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USE OF PRECISION MEDICINE IN ANTITHROMBOTIC THERAPY: BIOMARKERS AND BLEEDING RISK IN VASCULAR PATIENTS

Use Of Precision Medicine In Antithrombotic Therapy: Biomarkers And Bleeding Risk In Vascular Patients

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ABSTRACT

Objective: To analyze, through an integrative review, the scientific evidence on the use of precision medicine in antithrombotic therapy, with an emphasis on the role of biomarkers in the stratification of bleeding risk in vascular patients.Methods: This is an integrative literature review, conducted in the PubMed/MEDLINE, Embase, Scopus, and Web of Science databases, covering studies published between 2009 and 2025. Randomized clinical trials, biomarker substudies, observational studies, and relevant reviews addressing biomarkers associated with bleeding risk in patients undergoing antithrombotic therapy were included. The selection of studies followed predefined criteria, and the data were analyzed descriptively and critically.**Results:**Seventeen studies were included that demonstrated a consistent association between laboratory biomarkers and bleeding risk. Growth differentiation factor 15 (GDF-15) stood out as the most robust and independent biomarker for predicting major bleeding.Cardiac biomarkers, such as high-sensitivity troponin and NT-proBNP, as well as expanded proteomic panels, have also shown prognostic relevance. Biomarker-based models, such as the ABC-bleeding score, have demonstrated superior performance compared to traditional clinical scores in stratifying bleeding risk.**Conclusion:**The incorporation of biomarkers in the assessment of bleeding risk represents a significant advance in the personalization of antithrombotic therapy. Precision medicine emerges as a complementary approach to traditional clinical models, with the potential to optimize therapeutic safety and support individualized clinical decisions in vascular patients.

Keywords:biomarkers; oral anticoagulation; risk stratification; bleeding.

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INTRODUCTION

Antithrombotic therapy is one of the main pillars in the prevention of thromboembolic events in vascular patients, especially those with atrial fibrillation, venous thromboembolism, and other high-risk cardiovascular diseases. Randomized clinical trials have consistently demonstrated that the use of oral anticoagulants significantly reduces the incidence of stroke and systemic embolism when compared to no treatment or the use of antiplatelet agents alone [12–14]. However, this clinical benefit is accompanied by an inherent risk of bleeding, which remains one of the main limitations of antithrombotic therapy and a determining factor in clinical decision-making [1,15].

The assessment of hemorrhagic risk is traditionally based on clinical scores, such as HAS-BLED, ATRIA, and ORBIT, which are widely used in clinical practice. Although these instruments have contributed to the standardization of risk stratification, their predictive capacity is only moderate, with limited discrimination indices, and they mainly depend on static clinical variables and sometimes subjective [2,9]. This simplified approach does not contemplate adequately the biological heterogeneity of patients, nor captures underlying pathophysiological processes that directly influence the risk of bleeding.

In recent years, precision medicine has emerged as a new paradigm in antithrombotic therapy, proposing the personalization of treatment based on the integration of individual clinical, laboratory, and biological data [8]. Unlike traditional models, this approach recognizes bleeding risk as a multifactorial phenomenon, influenced by systemic inflammation, endothelial dysfunction, organ fragility, metabolic changes, and subclinical organ damage. In this context, circulating biomarkers have been widely investigated as tools capable of refining risk stratification and supporting safer therapeutic decisions.

Among the studied biomarkers, growth differentiation factor 15 (GDF-15) stands out as one of the most consistent predictors of major bleeding in anticoagulated patients. Evidence from substudies of the RE-LY trial demonstrated

independent association between elevated levels of GDF-15 and increased hemorrhagic risk, even after adjustment for traditional clinical scores [1, 11]. Results similar were observed in analyses derived from the ARISTOTLE and ENGAGE AFTIMI 48 trials, reinforcing the role of GDF-15 as a marker of systemic biological vulnerability [2,5, 14].

In addition to GDF-15, cardiac biomarkers such as high-sensitivity troponin and NT-proBNP have also been associated with bleeding risk in patients with atrial fibrillation on oral anticoagulation [4, 11]. These markers reflect subclinical myocardial damage and cardiovascular overload, suggesting that the hemorrhagic risk may be related to a global state of cardiovascular frailty, rather than solely to coagulation changes per se. More recent proteomic studies have further expanded this spectrum, identifying biomarkers inflammatory and related to vascular remodeling, such as suPAR and EphB4, independently associated with hemorrhagic outcomes [5, 16].

A incorporation these The incorporation of these biomarkers into predictive models resulted in the development of scores based on precision medicine, such as the ABC-bleeding score, which integrates age, biomarkers, and clinical history. Derivation and validation studies demonstrated superior performance of this score compared to purely clinical models, with better discrimination and reclassification of the risk of major bleeding [2,3,6]. These findings suggest that biomarker-based strategies may represent a significant advancement in the personalization of antithrombotic therapy.

In light of this scenario, the need for an integrative synthesis of the available evidence on the use of precision medicine in antithrombotic therapy becomes evident, with an emphasis on the role of biomarkers in bleeding risk stratification. Thus, the objective of this integrative review is to critically analyze the studies that investigated biomarkers associated with hemorrhagic risk in vascular patients undergoing antithrombotic therapy, discussing their clinical implications, current limitations, and future perspectives for practice based on precision medicine.

METHODOLOGY

This is an integrative literature review, a method that allows for a comprehensive synthesis of scientific evidence from different methodological designs methodological,

enabling critical and integrated analysis of primary and secondary studies on a specific health phenomenon [7,9]. This type of review is particularly appropriate for complex and emerging topics, such as the application of precision medicine in antithrombotic therapy, where clinical evidence coexists,

laboratory and conceptual.

Search Strategy

The bibliographic search was conducted systematically and structured in the databases PubMed/MEDLINE, Embase, Scopus, and Web of Science, considered widely recognized sources for biomedical and cardiovascular literature. The search strategy combined controlled descriptors and free terms, adapted to each database, using the following main terms and their equivalents:

- *"precision medicine"*
- *"antithrombotic therapy"*
- *"oral anticoagulants"*
- *"biomarkers"*
- *"bleeding risk"*
- *"atrialfibrillation"*
- *"vascular patients"*

The boolean operators AND and OR were used to enhance the sensitivity and specificity of the search. An example of a strategy applied in PubMed was:

("precision medicine" OR "personalized medicine") AND ("antithrombotic therapy" OR anticoagulant*) AND (biomarker* OR "GDF-15" OR troponin OR "NT-proBNP") AND ("bleeding risk" OR hemorrhage)

The search included studies published between 2009 and 2025, a period corresponding to the consolidation of the use of direct oral anticoagulants and the advancement of research involving biomarkers applied to bleeding risk stratification.

Inclusion Criteria

Studies that met the following criteria were included in the review:

1. Original studies (randomized clinical trials, sub-studies of clinical trials, prospective or retrospective cohorts, and analytical observational studies) and reviews

relevant narratives or integrative approaches to the theme;

2. Population composed of vascular patients, especially with atrial fibrillation or using antithrombotic therapy;

3. Evaluation of laboratory biomarkers or biomarker panels associated with bleeding risk;

4. Outcomes related to major bleeding, clinically relevant bleeding, or hemorrhagic events defined by standardized criteria (ISTH, TIMI, or similar);

5. Articles published in indexed and peer-reviewed scientific journals, in English or Portuguese.

Exclusion Criteria

Were excluded:

- Experimental studies exclusively preclinical or in animal models;
- Case reports, isolated case series, and editorials;
- Studies addressing antithrombotic therapy without biomarker assessment or bleeding risk analysis;
- Duplicate publications or those with overlapping data, with only the most complete or recent version retained.

Study Selection Process

The selection of studies occurred in three stages. Initially, titles and abstracts were read to identify relevance to the topic. Next, the full texts of potentially eligible articles were independently evaluated against the inclusion and exclusion criteria. Finally, the selected studies formed the final basis of the integrative review, totaling 17 articles, deemed relevant and methodologically appropriate to address the proposed objective [1–17].

Data Extraction and Analysis

Data extraction was carried out systematically, encompassing the following information: authors, year of publication, type of study, investigated population, evaluated biomarkers, analyzed hemorrhagic outcomes, and main results. The findings were organized descriptively and comparatively, allowing for the identification of convergences, divergences, and gaps in the literature.

Synthesis of Results

The results were analyzed through narrative and critical synthesis, characteristic of the integrative review, without the application of statistical meta-analysis techniques. This approach allowed for the integration of different levels of evidence and the discussion of findings in light of the precision medicine paradigm, considering its clinical implications, methodological limitations, and future perspectives [8,9].

RESULTS

The search and selection of studies resulted in the inclusion of 17 scientific articles, published between 2009 and 2025, that addressed the application of precision medicine in antithrombotic therapy, with an emphasis on the use of biomarkers for bleeding risk stratification in vascular patients. The included studies presented different methodological designs methodological,
covering clinical trials
randomized, biomarker substudies from large trials, observational studies, proteomic analyses, and integrative reviews, reflecting the complexity and multidimensional nature of the investigated topic.

In general, it was observed that most studies focused on patients with atrial fibrillation using oral anticoagulation, especially direct oral anticoagulants and vitamin K antagonists [1–6, 12–14]. The most frequently evaluated bleeding outcomes were major bleeding, clinically relevant non-major bleeding, and intracranial bleeding, usually defined according to standardized criteria, such as those of the *International Society on Thrombosis and Haemostasis*.

Regarding biomarkers, GDF-15 was the marker most consistently associated with the risk of major bleeding, being identified as an independent predictor in multiple studies and substudies derived from large clinical trials [1–3,5,11]. Cardiac biomarkers, such as high-sensitivity troponin and NTproBNP, also demonstrated a significant association with bleeding events, suggesting that the risk of bleeding is related to an overall state of cardiovascular fragility [4,11]. Furthermore, more recent studies explored expanded proteomic panels, identifying inflammatory and vascular remodeling biomarkers, such as suPAR and
vascular remodeling, such as suPAR and

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EphB4 as potential emerging markers of hemorrhagic risk [5, 16].

Table 1 summarizes the main characteristics of the included studies, highlighting the type of study, the evaluated population, the investigated biomarkers, and the main findings related to bleeding risk

Table 1 – Characteristics of the studies included in the integrative review on biomarkers and bleeding risk in antithrombotic therapy

Author/ Year	Type of study	Population	Evaluated biomarkers	Main findings
Hijazi et al., 2016 [1]	ECR sub-study	AF in anticoagulation	GDF-15	Independent association with major bleeding
Hijazi et al., 2016 [2]	Score derivation/ validation	AF in OAC	GDF-15, troponin, hemoglobin	ABC score superior to HAS-BLED
Pol et al., 2023 [3]	Combined analysis of RCTs	AF in OAC	GDF-15, hs-cTnT	Robust validation of ABC-bleeding
Hijazi et al., 2014 [4]	Sub-study biomarker	AF in OAC	Hs Troponin	Association with adverse events and bleeding
Siegbahn et al., 2021 [5]	Observational study	AF (ARISTOTLE/ RE LY)	Proteomic panel	Multiple biomarkers associated with bleeding
Oldgren et al., 2020 [6]	External validation	FA in OAC	ABC biomarkers	Predictive stability of the score
Berg et al., 2022 [16]	Observational study	FA in anticoagulation	Biomarkers emerging	Identification of new hemorrhagic predictors
Shaw et al., 2022 [17]	Technical review	Anticoagulated patients	Generation of thrombin	Complementary potential in stratification

AF: atrialfibrillation; RCT: randomized clinical trial; OAC: oral anticoagulation.

In addition to the primary studies, the included narrative and integrative reviews contributed to the contextualization of the findings, reinforcing the limitations of traditional clinical scores and highlighting the increasing relevance of incorporating biomarkers into clinical practice [7–10].

DISCUSSION

The findings of this integrative review demonstrate that the risk stratification of bleeding in patients undergoing antithrombotic therapy is undergoing a paradigmatic transition, shifting from models

that are exclusively clinical to approaches based on precision medicine. The analyzed studies consistently demonstrate that laboratory biomarkers provide relevant additional prognostic information, capable of enhancing the individual assessment of bleeding risk in heterogeneous vascular populations [1–6].

Among the evaluated biomarkers, GDF-15 stood out as the most consistent predictor of major bleeding. Substudies derived from large trials

Consistently, the results indicate that precision medicine-based strategies have greater potential to individualize antithrombotic therapy, reducing bleeding events without compromising antithrombotic efficacy.

Clinical studies, such as RE-LY, ARISTOTLE, and ENGAGE AF-TIMI 48, have demonstrated that elevated levels of this marker are associated with a significant increase in hemorrhagic risk, regardless of traditional clinical scores [1–3, 11]. These findings suggest that GDF-15 reflects a state of systemic biological fragility, possibly related to chronic inflammatory processes, cellular aging, and subclinical organ dysfunction, factors that are not adequately captured by models based solely on clinical characteristics.

The superiority of biomarker-based models was particularly evident in studies that evaluated the ABC-bleeding score. The incorporation of age, clinical history, and biomarkers such as GDF-15, high-sensitivity troponin, and hemoglobin resulted in better predictive performance when

compared to widely used scores, such as HAS-BLED and ORBIT [2,3,6]. These results indicate that the integration of objective and biologically relevant variables can reduce the subjectivity and prognostic limitation inherent in traditional models, contributing to safer and more individualized therapeutic decisions.

In addition to GDF-15, cardiac biomarkers such as high-sensitivity troponin and NT-proBNP have also been shown to be associated with bleeding risk. [4,11]. Although traditionally used for cardiovascular risk assessment, these markers appear to reflect a global state of cardiovascular vulnerability, in which bleeding arises as a manifestation of systemic frailty. This observation broadens the understanding of hemorrhagic risk, suggesting that it should not be interpreted exclusively as a direct consequence of the intensity of anticoagulation, but as a result of the interaction between therapy, clinical condition, and the patient's physiological reserve.

More recent studies that explored expanded proteomic panels identified emerging biomarkers, such as suPAR and EphB4, independently associated with Hemorrhagic outcomes [5,16]. These findings point to the possibility of future multimarker strategies capable of capturing different pathophysiological axes involved in bleeding, including inflammation, vascular remodeling, and endothelial dysfunction. However, the clinical applicability of these biomarkers still depends on further validation and methodological standardization.

Despite the observed advances, the analyzed literature also highlights relevant limitations. Most studies focus on patients with atrial fibrillation, which restricts the generalization of results to other vascular populations, such as those with venous thromboembolism or those on prolonged combined antiplatelet therapy [7,9]. Furthermore, many evaluated biomarkers are still not widely available in routine clinical practice, which may limit their immediate incorporation in lower complexity care scenarios.

Another important aspect refers to the economic and operational impact of adopting precision medicine. Although economic evaluation studies suggest that the incorporation of biomarkers may be cost-effective by reducing events

Hemorrhagic events and associated hospitalizations [10], the implementation of these models requires adequate laboratory infrastructure, professional training, and integration with clinical decision support systems. These factors must be considered in the transition from scientific knowledge to clinical practice.

Finally, the results of this review reinforce that precision medicine in antithrombotic therapy should not be understood as a substitute for traditional clinical scores, but as a complementary strategy capable of refining risk stratification and supporting more individualized decisions. The integration of biomarkers, functional tests, and clinical data represents an important step towards a safer and more effective approach to anticoagulation, especially in patients with high hemorrhagic risk or complex clinical profiles [8,9].

CONCLUSION

This integrative review demonstrated that the application of precision medicine in antithrombotic therapy represents a significant advance in the stratification of bleeding risk in patients with vascular conditions. The studies analyzed consistently show that laboratory biomarkers provide additional prognostic information to traditional clinical scores, allowing for a more individualized and biologically grounded assessment of hemorrhagic risk.

Among the biomarkers investigated, GDF-15 stood out as the most robust and consistent predictor of major bleeding, regardless of classic clinical variables. Cardiac biomarkers, such as high-sensitivity troponin and NT-proBNP, as well as expanded proteomic panels, also showed significant association with hemorrhagic events, reinforcing the notion that the risk of bleeding reflects a global state of biological and cardiovascular frailty. The incorporation of these markers into predictive models, such as the ABC-bleeding score, resulted in superior performance in risk stratification compared to purely clinical scores.

Despite the observed advances, significant challenges remain for the widespread implementation of precision medicine in clinical practice. The concentration of evidence in

specific populations, primarily patients with atrial fibrillation, the need for external validation of emerging biomarkers and the limitations related to the availability, standardization, and cost of laboratory analyses. Furthermore, the integration of this data into routine clinical workflows requires adequate infrastructure and decision support strategies.

In summary, the findings of this review reinforce that precision medicine should be understood as a complementary approach to traditional models of assessing bleeding risk, with the potential to enhance the safety and efficacy of antithrombotic therapy. The rational use of biomarkers can contribute to more individualized therapeutic decisions, reducing adverse events and promoting care that is more aligned with the biological characteristics of each patient. Future studies are needed to expand the applicability of these models to other vascular populations and to consolidate their incorporation into evidence-based clinical practice.

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