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ACENOCOUMAROL – A HISTORICAL OVERVIEW AND ITS PLACE IN MODERN ANTICOAGULANT THERAPY

D. Farandzha

Department of Cardiology, University Hospital St. Anna – Sofia, Bulgaria

АЦЕНОКУМАРОЛ – ИСТОРИЧЕСКИ ПРЕГЛЕД И МЯСТОТО МУ В СЪВРЕМЕННАТА АНТИКОАГУЛАНТНА ТЕРАПИЯ

Д. Фърнджъ

Клиника по кардиология, УМБАЛ „Св. Анна“ – София

Abstract.

Acenocoumarol, a vitamin K antagonist (VKA), has played a pivotal role in anticoagulant therapy for over 60 years. Derived from the coumarin family, acenocoumarol inhibits vitamin K epoxide reductase, disrupting the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and effectively preventing thromboembolic events. Compared to warfarin, acenocoumarol offers a rapid onset and shorter half-life, providing clinicians greater therapeutic flexibility. Despite advances and widespread adoption of direct oral anticoagulants (DOACs), acenocoumarol continues to hold clinical significance, particularly in Europe, Latin America, and Asia, owing to extensive clinical experience, reversibility, and cost-effectiveness. However, its use necessitates regular monitoring of international normalized ratio (INR), with individualized dosage adjustments required due to genetic variability (CYP2C9, VKORC1 polymorphisms), drug-drug interactions, dietary influences, and special considerations in the elderly and patients with chronic kidney disease (CKD). Recent clinical trials have expanded our understanding of its efficacy, safety, and optimal use. Precision dosing strategies, including genotype guidance and advanced INR monitoring based on body-surface area-adjusted estimated glomerular filtration rate (BSA-adjusted eGFR) dosing, promise enhanced safety and personalized treatment. Although DOACs are now widely adopted due to their predictable pharmacokinetics and lack of routine monitoring requirements, acenocoumarol remains indispensable in well-defined clinical scenarios such as in patients with mechanical heart valves, rheumatic mitral stenosis-associated atrial fibrillation, antiphospholipid syndrome, and other conditions in which individualized dose adjustment offers a therapeutic advantage.

Key words:

acenocoumarol; VKA; INR; DOAC; mechanical heart valves; rheumatic mitral stenosis

Address

for correspondence:

Dzhem Farandzha, MD, Department of Cardiology, University Hospital St. Anna, 1 Dimitar Mollov St., 1750 Sofia, Bulgaria, tel.: +359 886 156 014, e-mail: cemf@abv.bg, ORCID ID: 0000-0003-2011-354X

Резюме.

Аценокумаролът е витамин К-антагонист (ВКА) с ключова роля в антикоагулантната терапия в продължение на повече от 60 години. Произхождащ от семейството на кумарините, аценокумаролът инхибира витамин К-епоксид редуктазата, нарушавайки синтеза на витамин К-зависимите фактори на кръвосъсирването (II, VII, IX, X) и по този начин предотвратява тромбоемболични събития. В сравнение с варфарин, аценокумаролът е с по-бързо начало на действие и по-кратък полуживот, което предлага по-голяма терапевтична гъвкавост. Въпреки напредъка и широкото разпространение на директните перорални антикоагуланти (ДОАК), аценокумаролът продължава да има клинично значение, особено в Европа, Латинска Америка и Азия, благодарение на богатия клиничен опит, обратимостта и значително по-ниската цена. Употребата му обаче изисква редовно наблюдение на международното нормализирано съотношение (INR), като се изисква индивидуализирано коригиране на дозата поради генетични полиморфизми (CYP2C9, VKORC1), лекарствени и хранителни взаимодействия, както и специални съображения при възрастни хора и пациенти с хронично бъбречно заболяване (ХБЗ). Последните клинични проучвания разшириха разбирането за неговата ефикасност, безопасност и оптимална употреба. Стратегиите за прецизно дозиране, вкл. гено

типизиране и усъвършенствано наблюдение на INR, базирано на дозиране спрямо телесната повърхност и оценената скорост на гломерулна филтрация (BSA-adjusted eGFR), обещава повишена безопасност и персонализирано лечение. Въпреки че ДОАК вече са широко възприети поради предвидимата им фармакокинетика и липсата на изисквания за рутинно мониториране, аценокумаролът остава незаменим в добре дефинирани клинични сценарии, като например при пациенти с механични сърдечни клапи, предсърдно мъждене, свързано с ревматична митрална стеноза, антифосфолипиден синдром и други състояния, при които индивидуалното коригиране на дозата предлага терапевтично предимство.

Ключови думи:

аценокумарол; витамин К-антагонист; международното нормализирано съотношение; директни перорални антикоагуланти; механични сърдечни клапи; ревматична митрална стеноза

Адрес**за кореспонденция:**

д-р Джем Фърънджъ, Клиника по кардиология, УМБАЛ „Св. Анна“, ул. „Димитър Моллов“ 1, 1750 София, тел.: +359 886 156 014, e-mail: cemf@abv.bg, ORCID ID: 0000-0003-2011-354X

INTRODUCTION

Acenocoumarol, a prominent vitamin K antagonist (VKA), has been pivotal in anticoagulant therapy for several decades. First synthesized in the early 1950s, acenocoumarol emerged as part of the coumarin class of anticoagulants, sharing its mechanism of action with the widely known warfarin [1, 2]. Its primary role involves the inhibition of vitamin K epoxide reductase (VKOR), a critical enzyme required for the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X [3]. The resultant anticoagulant effect significantly reduces the risk of venous and arterial thromboembolic events, conditions responsible for substantial morbidity and mortality globally.

Historically, the anticoagulant effects of coumarins were serendipitously discovered following an outbreak of hemorrhagic disease among cattle consuming spoiled sweet clover [1]. Subsequently identified as dicoumarol, its clinical application in human medicine soon expanded, setting the foundation for related derivatives such as acenocoumarol [2, 4]. Acenocoumarol distinguished itself by offering a rapid onset and shorter half-life compared to warfarin, allowing clinicians greater flexibility in managing anticoagulation therapy [5].

Despite the introduction and growing popularity of direct oral anticoagulants (DOACs), acenocoumarol continues to maintain a significant clinical presence, particularly in regions such as Europe, Latin America, and parts of Asia. Its enduring usage is attributed to factors such as its easily reversible anticoagulation profile, established dosing protocols, and extensive clinical experience supported by decades of rigorous trials.

However, the use of acenocoumarol is not without challenges. It necessitates meticulous monitoring of the international normalized ratio (INR) to ensure therapeutic efficacy and mitigate bleeding risks. Furthermore, variations in patient response due to genetic polymorphisms (e.g., CYP2C9 and VKORC1), interactions with diet and medications, and adjustments required in specific patient populations such as the elderly and patients with chronic kidney disease (CKD),

underline the importance of tailored treatment strategies [6, 7, 8].

This review systematically examines the historical evolution, pharmacological properties, clinical applications, and comparative efficacy and safety of acenocoumarol. By integrating evidence from landmark trials such as RE-LY, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48, but also the results from such trials as REALIGN, FRAIL-AF, and INVICTUS, the article critically appraises the contemporary relevance of acenocoumarol within the dynamic landscape of anticoagulant therapy [9-15].

PHARMACOLOGICAL PROPERTIES OF ACENOCOUMAROL

Acenocoumarol, chemically related to other coumarin derivatives, exerts its anticoagulant action by competitively inhibiting vitamin K epoxide reductase (VKOR). This enzyme is vital for recycling vitamin K to its active form, necessary for carboxylation of glutamic acid residues on factors II, VII, IX, and X, and proteins C and S. By preventing the carboxylation process, acenocoumarol reduces the activity of these clotting factors, thereby prolonging clotting times. In the first days after starting therapy, the risk of prothrombotic events is increased due to the shorter half-lives of anticoagulant proteins C and S as compared to procoagulant factors II, VII, IX and X [3]. Thus, usually anticoagulation with low-molecular-weight heparins (LMWH) is used in the first two or three days of starting acenocoumarol.

Pharmacokinetically, acenocoumarol is characterized by rapid oral absorption, typically reaching peak plasma concentrations within 1-3 hours post-administration. Its shorter half-life, approximately 8-11 hours, facilitates rapid onset and offset of anticoagulant effects, distinguishing it from warfarin and phenprocoumon, which have longer half-lives [5]. This property provides clinicians flexibility in managing therapeutic anticoagulation, especially in scenarios requiring temporary discontinuation or adjustments.

Metabolism of acenocoumarol primarily involves hepatic enzymes, predominantly CYP2C9, leading to considerable variability in patient response. Genetic polymorphisms in the CYP2C9 and VKORC1 genes significantly influence dosing requirements and drug response. Patients carrying specific polymorphisms may require reduced dosages to achieve therapeutic INR levels, accentuating the necessity for individualized dosing strategies based on genetic profiling [6, 7].

The pharmacodynamics of acenocoumarol also include interactions with dietary vitamin K and various medications, which can significantly impact anticoagulant efficacy. Regular monitoring of INR levels and careful dose adjustments are crucial to maintaining optimal anticoagulant control and minimizing complications such as bleeding or thrombotic events.

CLINICAL INDICATIONS AND COMPARATIVE EFFECTIVENESS

VKAs, including acenocoumarol and warfarin, have established roles in preventing and treating thromboembolic disorders. However, the introduction of DOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban has significantly reshaped clinical practice in recent years, prompting detailed comparative analyses in various clinical indications (see Table 1).

Venous Thromboembolism (VTE)

For acute VTE, randomized controlled trials have compared DOACs directly against warfarin. The RE-COVER trial demonstrated dabigatran's non-inferiority to warfarin, with similar effectiveness and safety but fewer interactions and less monitoring [16]. EINSTEIN-PE and EINSTEIN-DVT trials similarly reported non-inferiority of rivaroxaban compared to warfarin, highlighting simplified administration due to fixed dosing without routine monitoring [17, 18]. Apixaban, investigated in the AMPLIFY trial, and edoxaban in the Hokusai-VTE trial also showed comparable efficacy, with apixaban notably associated with significantly reduced bleeding risks [19, 20]. Collectively, these studies position DOACs favorably in treating VTE, primarily due to convenience, safety, and predictable pharmacokinetics.

Non-valvular Atrial Fibrillation (AF)

In non-valvular AF, pivotal randomized trials consistently favor DOACs over VKAs regarding patient convenience and bleeding profiles. The RE-LY trial indicated dabigatran significantly reduces stroke risk and intracranial hemorrhage compared to warfarin, albeit with similar overall bleeding rates.[9] Similarly, ROCKET-AF (rivaroxaban), ARISTOTLE (apixaban), and ENGAGE AF-TIMI 48 (edoxaban) trials each demonstrated at

least non-inferiority in stroke prevention compared to warfarin, generally showing improved safety profiles, particularly reduced intracranial bleeding [10-12].

Mechanical Valves, Valvular AF, LVADs, LV Thrombi, and Antiphospholipid Syndrome

Certain clinical scenarios strongly favor continued VKA use over DOACs. The RE-ALIGN trial, investigating dabigatran in mechanical heart valves, demonstrated significantly higher thromboembolic and bleeding complications with DOAC use, resulting in DOAC contraindication in this setting [13]. Similarly, in patients with left ventricular assist devices (LVADs), VKAs significantly outperformed dabigatran, evidenced by increased thromboembolic events in patients randomized to dabigatran, underscoring the ongoing necessity for VKA therapy [21].

Additionally, DOAC use in left ventricular thrombus management remains controversial despite increasing off-label prescriptions. Some analyses report similar efficacy between DOACs and VKAs, while others note a higher incidence of persistent or recurrent thrombi with DOAC therapy [22-25]. Although the European Society of Cardiology (ESC) guidelines do not dismiss their use in LV thrombosis, these findings question the equivalence of DOACs to VKAs and emphasize the need for prospective randomized trials [26]. Until such data are published, VKAs remain the therapy with the best-established efficacy and safety in the treatment of left ventricular thrombosis.

In patients with antiphospholipid syndrome, randomized controlled trials, notably the TRAPS trial and subsequent meta-analyses, have demobest-established thromboembolic events with DOACs compared to VKAs [27, 28]. Consequently, VKAs remain the definitive choice for preventing thrombotic recurrence in antiphospholipid syndrome.

For valvular AF, especially rheumatic mitral stenosis-associated AF, trials like INVICTUS (Rivaroxaban in Rheumatic Heart Disease–Associated Atrial Fibrillation) have failed to establish DOAC superiority or equivalence, reinforcing VKAs as the primary therapeutic strategy [15]. Reflecting these findings, the 2025 ESC Guidelines for the Management of Valvular Heart Disease explicitly recommend against the use of DOACs in patients with AF and rheumatic mitral stenosis with a mitral valve area (MVA) ≤ 2.0 cm² [29]. This recommendation carries a level of evidence B grading, representing a stronger level of recommendation and higher evidence quality compared with the previous ESC guidelines on valvular heart disease, which limited the restriction to patients with moderate to severe mitral stenosis and assigned a level of evidence C [30]. Consequently, in patients with rheumatic heart disease–associated AF, VKAs such as acenocoumar-

ol remain the only evidence-based and guideline-endorsed oral anticoagulant therapy, underscoring their indispensable role in the management of this specific clinical population.

Special Populations and Frailty

The recent FRAIL-AF study specifically examined anticoagulation management in older, frail patients, highlighting the nuanced challenges in balancing thromboembolic prevention and bleeding risks. Switching from INR-controlled VKA therapy to a DOAC in this trial was associated with a higher risk of bleeding without a corresponding reduction in thromboembolic events [14].

Table 1. Preferred class of oral anticoagulants in different indications

Indication	Preferred agent
VTE (DVT, PE)	DOAC
Non-valvular AF	DOAC
Valvular AF	VKA
MHV	VKA
LVAD	VKA
LV thrombus	VKA or DOAC
APS	VKA
AF or VTE in ESRD	VKA

VTE – venous thromboembolism; DVT – deep vein thrombosis; PE – pulmonary embolism; AF – atrial fibrillation; MVH – mechanical heart valve; LVAD – left ventricular assist device; LV – left ventricular; APS – anti-phospholipid syndrome; ESRD – end-stage renal disease

DOSAGE MANAGEMENT AND REVERSAL AGENTS

Effective anticoagulation with acenocoumarol demands precise dosage adjustments tailored to individual patient characteristics. Initial dosing often involves empirical strategies, typically starting with a loading dose followed by titration based on INR responses. Standardized protocols frequently recommend initial dosages of 6 to 8 mg on the first day, 4 mg on the second day, and subsequent adjustments based on initial INR measurements or personal experience [31].

Maintenance dosing relies significantly on patient age, renal and hepatic function, genetic factors, and concurrent medications or diet. Elderly patients typically require lower dosages due to decreased elimination and altered pharmacodynamics [8]. Genetic testing for CYP2C9 and VKORC1 polymorphisms further assists personalized dosing strategies, minimizing risks of both subtherapeutic anticoagulation and bleeding.

Regular INR monitoring is critical in managing therapy, typically aiming for therapeutic INR ranges of 2.0-

3.0 or 2.5-3.5 for specific indications like mechanical valves [29, 32]. Management includes patient education on dietary consistency, recognition of drug interactions, and adherence to prescribed regimens. Clinical support tools such as anticoagulation clinics and computerized dosing systems may significantly enhance patient outcomes, reducing thromboembolic and hemorrhagic complications [6, 8]. One of the most widely used measures of anticoagulation quality in VKA therapy is the time in therapeutic range (TTR), which reflects the percentage of time a patient's INR remains within the prescribed target interval. The Rosendaal linear interpolation method estimates INR values between measurements to provide a more continuous assessment of control [33]. Studies have demonstrated that TTR < 65% is independently associated with significantly higher rates of thromboembolic and hemorrhagic complications, making TTR a powerful predictor of clinical outcomes [34]. Incorporating TTR assessment into routine clinical practice enhances therapeutic oversight and provides a quantitative benchmark for evaluating and improving anticoagulation quality [35].

An important aspect of acenocoumarol management is also the ability to rapidly reverse its anticoagulant effect when clinically indicated, such as in cases of major bleeding or urgent surgical intervention. The most widely used and effective reversal agent is vitamin K (phytonadione), which restores hepatic synthesis of vitamin K-dependent clotting factors [31]. It is inexpensive and is available both in oral and parenteral forms [3]. However, it may require 12 to 36 hours to take full effect. In emergent situations requiring immediate correction, prothrombin complex concentrate (PCC) or, if unavailable, fresh frozen plasma (FFP) can be administered to provide rapid replenishment of coagulation factors [36]. This capacity for swift and predictable reversibility represents a major clinical advantage of VKAs, particularly in settings where bleeding risk must be carefully balanced against thrombosis prevention.

By contrast, reversal options for DOACs are mostly agent-specific and often limited by availability and cost. Idarucizumab is used for dabigatran reversal, while andexanet alfa can neutralize the activity of factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) [3]. However, these agents are expensive, not universally available, and associated with variable reversal kinetics.

MODERN ROLE AND FUTURE DIRECTIONS

Despite its efficacy and extensive clinical use, acenocoumarol poses several challenges in clinical practice. Its narrow therapeutic window necessitates rigorous INR monitoring, increasing the logistical burden on patients and healthcare providers. The vari-

ability in dose-response due to genetic polymorphisms further complicates patient management, necessitating personalized approaches to optimize therapeutic outcomes.

Additionally, interactions with diet, particularly vitamin K-rich foods, and numerous medications require continuous patient education and adjustments in dosing. Elderly patients and those with CKD, in particular, often face heightened risks due to altered pharmacokinetics and pharmacodynamics, underscoring the importance of vigilant clinical oversight [6-8].

In the modern therapeutic landscape dominated by DOACs, the role of acenocoumarol is likely to benefit from continued progress in individualized anticoagulation strategies. Although more than two thirds of all patients requiring long-term anticoagulation do so for conditions such as atrial fibrillation and venous thromboembolism, clinical scenarios in which DOACs are now widely recommended, there remains a substantial patient population for whom VKAs continue to be necessary or advantageous [37, 38]. In recent years, the management of VKA therapy has been enhanced by the increasing availability of dosing calculators and clinical decision tools, some incorporating pharmacogenetic data (e.g., CYP2C9 and VKORC1 polymorphisms) and others relying on hepatic and renal function, age, body weight, and early INR response. These tools have shown promise in guiding initial dosing, helping patients reach the therapeutic range more rapidly, and maintaining stable anticoagulation for longer periods, addressing what has historically been regarded as a limitation of VKAs [5-7, 39].

Beyond the specific clinical scenarios where VKAs have demonstrated superior outcomes compared with DOACs, one of the most clinically meaningful advantages of acenocoumarol lies in its adjustability. Unlike DOACs, which rely on fixed-dose regimens, acenocoumarol allows clinicians to tailor the degree of anticoagulation to the individual patient and to adjust therapy in response to changes in clinical conditions, drug interactions, procedures, or bleeding/thrombotic risk. For many physicians, the idea that anticoagulation intensity can be modified according to patient-specific needs relates more closely to the principles of personalized medicine than the “one size fits all” model inherent to DOAC therapy.

CONCLUSIONS

The expanding use of direct oral anticoagulants has reshaped the anticoagulation landscape, offering simplified dosing and reduced monitoring needs. However, VKAs, including acenocoumarol, retain an essential role in several well-defined indications, such as mechanical heart valves, rheumatic mitral steno-

sis-associated atrial fibrillation, left ventricular assist devices, antiphospholipid syndrome, and certain cases of left ventricular thrombus. In these settings, available evidence and guideline recommendations continue to support VKA therapy as the preferred approach. Developments such as improved INR self-monitoring technologies, digital health tools, and structured dosing algorithms may enhance safety, reduce variability, and support long-term adherence. As anticoagulation therapy continues to evolve, acenocoumarol is expected to maintain a meaningful place in clinical practice, particularly in settings where individualized degree of anticoagulation, cost considerations, and established therapeutic protocols remain important.

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