Thrombosis and Haemostasis 2024 Editors' Choice Papers

Christian Weber[1,2,3] Anne Rigby[1] Gregory Y. H. Lip[4,5]

[1] Institute for Cardiovascular Prevention (IPEK), LMU Munich, Munich, Germany
[2] German Centre for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany
[3] Department of Biochemistry, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, The Netherlands
[4] Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom
[5] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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Address for correspondence Anne Rigby, PhD, Institute for Cardiovascular Prevention (IPEK), LMU Munich, Munich, Germany (e-mail: arigby@med.lmu.de).

Christian Weber, MD, Institute for Cardiovascular Prevention (IPEK), LMU Munich, Munich, Germany (e-mail: christian.weber@med.uni-muenchen.de).

Gregory Y. H. Lip, MD, Liverpool Centre for Cardiovascular Science, University of Liverpool, William Henry Duncan Building, 6 West Derby Street, Liverpool L7 8TX, United Kingdom (e-mail: gregory.lip@liverpool.ac.uk).

This year's Editors' Choice highlights some of the most impactful 2024 publications in *Thrombosis and Haemostasis (TH)* and its open-access companion journal *TH Open*. The selection reflects key trends in the field, including new guidelines, emerging therapies, and diagnostic technologies reshaping treatment approaches as well as practical challenges related to implementation, adherence, and patient outcomes. Additionally, the role of genetics, lifestyle, and recently emerged conditions such as COVID-19 in thrombosis came to the forefront of the research published in *Thrombosis and Haemostasis* last year.

Guidelines and Consensus

Recent updates in atrial fibrillation (AF) management, including new guidelines and expert consensus papers, not only provided comprehensive frameworks for patient care, but also raised important questions about practical implementation and adherence.

The 2024 ESC AF Guidelines introduced 57 new recommendations, 17 supported by Level of Evidence C. In their viewpoint from a practicing clinician's perspective, Potpara et al[1] questioned that some, such as recommending transthoracic echocardiograms to guide treatment, may have limited practical value. Also highlighted was the variability in evidence use, including shifts from strategies like the well-validated ABC pathway[2] to an unvalidated acronym, AF-CARE, as well as changes in stroke risk stratification to a non-sex CHA_2DS_2-VASc score (i.e., CHA_2DS_2-VA[3]). The latter is perhaps justified given the changes in sex-differences for stroke over time,[4] as illustrated by a thoughtful Viewpoint by Corica et al.[5] Although Potpara et al[1] acknowledged the importance of addressing comorbidities and risk factors in all heart disease patients (whether in AF or non-AF patients), they questioned the impact on implementation and outcomes of the new guidelines, especially in light of the already existing barriers to guidelines adherence.

The executive summary of the 2024 consensus guidelines of the Geriatric Society of Chinese Medical Association on the management of AF[6] building on prior editions from 2011 and 2016 provided a concise overview of the updated recommendations for managing AF in older adults. It highlighted key areas such as AF screening, the implementation of the AF Better Care (ABC) pathway, and the importance of comprehensive geriatric assessments. Additionally, it emphasized new focus on integrating smart technology for AF detection and improving anticoagulation management in elderly patients.

Despite the widespread adoption of direct oral anticoagulants (DOACs) for many indications, vitamin K antagonists (VKAs) are still used in certain situations. For clinicians seeking guidance on VKA in practice, the position paper by Galliazzo et al,[7] developed under the Italian Federation of Centers for the Diagnosis of Thrombotic Disorders and the Surveillance of Antithrombotic Therapies (FCSA), offered comprehensive recommendations. This is of particular interest, as there are currently no new specific guidelines available for VKAs, unlike for DOACs. This guideline covered critical topics, including initiating warfarin therapy with appropriate induction regimens, managing subtherapeutic

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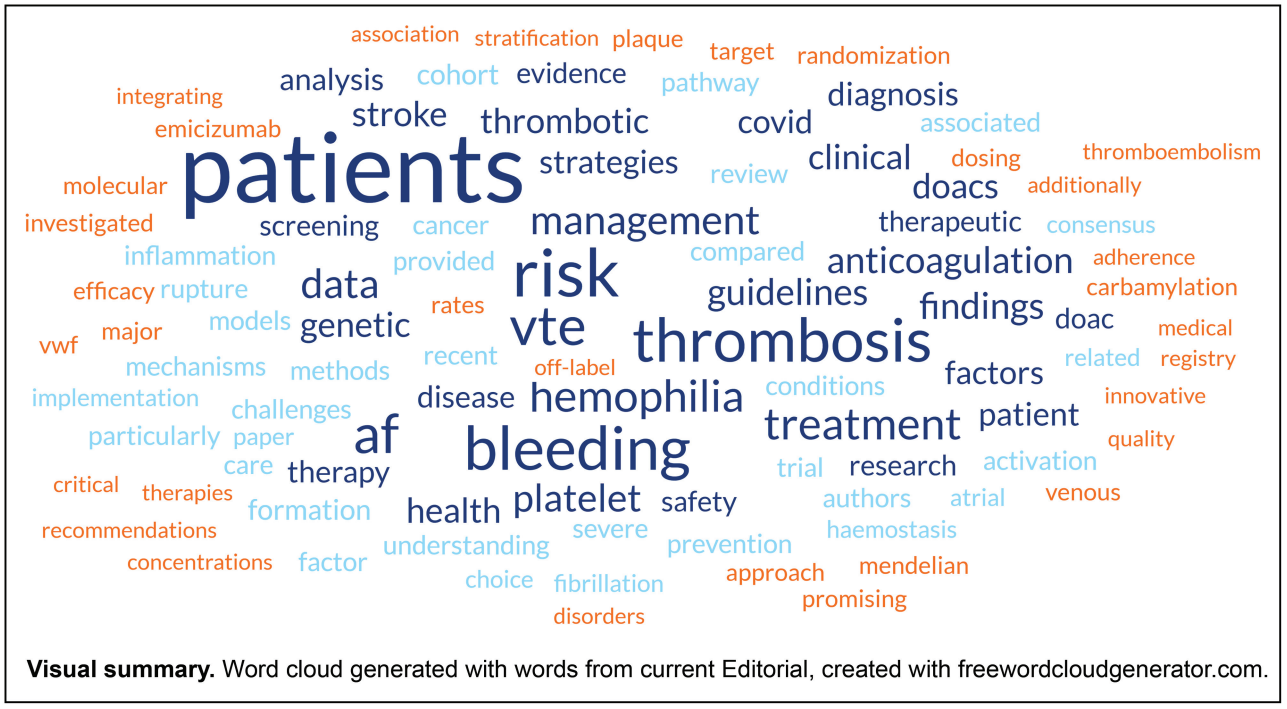

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or supratherapeutic international normalized ratio values in asymptomatic patients, and addressing drug interactions involving warfarin.

We also highlight a consensus "primer" paper on the appropriate use of DOACs[8] as well as an Executive Summary of the Scottish Intercollegiate Guidelines Network (SIGN) on the diagnosis and management of suspected dementia, focused on biomarkers.[9]

Advances in Anticoagulation Therapy

At *TH*, we are delighted to track and document how anticoagulation therapy continues to evolve, with new studies highlighting innovative approaches, dosing strategies, and tools to improve patient safety and optimize therapeutic outcomes.

A pre-specified substudy of the phase 3 ELDERCARE-AF trial[10] compared edoxaban concentrations with data from ENGAGE-AF-TIMI-48 and the Japanese Severe Renal Impairment study, contributing valuable pharmacokinetic insights for very elderly patients with AF, a population with limited available data. The results suggested potential for using dosages different from those currently approved. Although off-label dosing could provide some advantages in specific cases, it must be approached with caution, as improper use may lead to suboptimal outcomes. This is why Herron et al[11] evaluated the effectiveness of a registry-based intervention to correct inappropriate dosing practices in patients with AF and venous thromboembolism (VTE). Using the Michigan Anticoagulation Quality Improvement Initiative registry, the investigators found that "DOSE alerts" generated when off-label dosages were prescribed led to modifications in prescriptions in approximately 75% of cases. Although the data were underpowered to assess its impact on patient outcomes, the findings suggested that prescribing oversight can effectively reduce off-label DOAC use.[12] Importantly the authors raised the need for clinicians to actively review alerts rather than relying on unfiltered electronic medical record alerts.

Further expanding our understanding of anticoagulation therapy in less-studied settings, Dix et al[13] reported on a case series of 33 patients with inherited antithrombin deficiency (IATD) who were treated with standard-dose DOACs for secondary prevention of VTE. They found low rates of VTE recurrence and major bleeding, offering valuable insights into the safety and efficacy of DOACs in this patient population, where research remains scarce. This supported the growing body of evidence confirming the effectiveness of DOACs in managing patients with inherited thrombotic disorders over a 73-month follow-up period.

In addition to optimizing dosing practices, monitoring DOAC concentrations is crucial to ensure safe administration. Harenberg et al[14] proposed an algorithm for using the DOAC Dipstick, a rapid urine test to detect clinically relevant plasma levels of DOACs. By means of a systematic review they found that the test effectively excluded plasma DOAC concentrations $\geq$30 ng/mL, which could aid acute medical decisions such as managing bleeding risks, determining reversal needs, or timing urgent surgeries, and make it a valuable tool especially in hospitals lacking immediate access to advanced quantitative testing methods. However, availability of such test should not preclude the use of more accurate methods such a quantifying plasma DOAC concentration.

Thrombosis Diagnosis and Treatment

Recent advancements in thrombosis research have expanded our understanding of venous thrombosis through innovative

methods like artificial intelligence (AI), machine learning, and new insights into cardiovascular health, education, and lifestyle factors. These studies highlight the growing need for comprehensive, personalized approaches to screening and the prevention and management of thrombosis-related clinical conditions.

In our last Editors' Choice,[15] we highlighted the study by the AF-Screen and AFFECT-EU Collaborators,[16] which provided a comprehensive systematic review and meta-analysis protocol on AF screening and its potential impact on stroke prevention. Building on this, Chao et al[17]have implemented a community-based AF screening program in Taiwan, incorporating single-lead ECG into routine adult health checks. The program demonstrated feasibility and led to a significant increase in oral anticoagulant prescriptions, highlighting the value of integrating AF screening into public health systems.

In the era of AI and as the research community adapts to emerging computational methods,[18] the systematic review from Danilatou et al[19] was particularly welcome. The authors investigated the use of machine learning (ML) models to predict VTE risk, outcomes, diagnosis, and treatment. While relying on retrospective studies and lacking external validation, the study suggested that ML models may outperform traditional clinical prediction models in accuracy and predictive performance. The authors highlighted the need for standardized reporting and clinical validation through large-scale trials and proposed combining ML clinical prediction models with traditional models to enhance risk stratification, personalized treatment, and clinical decision-making.

Building on these advancements, we were delighted to report on TARGET,[20] a major European initiative funded under the Horizon Europe program, aiming to improve the personalized management of AF-related stroke. By integrating virtual human twin technology and AI, the project involves four multinational cohort studies to enhance risk prediction, diagnosis, management, and rehabilitation, followed by in silico interventional studies to improve clinical care. We expect this descriptive paper will lay a solid foundation for future TARGET publications.

Shifting focus to broader health factors, Liang et al[21] analyzed UK Biobank data from over 275,000 participants to examine the link between cardiovascular health and VTE. Using the American Heart Association's Life's Essential 8 (LE8) score,[22] they found that individuals with optimal cardiovascular health had up to a 41% lower risk of VTE over a 12.6-year median follow-up. This highlights that successful thrombosis prevention requires more than just effective anticoagulant medications and emphasizes the urgent need for a holistic approach to the management of thrombotic disease.[23]

Du and Deng[24] used Mendelian randomization to explore how educational attainment (EA) impacts the risk of varicose veins, VTE, and phlebitis, with obesity-related traits acting as mediators. Their findings suggest that higher EA is linked to lower risks of these conditions, with waist circumference emerging as a stronger mediator than body mass index, emphasizing the role of visceral fat in thrombosis. However, optimal weight loss required to reduce VTE risk and the best strategies to achieve this remain uncertain.[25] Another Mendelian randomization study performed by Wang et al[26] explored the potential association between migraines and VTE. It suggested an increased risk of VTE in patients with migraines, while the reverse association, if present, appeared negligible. Although Mendelian randomization is a robust epidemiological tool for investigating causal links, we have to keep in mind that the associations suggested by such studies do not definitively confirm causality.

Cancer-associated VTE (CAT) presents unique challenges and complexities, requiring tailored treatment strategies that take into account not only thrombotic risk but also patient safety and quality of life. In cancer patients, a prespecified post hoc analysis of the landmark CARAVAGGIO trial[27] confirmed that apixaban was comparable to dalteparin at multiple time points, with no significant differences in rates of recurrent VTE, VTE-related death, or bleeding events. These findings support the early use of oral anticoagulation, offering practical benefits such as easier administration and the potential for outpatient care, which may enhance the quality of life for cancer patients. This analysis helps address key knowledge gaps and supports prior evidence in the field.

In real-world settings, Sueta et al[28] conducted a subanalysis of the COMMAND VTE Registry 2, examining the safety and efficacy of DOACs in 1,197 patients with CAT. Unlike randomized clinical trials like CARAVAGGIO trial, this observational data included diverse patient characteristics across DOAC groups. Interestingly, cancer-related characteristics did not appear to influence the choice of DOACs, whereas the type of VTE and bleeding risk factors played a significant role in guiding selection.[29] The manuscript also highlighted a concerning trend of high anticoagulation discontinuation rate within 5 years.

Further real-world evidence came from the OSCAR-UK investigators,[30] who presented an observational cohort study conducted via UK registry data comparing efficacy and safety outcomes for rivaroxaban versus low-molecular-weight heparin (LMWH) for CAT. They concluded that rivaroxaban was a reasonable alternative to LMWH for treating patients with cancer thrombosis, who are not at high risk of bleeding, supporting current treatment guidelines.

Beyond thrombotic risk, cancer patients may also face additional health burdens. Using Danish population-based health registries, Steiner et al[31] conducted a population-based cohort study highlighting that VTE in patients with hematological cancer was associated with a 1.5- 2-fold increased risk of subsequent depression. This additional mental health burden emphasizes the need for strategies to identify and prevent depression in these patients.

Hemophilia and Beyond: Advances in Bleeding Risk Management

Recent innovations in hemophilia diagnosis and management have led to promising improvements in both molecular diagnostics and treatment strategies. Liu et al[32] introduced a novel assay, which they called Comprehensive Analysis of

Hemophilia A (HA), for molecular diagnosis of F8 gene variations in HA. This assay achieved 100% sensitivity and specificity, accurately detecting intron inversions, SNVs, indels, and large insertions or deletions. The authors suggested this approach could optimally identify causative variants and may allow detailed analysis of recombination mechanisms, and advance the genetic screening and diagnosis of HA.

However, treatment of HA, particularly in patients with inhibitors, continues to pose significant challenges. Castaman et al[33] provided insights from the STASEY study on the long-term prophylactic use of emicizumab in congenital HA with inhibitors (CHAWI).

These observations are particularly valuable in view of surgical management, which has historically posed significant challenges in these patients. Another well-received paper on emicizumab by Víctor Jiménez-Yuste and colleagues[34] presented a treatment algorithm for managing bleeding complications in patients on emicizumab. This algorithm could be particularly valuable for use in emergency situations by nonspecialists managing HA and bleeding under emicizumab prophylaxis.

Although these advancements are promising, challenges persist in managing the physical, mental, and social burdens of HA. Chowdary et al[35] examined self-reported data from adult and pediatric males with HA across Europe and found that the physical, mental, and social burdens of the disease persisted regardless of its severity. The findings highlighted the need for improved prophylactic treatment options, particularly for those with moderate forms of HA, as bleeding rates and target joints prevalence were similar across disease severity and treatment types. The treatment landscape for hemophilia B (HB) also saw advancements with the introduction of rIX-FP, a recombinant fusion protein designed to extend the half-life of coagulation factor IX. Lemons et al[36] presented promising safety and efficacy data from a study of rIX-FP in previously untreated patients with HB. The findings, though based on a small cohort, provide new hope for improving HB management, especially for young patients at risk of severe bleeding and inhibitor development.

Transitioning from hemophilia to broader bleeding risk considerations, understanding and managing bleeding complications are a critical aspect of treating AF patients. An interesting post-hoc analysis of the LOOP[37] trial investigated the risk of major bleeding in patients screened for AF using implantable loop recorders compared with those receiving usual care, with a focus on the impact of initiating oral anticoagulation. The analysis confirmed increased risk of major bleeding following oral anticoagulation initiation and suggested a potential difference in bleeding risk between patients with implantable loop recorders and those in the control group.

Winijkul et al[38] further explored outcomes in AF patients after bleeding events, with data from the COOL-AF Thailand. They found that AF patients who experienced bleeding during follow-up faced a heightened risk of subsequent death, stroke, or systemic embolism. Although consistent with previous findings in the field, these observations offer novel insights due to the specific focus on an Asian patient cohort, emphasizing the need for an integrated, holistic approach to managing AF patients.

In relation to these recent data on thrombosis and bleeding, it is worth a reminder that racial differences are evident. In an ecological study from UK Biobank and Korean nationwide databases, Kang et al compared Asian (Korean) and white Europeans (British), nicely highlighting clear racial differences in stroke and bleeding outcomes between Asians and non-Asians.[39,40] While East Asians had fewer overall bleeding events than Caucasians, they faced higher rates of intracerebral hemorrhage and respiratory system bleeding. Additionally, East Asians had a higher 5-year incidence of both ischemic and hemorrhagic strokes. These racial differences may need to be taken into consideration when large observational cohorts are analyzed. In addition, the impact of multimorbidity and polypharmacy on treatments and outcomes, for example, in patients with AF, was nicely highlighted in comprehensive analyses by Zheng et al[41] and Grymonprez et al,[42] along with its clinical implications.[43]

Mechanisms of Thrombosis and Emerging Therapeutic Approaches

Recent studies in the journal and beyond have strengthened our understanding of the mechanisms underlying thrombosis under various conditions, with an emphasis on genetic factors, platelet activation, and inflammation, accordingly deducing novel therapeutic approaches.

Zhao et al[44] investigated the role of platelet activation in the formation of portal vein thrombosis (PVT) in cirrhotic patients, showing that platelet activation was upregulated in those with PVT compared with non-PVT patients and healthy controls. Their data suggested that platelet activation is involved in PVT formation, potentially advancing a prethrombotic state in cirrhosis, and portal hypertension-related complications. These findings emphasize the need for further exploration of the molecular mechanisms underlying platelet activation in cirrhosis.

Babickova et al[45]explored the impact of carbamylation on von Willebrand factor (vWF) and platelet functionality in end-stage kidney disease (ESKD). They found that carbamylation of vWF led to decreased binding to collagen but increased affinity for factor VIII, while platelet carbamylation resulted in enhanced thrombin-dependent activation and improved adhesion to the endothelium. Thus, carbamylation of both vWF and platelets seems to disrupt hemostasis in ESKD, contributing to the complex bleeding and thrombotic risks associated with the disease.[46]

Roka-Moiia and colleagues[47] highlighted the pathological role of enhanced deglycosylation in patients who are undergoing mechanical circulatory support (MCS). They found that shear stress–induced platelet glycosylation remodeling was associated with platelet microvesiculation and thrombocytopenia. Inhibiting neuraminidase could represent be a promising strategy to reduce thrombocytopenia in MCS patients, although further preclinical studies are required.[48]

In the realm of coronary artery disease, Ueki et al[49] conducted an important sub-study of the PACMAN-AMI trial

to assess the impact of the PCSK9 inhibitor alirocumab, when added on top of high-intensity statin therapy, on platelet function in acute AMI patients undergoing PCI and receiving dual antiplatelet therapy (DAPT). They found that adding alirocumab to high-intensity statin therapy significantly reduced low-density lipoprotein cholesterol levels but had no significant impact on platelet reactivity or inflammation markers, as compared with placebo in AMI patients treated with potent P2Y12 inhibitors. The findings suggest that PCSK9 inhibition primarily benefits coronary plaque stabilization without directly affecting platelet function in AMI patients.[50]

Turning to the field of oncology, Kapteijn et al[51] reviewed the relationship between glioblastoma and VTE. Their work emphasized the role of genetic alterations in gliomas and hypercoagulability in promoting VTE. They proposed the development of a glioblastoma-specific VTE risk stratification model, incorporating procoagulant extracellular vesicle expression and genomic markers, to guide thromboprophylaxis decisions in these high-risk patients. Genetic factors also play a key role in thrombosis, as demonstrated by Wu et al,[52] who explored genetic variations in hemostasis and thrombosis-related genes in a cohort of Chinese patients with unprovoked VTE or a family history of thrombosis. They identified novel prothrombin mutations, thereby advancing our understanding of the genetic underpinnings of thrombophilia and the role of inherited risk factors in thrombosis.

The role of genetics in vascular disorders was also illustrated in the study by Dubacher et al[53] who developed a new mouse model readout for assessing the aortic rupture force in hereditary aortic diseases. This approach complements existing methods in aneurysm and highlighted that aneurysm development and rupture risk may depend on genetic defects in different extracellular matrix components, mirroring the clinical setting where aneurysm formation and aortic rupture, though often linked, may not always correlate.[54]

The link between thrombosis and COVID-19 is now well-established, but the underlying mechanisms remain to be fully understood. Yada et al[55] investigated the role of neutrophil extracellular traps (NETs) in COVID-19-associated coagulopathy. They found increased NETosis and thrombus formation in patients with severe COVID-19 and provided evidence for the potential of recombinant ADAMTS13 and caplacizumab in reducing NET accumulation and thrombus formation, highlighting novel therapeutic possibilities for COVID-19-related coagulopathy.

Li et al[56] used Mendelian randomization to explore the genetic factors contributing to COVID-19 severity. Their analysis suggested that lower levels of tissue factor pathway inhibitor (TFPI) and IL-1 receptor type 1 (IL-1R1) could be linked to more severe outcomes in COVID-19 patients. Whether these biomarkers are causally linked to COVID-19 pathology or reflect broader immunothrombotic responses remains unclear. Nonetheless, the study underscores the need for further research into the roles of TFPI and IL-1R1 in other thrombotic conditions and their potential as therapeutic targets for future pandemics.[57]

Chen et al[58] studied the role of another protein traditionally associated with inflammation, NLR family pyrin domain containing protein (NLRP) 3. NLRP3 is a part of the NLRP3 inflammasome complex where its role in the production of interleukin-1β and other caspase-1-dependent cytokines has been well studied.[59] However, the authors demonstrated that it promoted adhesion of platelets to both collagen and vWF independently of inflammasome activity. This process was regulated by the cAMP/PKA pathway, where dephosphorylation of NLRP3 facilitated its binding to filamin A. These findings may suggest that NLRP3 could be a potential therapeutic target for thrombotic diseases, such as deep vein thrombosis and stroke, alongside its known role in inflammation.[59]

Extending the discussion on the role of inflammation in atherosclerosis, data from Li et al[60] demonstrated how hemin-induced ferroptosis in macrophages contributed to the overexpression of matrix metalloproteinases (MMPs) 2 and 9 in hemorrhagic plaques, promoting plaque instability. The findings suggested that ferroptosis, triggered by increased iron from intraplaque hemorrhage, activated the p38 pathway and enhanced MMP expression, accelerating collagen degradation and plaque rupture, thus contributing to the progression of atherosclerosis.

Lastly Musialek et al[61] reviewed the critical relationship between atherosclerotic carotid artery stenosis and ischemic stroke, highlighting the link between plaque rupture or erosion and thrombus formation, causing occlusion or embolization of intracranial vessels. These events often result in significant brain infarction and poor outcomes, especially since such thrombotic strokes respond poorly to standard thrombolytic therapies. Altogether, the review underscored the importance of early intervention strategies, including revascularization, to mitigate stroke risk in patients with severe carotid stenosis.

This past year, we have had the privilege of sharing key advancements in thrombosis research, from innovative anticoagulation strategies and genetic insights to novel approaches in thrombosis prevention and treatment. We look forward to the exciting discoveries and further developments that the current year will surely bring along!

Conflict of Interest
None declared.

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