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Toward precision antithrombotic management

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A Viewpoint on the Frontiers in Science Lead Article
Precision cardiovascular medicine: shifting the innovation paradigm

Key points

- The transition toward precision cardiovascular medicine includes improved antithrombotic management.
- With an expanding array of antithrombotic drugs, selecting the right drug for the individual patients becomes imperative.
- Comprehensive phenotyping of patients' thrombosis and bleeding risk profiles is necessary.

In their lead article "Precision cardiovascular medicine: shifting the innovation paradigm," Aikawa et al. address a timely and highly relevant topic (1). The article delivers several key messages. On one hand, it summarizes recent technological advances—most notably, the revolution in artificial intelligence (AI)—that now enable large-scale characterization of heterogeneous diseases and patient populations. On the other hand, it paves the way for concerted efforts that could ultimately translate these technological advances into personalized cardiovascular medicine.

A crucial next step is to foster collaboration. Given the complexity and specialization of the required technical skills, successful translation to clinical practice demands close cooperation among all stakeholders, including physicians and patients, government bodies, and industry partners. In these challenging times, with growing restrictions on public funding for innovation, such collaborations—both national and international—are more critical than ever to ensure efficient progress.

This discussion is also timely because cardiovascular medicine has lagged behind oncology in adopting precision approaches. While this comparison may seem unfair—oncologists, after all, deal with highly heterogeneous malignancies—the molecular revolution has enabled deep genomic and phenotypic profiling in cancer care, leading to advances in personalized oncology. Cardiovascular disease (CVD) is even more complex than cancer, owing to its multifactorial and polygenic nature, and yet a similar precision

medicine approach is becoming increasingly feasible, thanks to breakthroughs in diagnostics, imaging, bioinformatics, and AI.

Even without the full application of the comprehensive methodologies described by Aikawa et al., the field of cardiovascular medicine is already trending toward personalization. First, there is growing awareness of sex-based biological differences in disease presentation, pathophysiology (e.g., plaque erosion vs. rupture), and response to therapy (2). Although this has not yet translated into sex-specific guidelines, research in this area—which also includes DNA-guided medication prescription—is expanding. Second, there is increasing advocacy for a holistic physician–patient relationship, recognizing the role of patient knowledge, preferences, and motivation in adherence to therapy. Shared decision-making is now embedded in contemporary guidelines, such as those for atrial fibrillation (AF), which include sections on patient context, emphasizing comprehensive care plans that consider side effects, adherence, and long-term goals (3).

The next frontier is truly individualized pharmacotherapy. Progress in this area has been slow, as exemplified by the use of antithrombotic medication.

Myocardial infarction (MI) and ischemic stroke account for 85% of all deaths due to CVD worldwide (4). Thrombosis is the central event in these conditions, as well as in venous thromboembolism (VTE). Around the world, millions are prescribed antithrombotic agents, and approximately one in three individuals will develop AF, often requiring anticoagulants (5).

Before 1970, the antithrombotic arsenal was limited to aspirin, heparin, and warfarin. While warfarin and heparin therapy were individualized using laboratory parameters—e.g., activated partial thromboplastin time and international normalized ratio (INR)—treatment success relied heavily on maintaining patients within a narrow therapeutic range (typically an INR of 2–3). Despite being a form of early personalized medicine, the practical difficulties of maintaining a stable INR made this strategy vulnerable. The advent of direct oral anticoagulants (DOACs), which offer fixed dosing without laboratory monitoring, marked a shift toward convenience, but arguably came at the expense of individualized care (6).

DOACs have more predictable pharmacokinetics than vitamin K antagonists (VKAs), obviating routine laboratory monitoring. However, a recent randomized trial in frail elderly patients with AF showed higher bleeding rates with DOACs compared with INR-guided VKA therapy, challenging assumptions about their safety (7). One relevant factor for this unexpected enhanced bleeding risk, among several possible factors, may be the variation in DOAC plasma levels seen in such elderly populations. Substantial individual variation in DOAC plasma levels—linked to both thrombotic and bleeding risks—has been well documented yet remains largely unmeasured in clinical practice. This represents a "known unknown" that compromises safety in certain populations (6). One potential improvement would be to reintroduce lab-guided dosing based on direct measurement of DOAC plasma levels rather than on INR. This could offer a path toward re-personalizing anticoagulant management without reverting to the burdens of VKA monitoring.

To truly achieve precision medicine in thrombosis, we must go further. As Aikawa et al. argue (1), comprehensive patient phenotyping could enable more accurate risk stratification, in this case for both thrombosis and bleeding. For instance, in unprovoked VTE, the risk of recurrence after stopping anticoagulation is approximately 20% at 2 years, while the annual risk of major bleeding during continued therapy is approximately 2–3%. Current risk prediction models are inadequate at the individual level. Laboratory biomarkers, including thrombin generation assays and viscoelastic tests such as thromboelastography, may help close this gap, but supporting clinical evidence is still scarce (8). Machine learning has shown promise in identifying endotypes of VTE patients at risk of recurrence, cancer, or arterial events (9). Incorporating such tools into individualized risk scores could greatly improve treatment decisions.

With emerging anticoagulants, such as factor XI(a) (FXIa) inhibitors, identifying the right patient becomes even more crucial. Unlike DOACs and VKAs, which act on central pathways, FXI is a peripheral clotting factor. Its role in thrombosis may be conditional: there is a possibility of bypassing it via alternative pathways, such as direct factor IX activation by kallikrein. This means FXI inhibition might only be effective in certain contexts or patient subgroups. Biomarkers detecting activated FXI in blood may theoretically help to select patients for such specific anticoagulant drugs, thus clarifying patient heterogeneity to limit the use of selective antithrombotic agents to those that may benefit most. A similar logic applies to novel antiplatelet agents targeting glycoprotein VI (GPVI) or C-type lectin-like receptor 2 (CLEC-2). These may be beneficial in subsets of patients with acute ischemic stroke, but not in all stroke patients, and (point-of-care) assays that detect specific platelet epitopes, such as GPVI or circulating biomarkers, may help to identify who will benefit the most.

The heterogeneity of diseases such as AF and VTE demands better patient profiling—not only to identify relevant thrombotic pathways but also to understand the *dynamic* and multifactorial nature of these conditions. Thromboinflammatory mechanisms are central to conditions such as MI and stroke, but targeted drug treatment is still in its early days. History offers cautionary lessons. Three decades ago, promising therapies (activated protein C, antithrombin, and tissue pathway factor inhibitor) failed in clinical sepsis trials despite convincing efficacy data being collected from primate sepsis models. A major reason was the heterogeneity of sepsis in humans—something not reflected in standardized animal models. Other issues relate to limitations in drug dosing given the bleeding potential of these agents in patients with sepsis-associated coagulopathy. Lacking tools to stratify or subgroup patients, these trials were doomed to miss potential responders.

Despite vastly improved technologies, we still risk repeating similar mistakes. A recent example is the OCEANIC-AF trial of the FXIa inhibitor asundexian, which failed to demonstrate superiority over apixaban in patients with AF (10). Whether this reflects underdosing, biochemical escape pathways, or patient

heterogeneity is unclear. But it reinforces the need for deep phenotyping: AF, though generally thrombogenic, encompasses a wide spectrum of risk profiles. While oral anticoagulants outperform antiplatelet agents in preventing stroke, the pathophysiology, and specifically, the coagulation pathways that are engaged (including FXI activation or not) probably differ among patients. Grouping all AF patients under the same anticoagulation strategy—especially with novel agents acting on non-central pathways—may miss therapeutic windows in key subgroups (11).

As Aikawa and colleagues state, "Heterogeneity in the complex pathobiology and presentations of cardiovascular diseases (CVDs) limits the effectiveness of conventional 'one size fits all' therapies for some of the world's leading causes of death" (1).

In sum, precision medicine in thrombosis management holds promise for improving efficacy and safety through better risk stratification, therapy selection, and monitoring. Next-generation antithrombotics targeting non-essential pathways such as GPVI, FXI, FXII, and kallikrein may offer reduced bleeding risks—but only if matched to the right patients. These factors are not universally active, and individualized profiling thus becomes indispensable.

This is not only a scientific challenge but an opportunity—one we must seize by leveraging the powerful analytical and bioinformatics tools that are now at our disposal and will continue to evolve.

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Conflict of interest

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References

1. Aikawa M, Sonawane AR, Chelvanambi S, Asano T, Halu A, Matamalas JT, et al. Precision cardiovascular medicine: shifting the innovation paradigm. *Front Sci* (2025) 3:1474469. doi: 10.3389/fsci.2025.1474469

2. Manzo-Silberman S, Hawranek M, Banerjee S, Kaluzna-Oleksy M, Alasnag M, Paradies V, et al. Call to action for acute myocardial infarction in women: international multi-disciplinary practical roadmap. *Eur Heart J Open* (2024) 4(6):oeae087. doi: 10.1093/ehjopen/oeae087

3. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* (2024) 45(36):3314–414. doi: 10.1093/eurheartj/ehae176

4. World Health Organization. Cardiovascular diseases [online]. Available at: https://www.who.int/health-topics/cardiovascular-diseases

5. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol* (2020) 76(25):2982–3021. doi: 10.1016/j.jacc.2020.11.010

6. Ten Cate H. The wonders of anticoagulation. *Front Cardiovasc Med* (2025) 11:1517109. doi: 10.3389/fcvm.2024.1517109

7. Joosten LPT, van Doorn S, van de Ven PM, Köhlen BTG, Nierman MC, Koek HL, et al. Safety of switching from a vitamin K antagonist to a non-vitamin K antagonist oral anticoagulant in frail older patients with atrial fibrillation: results of the FRAIL-AF randomized controlled trial. *Circulation* (2024) 149(4):279–89. doi: 10.1161/CIRCULATIONAHA.123.066485

8. Shaw JR, Nopp S, Stavik B, Youkhana K, Michels AL, Kennes S, et al. Thrombosis, translational medicine, and biomarker research: moving the needle. *J Am Heart Assoc* (2025) 14(1):e038782. doi: 10.1161/JAHA.124.038782

9. Iding AFJ, Pallares Robles A, Ten Cate V, Ten Cate H, Wild PS, Ten Cate-Hoek AJ. Exploring phenotypes of deep vein thrombosis in relation to clinical outcomes beyond recurrence. *J Thromb Haemost* (2023) 21(5):1238–47. doi: 10.1016/j.jtha.2023.01.025

10. Piccini JP, Patel MR, Steffel J, Ferdinand K, Van Gelder IC, Russo AM, et al. Asundexian versus Apixaban in patients with atrial fibrillation. *N Engl J Med* (2025) 392(1):23–32. doi: 10.1056/NEJMoa2407105

11. Rocca B, Ten Cate H. Factor XI and atrial fibrillation: a mismatched pairing? *Eur Cardiol* (2025) 20:e08. doi: 10.15420/ecr.2024.61