems (DTPs). The objective of the study was to identify and characterize DTPs among adult patients on anticoagulant therapy at the Kenyatta National Hospital medical wards in the between May and August 2023. For this purpose, subjects were interviewed and data extracted from their medical records. The data was analysed to give the prevalence of the DTPs in the study population and the associated factors. The enrolment phase garnered 125 participants into the study, 37.6% of whom had DTPs. The main DTPs encountered were drug-drug interactions and treatment safety problems in 23 (18.4%) and 20 (16%) participants, respectively. Associations between either the sociodemographic or clinical factors with the DTPs were not identified. The study demonstrated that Drug therapy problems are common in patients using anticoagulants. In conclusion, pharmacists should be vigilant to identify and intervene in case these problems arise.**

**Key words:** Drug therapy problems, anticoagulants

## INTRODUCTION

Drug therapy problems (DTPs) are any unwelcome incidences that occur during the use of medication and interfere with the achievement of the desired goals of therapy.[1] These medication related problems (MRPs) should be resolved for the patient to experience optimal outcomes of therapy. The Pharmaceutical Care Network of Europe (PCNE) validated and updated their system for classification of DTPs in February 2019.[2] The PCNE classification V 9.0 has three primary domains for problems, nine primary domains for causes and five primary domains for interventions.

The DTPs under the PCNE classification V 9.0 are treatment safety, treatment effectiveness and others. The causes of DTPs are classified into drug selection, drug form, dose selection, treatment duration, dispensing, drug use process, patient related, patient transfer related and others. Planned interventions for DTPs are classified as no intervention, at prescriber level, at patient level, at drug level and others.[2]

Anticoagulant therapy is a common pharmacological intervention employed in the management of myocardial infarction, ischaemic stroke, pulmonary embolism, deep vein thrombosis and atrial fibrillation. The high burden of disease caused by thrombosis indicates that anticoagulant therapy is critical in managing morbidity and mortality. The increase in risk factors for non-communicable illnesses such as obesity, sedentary lifestyle, poor diet and increased lifespan means that the use of anticoagulant therapy will remain high, if not increase. Medication related problems in patients using

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anticoagulant therapy are common due to narrow therapeutic window of some of the drugs, drug-food interactions, drug-drug interactions (DDIs), poor monitoring of therapy and patient errors in ambulatory use of these drugs.

Studying DTPs among patients on anticoagulants, their causes and potential interventions will lead to improved therapeutic outcomes and a reduction in morbidity and mortality. Currently, a dearth of information regarding DTPs in patients on anticoagulant therapy in Kenya exists. The main objective of the study was therefore to identify and characterize DTPs and associated factors among patients using anticoagulants.

## METHODS

### Study Design and Sample Size Calculation

This was a cross-sectional study conducted among adult patients admitted in the medical wards of Kenyatta National Hospital for anticoagulant therapy. The calculated sample size was 165 participants arrived at using the Cochran formula based on the prevalence of DTPs in venous thromboembolism patients in Ethiopia.[3]

### Inclusion and exclusion criteria

Patients were eligible if they were 18 years of age or older, on anticoagulant therapy and provided written informed consent. They were excluded if they were unable to communicate verbally, were pregnant or had missing/incomplete records.

### Participant recruitment, data collection and ethical considerations

Participants selection began with perusal of the list of patients admitted in each ward that were availed by the nursing staff. From this list, patients with diagnoses that led to prescription of anticoagulants were identified. The use of anticoagulant drugs was then confirmed using the treatment sheets in the respective patient files. The filtered list formed the sampling frame from which patients were selected using simple random sampling and eligibility as study participants ascertained using the inclusion and exclusion criteria. Potential participants were taken through the consenting process that culminated in the voluntary provision of written informed consent.

A questionnaire was used to collect data on DTPs from the patients who were interviewed by the researchers. Additional information such as International Normalization Ratio (INR), dose administered, and clinical signs of adverse drug reactions was abstracted from the patient files. The Kenyatta National Hospital and University of Nairobi Ethics and Research Committee approved the study (KNH- ERC/A/128).

### Data analysis

Data collected was entered into Microsoft Excel©. All data collected was coded, cleaned, processed and saved daily. Data was password-protected to maintain patient confidentiality. After the end of the data collection period, analysis was carried out using Stata© Version 13. Descriptive statistics such as mean, standard deviation and frequencies were used to summarize and describe patient demographics and clinical characteristics, and the types and prevalence of DTPS. Inferential statistics such as chi-square, Fischer's test and logistic regression analysis were used to determine the relationships between DTPs and associated factors.

## RESULTS

### Sociodemographic characteristics of the study participants

Between May and August 2023, 125 participants were enrolled in the study. Participants were nearly evenly distributed in terms of sex, though females were slightly over half of those enrolled (66 (52.8%)) (Table 1). Most were in the 20 – 40 years age bracket and a large proportion reported that they neither smoked (102, 81.6%) nor consumed alcohol (96, 76.8%). Of the 125 participants, slightly more than a third (47, 37.6%) experienced DTPs.

Majority of patients, 105 (84.8%), reported an improvement in their symptoms while a similar number reported satisfaction with their drug therapy. About 62 (50%) participants reported an exacerbation of VTE symptoms with a variety of side effects such as episodes of bleeding, bruising and black stools being reported (Figure 1).

### Drug therapy problems identified among study participants

The main DTP experienced was classified under 'others', which was mostly DDIs between anticoagulants and other classes of drugs such as antibiotics. This category of DTPs accounts for any other drug therapy problem except treatment effectiveness and treatment safety. In the case of this study, DDIs were the main DTP that fell under this category (Table 2). The main cause of DTPs was drug selection (24%). For most patients with DTPs (34, 27.2%), no interventions were initiated. Most interventions (6.4%) were done at prescriber level, and only a small number of DTPs, 19.2%, were solved.

**Table 1: Sociodemographic characteristics of participants on anticoagulant therapy (n=125)**

| Variable | Category | Frequency n (%) | |
|---|---|---|---|
| Age | Below 20 years | 7 | (5.6) |
| | 20-40 yrs | 47 | (37.6) |
| | 40-60 yrs | 43 | (34.4) |
| | Above 60 yrs | 28 | (22.4) |
| Gender | Male | 59 | (47.2) |
| | Female | 66 | (52.8) |
| Marital status | Single | 34 | (27.2) |
| | Separated | 8 | (6.4) |
| | Married | 73 | (58.4) |
| | Divorced | 2 | (1.6) |
| | Widowed | 8 | (6.4) |
| Employment | Employed | 22 | (17.6) |
| | Self-Employed | 55 | (44.4) |
| | Unemployed | 25 | (20.0) |
| | Student | 6 | (4.8) |
| | Retired | 17 | (13.6) |
| Level of Education | Primary | 44 | (35.2) |
| | Secondary | 64 | (51.2) |
| | Diploma | 7 | (5.6) |
| | Degree | 7 | (5.6) |
| | Masters | 2 | (1.6) |
| | PHD | 1 | (0.8) |
| Smoke cigarettes | Yes | 23 | (18.4) |
| | No | 102 | (81.6) |
| Drink Alcohol | Yes | 29 | (23.2) |
| | No | 96 | (76.8) |

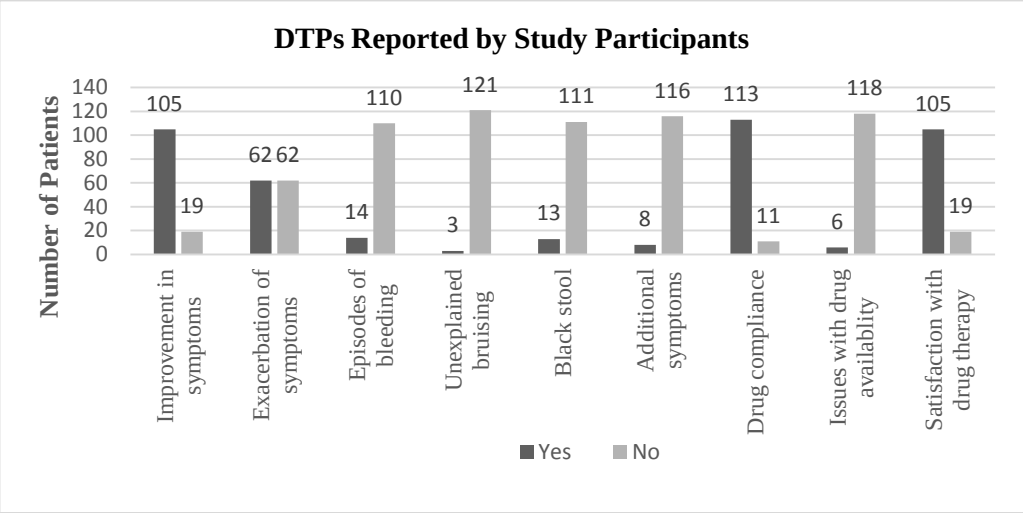


**Figure 1: Drug Therapy Problems as Reported by Study Participants**

**Table 2: DTPs Encountered by patients on anticoagulant therapy (n=125)**

| | Primary Domains | Yes n (%) | No n (%) |
|---|---|---|---|
| **Problems** | Treatment effectiveness | 4 (3.2) | 121 (96.8) |
| | Treatment safety | 20 (16) | 105 (84) |
| | Others | 23 (18.4) | 102 (81.6) |
| **Causes** | Drug selection | 30 (24) | 95 (76) |
| | Drug form | 0 | 125 (100) |
| | Dose selection | 5 (4) | 120 (96) |
| | Treatment Duration | 0 | 125 (100) |
| | Dispensing | 2 (1.6) | 123 (98.4) |
| | Drug Use process | 0 | 125 (100) |
| | Patient related | 3 (2.4) | 122 (97.6) |
| | Patient transfer related | 1 (0.8) | 124 (99.2) |
| | Other | 6 (4.8) | 119 (95.2) |
| **Planned interventions** | No intervention | 34 (27.2) | 91 (72.8) |
| | At prescriber level | 8 (6.4) | 117 (93.6) |
| | At patient level | 1 (0.8) | 124 (192) |
| | At drug level | 2 (1.6) | 123 (98.4) |
| | Other | 2 (1.6) | 123 (98.4) |
| **Intervention Acceptance** | Intervention accepted | 11 (8.8) | 114 (91.2) |
| | Intervention not accepted | 0 | 125 (100) |
| | Other | 36 (28.8) | 89 (71.2) |
| **Status of DTP** | Problem Status Unknown | 11 (8.8) | 114 (91.2) |
| | Problem solved | 24 (19.2) | 101 (80.8) |
| | Problem partially solved | 4 (3.2) | 121 (96.8) |
| | Problem not solved | 8 (6.4) | 117 (93.6) |

**Univariate, bivariable and multivariable analyses**

During univariate analysis, no significant associations were identified between baseline characteristics and DTPs (Table 3). Variables were largely categorical in nature and were tested using either the Chi Square or Fisher's exact test, the closest to an association with DTPs being marital status (p =0.076). Univariate analysis of DTPs and clinical characteristics of the participants, by Chi Square and Fisher's Exact tests did not yield any significant associations (T**able 4)**. The attendant variables had very small cell counts, for comorbidities in particular, which may have reduced the ability to detect any significant differences between the groups of patients with and without DTPs.

**Table 3: DTPs by baseline characteristics and their association**

| Variable | Category | DTPs | | p value |
|---|---|---|---|---|
| | | Yes n (%) | No n (%) | |
| Gender | Male | 22 (47.83) | 37 (46.84) | 0.915 |
| | Female | 24 (52.17) | 41 (53.16) | |
| Age | Below 20 yrs | 3 (6.52) | 4 (5.06) | 0.273* |
| | 20-40 yrs | 17 (36.96) | 30 (37.97) | |
| | 40-60 yrs | 13 (28.26) | 30 (37.97) | |
| | Above 60 | 13 (28.26) | 15 (18.99) | |
| Marital status | Single | 17 (36.96) | 17 (21.52) | 0.076* |
| | Separated | 1 (2.17) | 7 (8.86) | |
| | Married | 22 (47.83) | 51 (64.56) | |
| | Divorced | 1 (2.17) | 1 (1.27) | |
| | Widowed | 5 (10.87) | 3 (3.80) | |
| Level of Education | Primary | 22 (47.83) | 22 (27.85) | 0.305* |
| | Secondary | 20 (43.48) | 44 (55.70) | |
| | Diploma | 2 (4.35) | 5 (6.33) | |
| | Degree | 2 (4.35) | 5 (6.33) | |
| | Masters | 0 (0.00) | 1 (1.27) | |
| | PhD | 0 (0.00) | 1 (1.27) | |
| Employment | Employed | 6 (13.04) | 16 (20.25) | 0.725* |
| | Unemployed | 10 (21.74) | 15 (18.99) | |
| | Self-employed | 20 (43.48) | 35 (44.3) | |
| | Student | 3 (6.52) | 3 (3.80) | |
| | Retired | 7 (15.22) | 10 (12.66) | |
| Drinking Alcohol | Yes | 12 (26.09) | 17 (21.52) | 0.560 |
| | No | 34 (73.91) | 62 (78.48) | |
| Units of alcohol | < 7 Units | 2 (16.67) | 3 (17.65) | 0.915* |
| | 8 to 10 Units | 3 (25.00) | 3 (17.65) | |
| | > 14Units | 7 (58.33) | 11 (64.71) | |
| Smoking cigarettes | Yes | 9 (19.57) | 14 (17.72) | 0.798 |
| | No | 37 (80.43) | 65 (82.28) | |
| Years of smoking cigarettes | Less than 10 yrs | 2 (22.2) | 3 (21.43) | 0.694* |
| | 10-19 yrs | 4 (44.44) | 3 (21.43) | |
| | >20 yrs | 3 (33.33) | 8 (57.14) | |
| Physical activity | Yes | 35 (78.09) | 55 (69.52) | 0.437 |
| | No | 11 (23.91) | 24 (30.38) | |

* Fisher's Exact

**Table 4: Association between clinical profiles of study participants and DTPs**

| Variable | Category | DTPs | | p-value |
|---|---|---|---|---|
| | | **Yes n (%)** | **No n (%)** | |
| Comorbidity | Yes | 18 (39.13) | 41 (51.90) | 0.168 |
| | No | 28 (60.87) | 38(48.10) | |
| Which Comorbidity | Hypertension, HIV | 0 (0.00) | 1 (0.81) | 0.526* |
| | Hypertension, hyperthyroidism | 0 (0.00) | 1 (0.81) | |
| | Hypertension, asthma | 0 (0.00) | 1 (0.81) | |
| | Hypertension, diabetes mellitus | 4 (3.22) | 7 (5.65) | |
| | HIV | 6 (4.84) | 3 (2.42) | |
| | Acromegaly | 0 (0.00) | 1 (0.81) | |
| | Asthma | 0 (0.00) | 1 (0.81) | |
| | Diabetes mellitus | 2 (1.61) | 8 (6.45) | |
| | Dyspepsia | 0 (0.00) | 1 (0.81) | |
| | Gout | 0 (0.00) | 1 (0.81) | |
| | Heart failure | 0 (0.00) | 2 (1.61) | |
| | Hypertension | 5 (4.03) | 11 (8.87) | |
| Drug allergies | Yes | 6 (13.04) | 6 (7.59) | 0.652 |
| | No | 40 (86.96) | 73 (92.41) | |

***** Fisher's Exact

When logistic regression analysis was utilized at the inferential stage, no significant associations were identified between the categories of DTPs and the sociodemographic and clinical characteristics of the participants (Table 5). At bivariable regression analysis, several associations were identified. These included: **treatment effectiveness** and; red cell count (cOR = 0.085, 95% CI: 0.008 – 0.895, p value = 0.040); haemoglobin (cOR= 0.031 95% CI: 0.002 – 0.547, p value = 0.018); **treatment safety** and; comorbidity (cOR = 0.420 95% CI: 0.150 – 1.178, p value = 0.099); red cell count (cOR= 0.218 95% CI: 0.053 – 0.896, p value = 0.035); haemoglobin (cOR= 0.274 95% CI: 0.073 – 1.030, p value = 0.055); **other DTPs** and; red cell count (cOR = 0.341 95% CI: 0.098 – 1.187, p value = 0.091.

When multivariable regression analysis was undertaken, the associations found at bivariable stage were lost (e.g **treatment effectiveness** and; red cell count (aOR = 1.181, 95% CI: 0.001 – 1471.382, p value = 0.963); haemoglobin (aOR= 0.027, 95% CI: 0.001 – 50.009, p value = 0.346) (Table 5).

## DISCUSSION

The prevalence of DTPs in patients on anticoagulant therapy was 37.6%. A 2016 study in Ethiopia reported a prevalence of 51%[3] while a 2022 study done in Lebanon had a prevalence of 87.2%. [3,4] Viprey *et al.* established a prevalence of 8.4%. [5] The differences in burden of DTPS could be due to different study designs and differences in study populations.

Bleeding was one of the adverse effects that occurred in study participants. A study conducted in 2008, estimated that the incidence of bleeding as a complication of anticoagulants ranged from 1.5 – 4.5 %. [6] One of the main interventions was stopping anticoagulant therapy in study participants who had signs of bleeding. The prevalence of events of bleeding with anticoagulant use was higher in this study.

**Table 5: Bivariable and multivariable logistic regression analysis of sociodemographic and clinical characteristics and DTPs**

| DTPs | Variables | Bivariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | cOR (95% CI) | p-value | aOR (95% CI) | p-value |
| Treatment | Marital status | 1.03 (0.416 – 2.554) | 0.947 | - | - |
| Effectiveness | Comorbidities | 1.123 (0.153 – 8.232) | 0.909 | - | - |
| | RBCs | 0.085 (0.008 – 0.895) | **0.040** | 1.181 (0.001 – 1471.382) | 0.963 |
| | Haemoglobin | 0.031 (0.002 – 0.547) | **0.018** | 0.027 (0.001 – 50.009) | 0.346 |
| Treatment | Marital status | 0.851 (0.550 – 1.316) | 0.468 | - | - |
| Safety | Comorbidity | 0.420 (0.150 – 1.178) | **0.099** | 0.506 (0.175 – 1.460) | 0.207 |
| | RBCs | 0.218 (0.053 – 0.896) | **0.035** | 0.382 (0.676 – 2.154) | 0.275 |
| | Haemoglobin | 0.274 (0.073 – 1.030) | **0.055** | 0.520 (0.114 – 2.379) | 0.400 |
| Others | Marital status | 1.269 (0.834 – 1.930) | 0.265 | - | - |
| | Comorbidity | 1.031 (0.417 – 2.551) | 0.947 | - | - |
| | RBC | 0.341 (0.098 – 1.187) | **0.091** | 0.341 (0.098 – 1.186) | 0.091 |
| | haemoglobin | 0.504 (0.171 – 1.487) | 0.215 | - | - |

A number of study subjects had black stools, which is a sign of gastrointestinal bleeding. The risk of gastrointestinal bleeding with warfarin was 3.9% per patient-year while direct oral anticoagulants had a 25% higher risk of gastrointestinal bleeding than warfarin in a study done on patients using anticoagulants for atrial fibrillation. [7] The rate of gastrointestinal bleeding was 1.19% in patients on anticoagulants in a study by Gu *et al.* [8] Gastrointestinal bleeding is a major contributor to drug therapy problems in a significant number of patients on anti-coagulant therapy. Among the DTPs reported by a small proportion of participants was missed doses of anticoagulant. The frequency of this DTP was nearly similar to that reported at a hospital in the United Kingdom by Fanikos *et al.* (2004) among hospitalized patients also on anticoagulant therapy. [9]

The main type of DTP experienced by study participants was DDI which was classified under the category, 'other' in the PCNE drug therapy problems classification tool. Some participants experienced DDI involving anticoagulants during their hospitalization.

The main classes of drugs involved in these drug interactions were low molecular weight heparins and antibiotics. An Indian research paper revealed similar findings on drug-drug interactions being the main DTP encountered in hospitalized patients. [10] Bassam *et al*. derived similar conclusions while investigating DTPs in patients on anticoagulant therapy where a majority (86.2%) of their participants suffered from DDI. [4]

Treatment safety was the second most common DTP in the study population. Patients who had adverse effects such as bleeding, melena stools and unexplained bruises were put in this category. Wung *et al*. found a higher proportion of patients on anticoagulant therapy reporting treatment safety as the main DTP (68.4%), giving a greater burden compared to this study. [11] The difference in findings between the two studies could be attributed to the fact that the Wung *et al.* study was retrospective in nature, with a bigger sample size.

Treatment effectiveness was the least common DTP affecting the study subjects. This DTP was most likely due to sub-therapeutic levels of anticoagulants arising from under-dosing or missed doses. Bassam *et al.* found that problems with treatment effectiveness were caused by too low drug dose in 26.7% and too high drug dose in 15.5% of their participants. [4] the divergence of findings between the referenced study and the current enquiry may be attributed to differences in choice of study design; cross sectional versus prospective.

The main cause of DTPs was drug selection. This was due to choosing unsuitable drug combinations, or choosing a contraindicated drug. These errors are attributable to the prescriber. In a Taiwanese study published in 2022, drug selection was not one of the causes of DTPs. [11] Another study in Northern Cyprus concluded that drug selection and drug dose were the main causes of DTPs. [12] Stafford *et al., 2011* also concluded that drug selection was the main cause of DTPs. [13] The different results for the main cause of DTPs may be due to differences in study population.

Dose selection was the second most common cause of DTPs. Giving too high dose or too low dose leads to suboptimal therapeutic levels of the anticoagulant drug. Daba *et al.* concluded that a majority of the DTPs in patients taking anticoagulants for VTE management were caused by sub-therapeutic and over-therapeutic doses. [3] Stafford *et al.* had dose selection as a minor cause of DTPs, contributing to 2.6% of DTPs. This variation between the studies may be due to this study looking at anticoagulation medication as a broad class while the other two studies concentrated on specific anticoagulants such as warfarin and direct oral anticoagulants.

No association between the socio-demographic, clinical characteristics and DTPS were identified. Bassam *et al.* established that renal disease, smoking, concurrent intake of PPIs and NSAIDs were significant factors contributing to DTPs in patients taking anticoagulants. [4] Ruiz Ortiz *et al. (2*018) found the factors associated with DTPs in patients taking anticoagulants are concurrent use of antiplatelet drugs, concurrent use of angiotensin receptor blockers, concurrent use of aldosterone antagonists, older age and higher body mass index.[14]

This research had some limitations. Due to the small sample size, there was limited ability to identify factors associated with drug therapy problems. However, the enquiry was still able to contribute to the body of knowledge on DTPs among patients on anticoagulants.

## CONCLUSION

Drug therapy problems are common in patients taking anticoagulant therapy. Drug-drug interactions are a major DTP in patients taking anticoagulant therapy. Pharmacists and other healthcare practitioners should remain vigilant to identify and mitigate against occurrence of DTPs. Other factors among those studied may have contributed to the presence of DTPs, a follow up study with a larger sample size is recommended.

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