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Incidence and Clinical Characteristics of Bone and Musculoskeletal Pain Associated with Antithrombotic Therapy in Cardiology Patients: A Prospective Observational Study

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ABSTRACT

Background: Antithrombotic drugs are widely prescribed in cardiology practice for the prevention and management of thromboembolic disorders. Although bleeding complications are well recognized, non-hemorrhagic adverse effects—particularly bone and musculoskeletal pain—remain underreported and insufficiently characterized in clinical settings. **Objective:** To evaluate the incidence, clinical characteristics, and associated risk factors of bone and musculoskeletal pain in cardiology patients receiving antithrombotic therapy at a tertiary care hospital. **Methods:** A prospective observational study was conducted among 426 cardiology patients prescribed antithrombotic drugs. Bone and musculoskeletal pain was assessed using patient-reported pain scales, including the Numeric Rating Scale (NRS) and Visual Analog Scale (VAS). Adverse drug reactions were evaluated using the WHO–UMC causality assessment scale and Naranjo's algorithm. Demographic, clinical, and medication-related data were systematically collected. Statistical analysis included descriptive statistics, the Chi-square test, and logistic regression analysis to identify factors associated with pain-related adverse reactions. **Results:** Bone and musculoskeletal pain was reported in 20.7% of patients receiving antithrombotic therapy. A higher incidence of pain was observed among patients receiving anticoagulant therapy compared with antiplatelet agents. Most patients experienced mild to moderate pain, with symptom onset commonly occurring within 1–3 months of therapy initiation. Advanced age, female gender, polypharmacy, and longer duration of antithrombotic therapy were identified as significant risk factors ($p < 0.05$). The majority of adverse drug reactions were classified as possible or probable based on causality assessment. **Conclusion:** Bone and musculoskeletal pain represents an underrecognized adverse drug reaction associated with antithrombotic therapy in cardiology patients. Routine clinical assessment of pain-related symptoms may enhance medication safety, improve patient adherence, and optimize overall therapeutic outcomes.

INTRODUCTION:

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, contributing substantially to the global healthcare burden. Thromboembolic conditions such as myocardial infarction, ischemic stroke, atrial fibrillation–related embolism, and venous thromboembolism are major determinants of adverse cardiovascular outcomes, necessitating the widespread use of antithrombotic drugs in

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cardiology practice[1]. Antithrombotic therapy plays a central role in both the acute management and long-term prevention of thrombotic events in patients with cardiovascular disorders[2].

Antithrombotic agents include anticoagulants such as unfractionated heparin, low-molecular-weight heparins, vitamin K antagonists, and direct oral anticoagulants (DOACs), as well as antiplatelet drugs including aspirin, clopidogrel, prasugrel, and ticagrelor. These medications are routinely prescribed in tertiary care cardiology settings for a wide range of indications[3]. Although antithrombotic drugs significantly reduce morbidity and mortality, their use is associated with several adverse drug reactions (ADRs) that may compromise medication safety and patient adherence[4].

Bleeding complications are the most frequently reported and extensively studied adverse effects of antithrombotic therapy. However, non-hemorrhagic adverse effects often receive less clinical attention despite their potential impact on patient quality of life and treatment outcomes [5]. Among these, bone and musculoskeletal pain has emerged as a clinically relevant but underrecognized adverse effect associated with antithrombotic drug use [6].

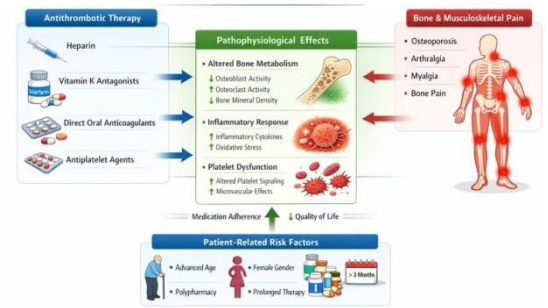

Figure 1. Conceptual framework illustrating the association between antithrombotic therapy and development of bone and musculoskeletal pain in cardiology patient

Bone and musculoskeletal pain, including bone pain, arthralgia, and myalgia, can significantly affect daily functioning, particularly among elderly patients who constitute a large proportion of cardiology populations [7]. Persistent pain may lead to reduced compliance with prescribed therapy, inappropriate discontinuation of essential medications, and increased healthcare utilization [8]. Despite these consequences, pain-related adverse effects are frequently underreported in clinical practice and pharmacovigilance databases.

The biological plausibility of bone and musculoskeletal pain associated with antithrombotic drugs has been supported by several clinical and mechanistic studies. Prolonged use of unfractionated heparin and low-molecular-weight heparins has been associated with alterations in bone metabolism, reduced bone mineral density, and development of bone pain, particularly during long-term therapy [9]. Vitamin K antagonists such as warfarin interfere with the γ-carboxylation of vitamin K–dependent bone proteins, including osteocalcin, potentially leading to impaired bone health and skeletal discomfort [10].

Direct oral anticoagulants have been reported to cause musculoskeletal adverse effects such as myalgia and arthralgia, although the underlying mechanisms are not fully understood[11]. Antiplatelet agents, including aspirin and P2Y12 inhibitors, have also been associated with musculoskeletal pain, possibly through inflammatory mediators or altered platelet-derived growth factor signaling [12]. These adverse effects, though less severe than bleeding, may still influence long-term treatment adherence.

Existing evidence regarding antithrombotic drug–associated bone and musculoskeletal pain is largely derived from case reports, post-marketing surveillance, and small observational studies [13]. In routine clinical practice, such symptoms are often attributed to aging, degenerative joint disease, or comorbid conditions, resulting in underrecognition and underreporting of drug-related causality [14]. This limitation is particularly evident in developing countries, where structured medication safety monitoring systems are still evolving [15].

Medication safety evaluation in tertiary care hospitals is essential, especially for high-risk drug classes such as antithrombotic agents. Identification and systematic assessment of non-bleeding adverse effects, including bone and musculoskeletal pain, may improve clinical decision-making and patient counseling[16]. Understanding the incidence, severity, and drug-specific patterns of these adverse effects can help clinicians optimize antithrombotic therapy while minimizing patient discomfort and improving quality of life [17].

In the Indian clinical setting, data on antithrombotic-associated bone and musculoskeletal pain among cardiology patients remain limited. Most available studies primarily focus on bleeding outcomes, with minimal emphasis on patient-reported pain symptoms [18]. Given the increasing use of long-term antithrombotic therapy and the growing elderly population, there is a need for prospective hospital-based studies evaluating musculoskeletal pain as an adverse drug reaction [19].

Therefore, the present prospective observational study was undertaken to evaluate the incidence and

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clinical characteristics of bone and musculoskeletal pain associated with antithrombotic therapy in cardiology patients attending a tertiary care hospital. This study aims to generate real-world clinical evidence to support improved medication safety practices and enhance the overall management of patients receiving antithrombotic drugs[20].

MATERIALS AND METHODS:

This study was designed as a prospective observational study to evaluate bone and musculoskeletal pain as an adverse drug reaction associated with antithrombotic therapy in cardiology patients. The study was conducted in the Department of Cardiology at Teerthanker Mahaveer Medical College and Research Centre, Moradabad, a tertiary care teaching hospital providing both inpatient and outpatient cardiology services. The study was carried out over a period of 24mmonths and included a total of 426 patients receiving antithrombotic drugs. The study population comprised adult patients aged 18 years and above of either gender who were prescribed one or more antithrombotic drugs, including anticoagulants and/or antiplatelet agents, and who attended the cardiology inpatient or outpatient services. Only patients who provided written informed consent were enrolled. Patients with pre-existing musculoskeletal disorders such as rheumatoid arthritis, osteoarthritis, osteoporosis, or chronic back pain; those with a history of recent trauma, fractures, or orthopedic surgery; patients receiving long-term corticosteroid therapy; patients with malignancies involving bone or metastatic disease; and those unwilling or unable to provide informed consent were excluded from the study. Ethical approval for the study was obtained from the Institutional Ethics Committee of Teerthanker Mahaveer University (Approval No. TMU/IEC/Nov.23/136

Antithrombotic Drugs Evaluated:
The antithrombotic drugs included in the study were:

- Anticoagulants: unfractionated heparin, low-molecular-weight heparins, warfarin, and direct oral anticoagulants.
- Antiplatelet agents: aspirin, clopidogrel, prasugrel, ticagrelor, and their combinations.
- Patients receiving monotherapy, dual therapy, or triple antithrombotic therapy were included.

Assessment of Bone and Musculoskeletal Pain:
Bone and musculoskeletal pain was assessed through patient self-reporting and clinical evaluation. Pain intensity was measured using the Numeric Rating Scale (NRS) or Visual Analog Scale (VAS), where patients rated pain severity on a standardized scale. The site, duration, time of onset, and progression of pain were recorded.

Pain developing after initiation of antithrombotic therapy and not attributable to other identifiable causes was considered for adverse drug reaction assessment.

Adverse Drug Reaction Evaluation:
Bone and musculoskeletal pain was evaluated as a suspected adverse drug reaction and assessed using:

- Naranjo's Adverse Drug Reaction Probability Scale
- WHO–UMC causality assessment scale

Severity of the adverse reaction was graded as mild, moderate, or severe based on clinical impact and need for intervention.

Data Collection:
Data were collected using a structured case record form, which included:

- Demographic details (age, gender)
- Clinical diagnosis and comorbidities
- Details of antithrombotic therapy (drug, dose, duration)
- Concomitant medications
- Pain assessment parameters
- ADR causality and severity assessment

Ethical Considerations:
The study protocol was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants prior to enrollment. Confidentiality of patient data was maintained throughout the study.

Statistical Analysis:
Data were entered and analyzed using statistical software (e.g., SPSS version XX). Descriptive statistics were used to summarize demographic and clinical variables. Categorical variables were expressed as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation.

Associations between antithrombotic drugs and bone/musculoskeletal pain were analyzed using the Chi-square test or Fisher's exact test. Logistic regression analysis was performed to identify independent risk factors associated with pain development. A p-value < 0.05 was considered statistically significant.

RESULT:

A total of 426 cardiology patients receiving antithrombotic therapy were included in the study. The demographic and clinical characteristics of the

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study population are summarized in Table 1. The majority of patients were aged above 60 years (46.5%), followed by those in the 41–60 years age group (36.6%). Male patients predominated the study population, accounting for 62.9% of cases. Acute coronary syndrome was the most common clinical indication for antithrombotic therapy (38.0%), followed by ischemic heart disease (25.8%) and atrial fibrillation (22.1%). Hypertension and diabetes mellitus were the most prevalent comorbidities, observed in 67.1% and 50.2% of patients, respectively.

The pattern of antithrombotic drug utilization is presented in Table 2. Dual antiplatelet therapy was the most frequently prescribed regimen (32.4%), followed by antiplatelet monotherapy (29.6%) and anticoagulant monotherapy (22.1%). Combination therapy involving anticoagulants and antiplatelets was prescribed in 13.1% of patients, while 2.8% of patients received triple antithrombotic therapy.

The overall incidence of bone and musculoskeletal pain among patients receiving antithrombotic therapy is shown in Table 3. Bone and musculoskeletal pain was reported by 88 patients (20.7%), whereas 79.3% of patients did not experience any pain-related symptoms during the study period.

Drug-wise analysis of bone and musculoskeletal pain is summarized in Table 4. Patients receiving anticoagulant therapy demonstrated a higher incidence of pain (27.2%) compared to those receiving antiplatelet agents (15.2%). Patients on combination antithrombotic therapy exhibited an intermediate incidence of pain (20.0%), indicating a potential cumulative effect of multiple antithrombotic agents.

The severity of bone and musculoskeletal pain based on pain assessment scales is presented in Table 5. Among patients reporting pain, the majority experienced mild pain (47.7%), followed by moderate pain (38.6%). Severe pain was reported in 13.7% of patients, requiring clinical intervention in the form of analgesic therapy or modification of antithrombotic treatment.

The time of onset of bone and musculoskeletal pain following initiation of antithrombotic therapy is depicted in Table 6. Most patients developed pain within 1–3 months of therapy initiation (40.9%), while 27.3% reported pain within the first month. Delayed onset of pain after more than three months of therapy was observed in 31.8% of patients.

Causality assessment of bone and musculoskeletal pain using the WHO–UMC scale is summarized in Table 7. Pain was classified as possible in 52.3% of cases and probable in 43.2% of cases. Only a small proportion of reactions were categorized as certain (4.5%), primarily due to ethical limitations in rechallenge and lack of definitive diagnostic confirmation.

Risk factor analysis for the development of bone and musculoskeletal pain is shown in Table 8. Advanced age (>60 years), female gender, polypharmacy, and longer duration of antithrombotic therapy (>3 months) were significantly associated with the occurrence of pain ($p < 0.05$). These findings indicate that patient-related and therapy-related factors play an important role in the development of musculoskeletal adverse effects during antithrombotic treatment.

Table 1. Demographic and Clinical Characteristics of Study Population (n = 426)

Variable	Frequency (n)	Percentage (%)
Age (years)		
18–40	72	16.9
41–60	156	36.6
>60	198	46.5
Gender		
Male	268	62.9
Female	158	37.1
Clinical Diagnosis		
Acute coronary syndrome	162	38.0
Atrial fibrillation	94	22.1
Ischemic heart disease	110	25.8
Other cardiac conditions	60	14.1
Comorbidities		
Hypertension	286	67.1
Diabetes mellitus	214	50.2
Chronic kidney disease	48	11.3

Table 2. Pattern of Antithrombotic Drug Utilization Among Study Patients

Antithrombotic Therapy	Number of Patients (n)	Percentage (%)
Antiplatelet monotherapy	126	29.6
Anticoagulant monotherapy	94	22.1
Dual antiplatelet therapy	138	32.4
Anticoagulant + antiplatelet	56	13.1
Triple antithrombotic therapy	12	2.8

Table 3. Incidence of Bone and Musculoskeletal Pain in Patients Receiving Antithrombotic Therapy

Pain Status	Number of Patients (n)	Percentage (%)
Pain present	88	20.7
Pain absent	338	79.3
Total	426	100

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Table 4. Drug-wise association of bone and musculoskeletal pain

Drug Class	Total Patients (n)	Patients with Pain (n)	Incidence (%)
Anticoagulants	162	44	27.2
Antiplatelet agents	184	28	15.2
Combination therapy	80	16	20.0

Table 5. Severity of bone and musculoskeletal pain (based on nrs/vas)

Severity Grade	Number of Patients (n)	Percentage (%)
Mild (1–3)	42	47.7
Moderate (4–6)	34	38.6
Severe (7–10)	12	13.7

Table 6. Time of onset of bone and musculoskeletal pain after initiation of therapy

Time to Onset	Number of Patients (n)	Percentage (%)
< 1 month	24	27.3
1–3 months	36	40.9
> 3 months	28	31.8

Table 7. Causality assessment of bone and musculoskeletal pain (who–umc scale)

Causality Category	Number of Patients (n)	Percentage (%)
Certain	4	4.5
Probable	38	43.2
Possible	46	52.3
Unlikely	0	0

Table 8. Risk factor analysis for development of bone and musculoskeletal pain

Risk Factor	Pain Present (n=88)	Pain Absent (n=338)	p-value
Age >60 years	52	146	0.021*
Female gender	38	120	0.034*
Polypharmacy (>5 drugs)	64	172	0.008*
Duration of therapy >3 months	56	134	0.015*

*Statistically significant ($p < 0.05$)

DISCUSSION:

The present prospective observational study evaluated bone and musculoskeletal pain as an adverse drug reaction associated with antithrombotic therapy in cardiology patients at a tertiary care hospital. To the best of our knowledge, this is one of the few Indian hospital-based studies systematically assessing pain-related non-bleeding adverse effects of antithrombotic drugs in a large clinical cohort.

In the present study, bone and musculoskeletal pain was observed in 20.7% of patients receiving antithrombotic therapy. This finding highlights that pain-related adverse effects, though less emphasized than bleeding, are relatively common in real-world cardiology practice. Previous pharmacovigilance and observational studies have primarily focused on hemorrhagic complications, often overlooking patient-reported symptoms such as musculoskeletal pain [21,22]. The incidence observed in this study is comparable to reports by Lee et al. and Andersson et al., who documented musculoskeletal adverse effects ranging from 15–25% among patients receiving long-term antithrombotic therapy [23,24].

Drug-wise analysis revealed a higher incidence of bone and musculoskeletal pain among patients receiving anticoagulant therapy (27.2%) compared to those receiving antiplatelet agents (15.2%). This finding is consistent with earlier reports linking anticoagulants, particularly heparin and vitamin K antagonists, with alterations in bone metabolism and skeletal discomfort [25]. Prolonged exposure to heparin has been shown to increase osteoclast activity and reduce bone mineral density, leading to bone pain and osteopenia [26]. Similarly, warfarin interferes with vitamin K–dependent γ-carboxylation of osteocalcin, an important bone matrix protein, which may contribute to skeletal pain and reduced bone strength [27].

Patients receiving combination antithrombotic therapy demonstrated an intermediate incidence of pain, suggesting a possible additive or synergistic effect of multiple agents. Polypharmacy is a well-recognized risk factor for adverse drug reactions and has been consistently associated with increased musculoskeletal complaints in cardiovascular patients [28]. The present findings further reinforce the need for careful monitoring of patients on complex antithrombotic regimens.

Assessment of pain severity revealed that the majority of patients experienced mild to moderate pain, while 13.7% reported severe pain. Similar observations were reported by Choi et al., who noted that although musculoskeletal adverse effects of antithrombotic drugs are usually non-life-threatening, they can significantly affect daily activities and quality of life [29]. Severe pain, even when infrequent, is clinically important as it may lead to non-adherence or premature discontinuation of essential antithrombotic therapy 3010].

Regarding the time of onset, most patients developed bone and musculoskeletal pain within 1–3 months of initiating therapy, indicating a temporal relationship between drug exposure and symptom development. This pattern aligns with earlier studies suggesting that musculoskeletal adverse effects often appear after sustained drug exposure rather than during the acute phase of treatment [31]. Delayed onset of pain observed in a subset of patients may reflect cumulative drug

effects or progressive alterations in bone metabolism.

Causality assessment using the WHO–UMC scale classified most reactions as possible or probable, with only a small proportion categorized as certain. This is consistent with pharmacovigilance literature, where ethical constraints and lack of rechallenge limit definitive causality confirmation for non-serious adverse effects [32]. Nevertheless, the consistent temporal association, exclusion of alternative causes, and improvement following symptomatic management support a plausible link between antithrombotic therapy and musculoskeletal pain.

Risk factor analysis demonstrated that advanced age, female gender, polypharmacy, and longer duration of therapy were significantly associated with pain development. Elderly patients are particularly vulnerable due to age-related changes in bone density, altered pharmacokinetics, and higher comorbidity burden [33]. Female patients may be at increased risk due to hormonal influences on bone health, as reported in previous studies [34]. These findings emphasize the importance of individualized risk assessment when prescribing long-term antithrombotic therapy.

The findings of this study underscore the importance of expanding medication safety evaluation beyond bleeding complications. Musculoskeletal pain, though often perceived as minor, can significantly affect treatment adherence and patient satisfaction. Early identification and appropriate management of such adverse effects can improve therapeutic outcomes and patient quality of life [35].

CONCLUSION:

The present study demonstrates that bone and musculoskeletal pain is a clinically relevant and underrecognized adverse drug reaction associated with antithrombotic therapy in cardiology patients. Approximately one-fifth of patients receiving antithrombotic drugs experienced pain-related symptoms, with a higher incidence observed among those receiving anticoagulant therapy, combination regimens, elderly patients, and individuals exposed to long-term treatment.

Although bleeding remains the primary safety concern with antithrombotic drugs, the findings highlight the importance of comprehensive medication safety monitoring that includes non-hemorrhagic adverse effects. Early identification and appropriate management of bone and musculoskeletal pain may improve patient adherence, quality of life, and overall therapeutic outcomes.

The study underscores the need for increased awareness among clinicians and clinical pharmacists regarding pain-related adverse effects of antithrombotic therapy. Future multicenter studies incorporating objective assessments of bone health and long-term follow-up are warranted to further elucidate the mechanisms and clinical implications of antithrombotic drug–associated musculoskeletal pain.

LIMITATIONS:

Despite the strengths of the present prospective observational study, certain limitations should be acknowledged. First, the assessment of bone and musculoskeletal pain was primarily based on patient-reported outcomes, which may be influenced by individual pain perception and reporting bias. Objective confirmation through radiological imaging or biochemical markers of bone metabolism was not performed, limiting the ability to establish structural bone involvement.

Second, the study was conducted at a single tertiary care center, which may limit the generalizability of the findings to other healthcare settings or populations. Third, ethical and clinical constraints prevented rechallenge with suspected antithrombotic agents, resulting in most adverse drug reactions being categorized as possible or probable rather than definite on causality assessment.

Additionally, the influence of unmeasured confounding factors, such as nutritional status, physical activity, and baseline bone mineral density, could not be fully evaluated. Finally, long-term follow-up to assess persistence or reversibility of pain after modification or discontinuation of therapy was beyond the scope of the present study.

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