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Biological Age in Coronary Artery Disease: Advancing Therapeutic Evaluation and Precision Intervention

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Abstract: Coronary artery disease (CAD) is a typical age-related chronic condition, with its development and progression spanning a long course of life and exhibiting significant inter-individual heterogeneity. Traditional risk assessment models based on chronological age and single risk factors are often insufficient to capture the cumulative physiological decline and the dynamic progression of disease. In this review, biological age, as a comprehensive indicator reflecting an individual's true aging status, has gradually emerged as an important tool for understanding differences in CAD risk and disease progression. In recent years, various methods for assessing biological age have been applied in CAD research, primarily including composite biological age derived from routine clinical indicators, telomere length, and epigenetic clocks. Evidence suggests that different biological age markers provide complementary information and are suited into distinct applications. Among them, composite clinical biological age, based on routine clinical measurements, can dynamically reflect multi-system functional changes and has demonstrated feasibility and stability in CAD risk stratification, disease progression monitoring, and evaluation of intervention effects, highlighting its potential clinical utility. Telomere length and epigenetic clocks, on the other hand, provide supplementary information at the cellular and molecular regulatory levels regarding cumulative physiological burden and aging mechanisms. Looking forward, integrating molecular-level aging markers with composite clinical biological age to establish a multi-tiered assessment framework may improve early identification and precision intervention for CAD and other chronic diseases.

Keywords: biological age; coronary artery disease; composite clinical biomarkers; telomere; epigenetic clocks

1. Introduction

Cardiovascular disease (CVD) is characterized by a complex pathophysiology involving endothelial dysfunction, atherosclerosis, chronic inflammatory responses, increased cardiac workload, and genetic susceptibility, and it remains a leading cause of global mortality and disease burden [1]. Biological aging, as a fundamental physiological feature of the organism, is closely associated with the progressive decline of multiple organ functions and the disruption of immune homeostasis. Chronic low-grade inflammation and enhanced oxidative stress can substantially accelerate biological age, increasing the risk of CVD and other chronic diseases, as well as mortality [2,3]. It is important to note that biological aging does not necessarily progress in parallel with chronological age (CA); even individuals of similar chronological age may exhibit significant differences in health outcomes and disease susceptibility [4]. For this reason, biological age (BA) has long been used to assess an individual's true aging status and functional capacity, addressing the limitations of chronological age in capturing aging heterogeneity [5]. The difference or residual between biological and chronological age is often employed to quantify the rate of aging, with accelerated aging closely associated with adverse health outcomes. Identifying individuals whose BA substantially exceeds their chronological age and implementing timely interventions is considered beneficial for reducing the risk of chronic disease and premature mortality [6].

Notably, coronary artery disease (CAD) is not an isolated acute event but a progressive condition that develops over a lifetime, accumulating through multiple stages of subclinical alterations before its ultimate clinical manifestation [7]. From endothelial dysfunction and atherogenesis to plaque progression and rupture, the disease

typically undergoes decades-long latency [8]. Conventional risk assessment models, which depend on chronological age and single-timepoint risk factor measurements, fail to capture the dynamic, long-term inter-individual variability in disease evolution. In contrast, biological age, as a composite metric derived from multisystem biomarkers and integrated through statistical or machine learning approaches, may better reflect an individual's functional aging status than chronological age alone [5,9–12]. By incorporating the cumulative influence of genetic background, environmental exposures, and lifestyle factors, BA provides a more accurate indicator of inter-individual differences in disease susceptibility, progression, and prognosis [5,6]. In this context, BA offers a quantitative metric that links early adverse exposures and subclinical pathological changes to late-stage cardiovascular events, providing a novel perspective for understanding the life-course trajectory and progression rate of CAD.

Over recent decades, various biomarker-based systems have been proposed to define and measure BA [9–12]. To explore its value in the cardiovascular field, this review focuses on commonly used methods for assessing BA in CAD research and systematically summarizes recent advances in its application for disease risk evaluation and progression studies.

2. Methods for Assessing BA

Representative published studies reporting quantitative associations of different BA markers with CAD-related outcomes are summarized in Table 1.

Table 1. Representative published studies reporting quantitative associations of different BA markers with CAD-related outcomes.

BA Marker	Representative Study	Population	Outcome	Main Finding
KDM-BA acceleration	Yang et al. [13]	UK Biobank	Incident CAD	HR = 1.67 for incident CAD
PhenoAge acceleration	Yang et al. [13]	UK Biobank	Incident CAD	HR = 1.33 for incident CAD; improved Framingham CAD risk prediction
PhenoAge	Ma et al. [14]	Patients with multivessel CAD	All-cause mortality	Each 10-year increase in PhenoAge was associated with a 51% increase in mortality risk
LTL	Sun et al. [15]	366 CAD patients	Short-term MACEs	AUC = 0.769 ($p < 0.001$); shorter LTL independently predicted MACEs (HR = 2.866, $p < 0.001$)
LTL	Farzaneh-Far et al. [16]	780 patients with stable CAD	All-cause mortality; HF hospitalization	Lowest versus highest telomere quartile: death HR 2.1 after clinical adjustment; HF hospitalization HR 2.6
LTL	Perez-Rivera et al. [17]	150 male patients with ACS	Long-term composite endpoint	Long telomere length (third tertile) was an independent protective factor for follow-up combined events (HR = 0.279, 95% CI 0.096–0.812; $p = 0.019$)
GrimAge	Srivatsa et al. [18]	1264 MESA participants	Composite CVD; stroke	Composite CVD HR 1.05 (95% CI 1.02–1.08); stroke HR 1.08 (95% CI 1.04–1.13)

BA, biological age; CAD, coronary artery disease; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; KDM-BA, Klemera–Doubal method biological age; MACE, major adverse cardiovascular events. Owing to differences in study populations, outcomes, and statistical metrics, these studies are summarized descriptively rather than as a strict head-to-head comparison.

2.1. Clinical Composite Biomarkers

Clinical indicators are commonly used to evaluate physiological function and disease progression. However, aging involves multiple biological systems and their interactions, and a single biomarker often reflects only one aspect, failing to capture an individual's overall aging status comprehensively. In contrast, composite biomarkers derived from multiple routine clinical measurements can cover dimensions such as metabolism, inflammation, and organ function simultaneously, providing a more integrated reflection of progressive multi-system decline. Among the methods widely applied and validated in numerous studies, the Klemera–Doubal Method Biological Age (KDM-BA) and Phenotypic Age (PhenoAge) are most notable, alongside traditional approaches such as multiple linear regression (MLR) and principal component analysis (PCA) [19,20].

KDM-BA, introduced by Klemera and Doubal in 2006, is distinguished by its incorporation of a weighted modeling framework that better accommodates age-biomarker relationships when integrating chronological age and multiple biomarkers [19]. Commonly included indicators in this model are albumin, alkaline phosphatase, blood urea nitrogen, creatinine, C-reactive protein, cytomegalovirus optical density, glycated hemoglobin, total cholesterol, systolic blood pressure, and forced expiratory volume in one second (FEV_1) [21,22]. Compared with conventional linear models, KDM-BA demonstrates greater stability in younger populations, though its broader application is limited by computational complexity and dependence on programming environments. The release of the "BioAge" R package in 2021 has partially lowered these barriers and facilitated its use in epidemiological studies [23]. Traditional MLR approaches construct linear predictive equations based on biomarkers correlated with chronological age, offering simplicity but failing to fully account for the nonlinear characteristics of human aging, which may lead to estimation bias at age extremes [22,24]. PCA can mitigate some boundary distortion through dimensionality reduction, yet its reliance on linear regression still limits its ability to capture inter-individual differences in aging speed [22,24]. A study in a Korean female cohort comparing MLR, PCA, and KDM methods demonstrated that KDM-BA exhibited superior stability and reliability [25].

PhenoAge, proposed by Liu et al. using large cohort data, involves three steps: variable selection, model fitting, and aging velocity quantification [20]. Starting with 42 candidate clinical biomarkers, a penalized Cox proportional hazards regression identifies nine markers most strongly associated with all-cause mortality (albumin, creatinine, fasting glucose, C-reactive protein, lymphocyte percentage, mean cell volume, red blood cell distribution width, alkaline phosphatase, and white blood cell count), which are then combined with chronological age in the model [20]. Individual PhenoAge is calculated using a Gompertz proportional hazards model, and its residual relative to chronological age quantifies accelerated biological aging. PhenoAge has been shown to maintain a stable association with all-cause mortality across age groups, retaining predictive power even after accounting for short-term health events [20]. Recent studies further demonstrate that PhenoAge acceleration is significantly associated with risks of CAD, diabetes, and various chronic inflammatory conditions, independent of chronological age and traditional risk factors [13,26,27].

2.1.1. KDM-BA, PhenoAge, and CAD

Multiple studies have systematically examined the relationship between KDM-BA, PhenoAge, and the incidence and prognosis of CAD. A large prospective study using UK Biobank data showed that both KDM-BA and PhenoAge acceleration were significantly associated with CAD risk, with hazard ratios (HR) of 1.67 and 1.33, respectively. The study further identified an interaction between BA acceleration and polygenic risk scores for CAD, with individuals exhibiting high levels in both metrics demonstrating the highest disease risk. Incorporating BA acceleration into the traditional Framingham CAD risk model significantly improved its predictive performance [13].

In populations with established CAD, BA also holds prognostic value. A study of patients with multi-vessel CAD reported that, over a median follow-up of 33.5 months, PhenoAge and its acceleration measure were significantly associated with all-cause mortality, with each 10-year increase in PhenoAge corresponding to a 51% increase in death risk [14]. Multistate model analyses further indicated that accelerated biological aging predicts the dynamic transition from healthy status to hypertension, CAD, and ultimately death [28]. These findings suggest that accelerated biological aging not only increases the likelihood of developing CAD at a given time but also reflects an earlier and faster progression along the CVD continuum. Conversely, deceleration of biological aging or transition from an accelerated to a non-accelerated state is associated with markedly reduced cardiovascular and mortality risk, highlighting the potential role of BA in modulating disease progression timing [29].

2.1.2. Potential Mechanisms

Although the association of KDM-BA and PhenoAge with CAD has been validated, the underlying biological mechanisms remain to be fully elucidated. Current evidence suggests that accelerated biological aging may affect cardiovascular health through multiple pathways. It appears to reflect cumulative dysfunction across systems, with chronic low-grade inflammation, immune dysregulation, and metabolic imbalance as central mechanisms.

Many of the biomarkers constituting PhenoAge are related to immune and inflammatory processes, including C-reactive protein, white blood cell count, lymphocyte percentage, and red blood cell distribution width [20,30]. Consequently, PhenoAge acceleration is often accompanied by persistent low-grade inflammatory activation, characterized by elevated pro-inflammatory cytokines, enhanced innate immune responses, and gradually impaired adaptive immunity. This immune imbalance can contribute to endothelial dysfunction, vascular inflammation, and increased plaque instability. Genetic studies support these mechanistic links: PhenoAge acceleration–associated

variants are enriched in pathways related to immune regulation, cellular homeostasis, and glucose metabolism, whereas KDM-BA acceleration is more associated with lipid metabolism and lipoprotein clearance pathways, including APOE-related signaling [31,32]. These differences may be related not only to the distinct biomarker composition of the two metrics, but also to differences in their model construction. PhenoAge was developed using clinical biomarkers selected for their strong association with all-cause mortality and therefore may more strongly reflect mortality-related biological vulnerability, particularly inflammation- and immune-related aging, whereas KDM-BA was designed to integrate chronological age with multiple physiological biomarkers and may better capture multisystem physiological deviation from chronological aging, particularly metabolic and organ-functional decline [19,20,31,32]. These distinctions suggest that different BA metrics may reflect distinct aging phenotypes: "inflammation–immune type" aging represented by PhenoAge and "metabolic–lipid type" aging represented by KDM-BA. It is also possible that these two aging phenotypes may act synergistically in CAD progression. Chronic inflammation, immune dysregulation, and metabolic impairment may interact with each other, together promoting endothelial dysfunction, atherosclerotic progression, plaque instability, and thrombosis; however, direct evidence from joint-model or longitudinal studies remains limited [13,29]. Such interactions may contribute to CAD development, progression, and adverse outcomes.

Furthermore, accelerated biological aging may integrate genetic susceptibility and environmental exposures, consolidating multi-source risk factors into quantifiable phenotypic measures. Life course studies indicate that adverse exposures during childhood or adulthood (e.g., chronic psychological stress, socioeconomic disadvantage, unhealthy lifestyle) may activate the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, triggering chronic inflammation and metabolic remodeling, ultimately manifesting as accelerated PhenoAge or KDM-BA over time [33]. Notably, polygenic risk scores and adverse environmental factors may interact synergistically, rather than additively, to accelerate biological aging. High-risk individuals under unfavorable environmental conditions tend to experience pronounced aging acceleration, entering high cardiovascular risk trajectories earlier [13]. Multistate model analyses further support that accelerated biological aging drives transitions from relative health to accumulation of cardiovascular risk factors and CAD events, whereas deceleration is associated with reduced cardiovascular and mortality risk [29]. These findings suggest that KDM-BA and PhenoAge may serve not only as risk markers but also reflect biologically meaningful stages in CAD development, providing important insights for early identification of high-risk populations and intervention windows.

Overall, composite clinical BA metrics such as KDM-BA and PhenoAge capture multi-system aging differences, and their accelerated states are closely associated with CAD risk, adverse outcomes, and disease progression. Their dynamic, easily measurable characteristics make them valuable tools for early risk identification, disease monitoring, and intervention evaluation, offering a clear clinical utility for individualized management and therapeutic decision-making.

2.2. Telomere Length

Telomeres are specialized DNA-protein structures located at the ends of eukaryotic chromosomes, primarily responsible for maintaining chromosomal integrity and genomic stability [34]. With successive somatic cell divisions, telomeres gradually shorten, and when their length reaches at a critical threshold, cellular senescence or apoptosis may be triggered [35,36]. Based on this biological property, leukocyte telomere length (LTL) is widely regarded as a molecular biomarker reflecting an individual's BA. The cardiovascular system is particularly sensitive to aging. Previous studies indicate that telomere shortening can promote atherosclerosis through multiple mechanisms, including induction of endothelial dysfunction, phenotype switching of vascular smooth muscle cells, enhanced chronic inflammation, and increased oxidative stress [37–44]. These pathological processes occupy central roles in the onset and progression of CAD, making telomere length a key biological link connecting cellular aging with cardiovascular pathology.

Telomere Length and CAD

Numerous observational studies consistently demonstrate that shorter telomeres are significantly associated with increased risk of CAD [45–47]. Individuals with shorter LTL are more prone to coronary atherosclerosis, greater coronary calcification, and myocardial infarction, with these associations remaining significant after adjusting for chronological age, sex, smoking, lipid profiles, and other traditional cardiovascular risk factors [48–51]. These findings suggest that telomere shortening is not merely a passive marker of aging but may actively participate in the pathogenesis of atherosclerosis. It is noteworthy that chronic inflammation, oxidative stress, and adverse lifestyle factors can accelerate telomere attrition while also representing classical risk factors for CAD, which may explain the strong correlation between telomere length and CAD risk [52].

Regarding disease severity, telomere length is closely associated with coronary lesion burden and clinical phenotypes. Several coronary imaging-based studies have shown that CAD patients with shorter telomeres are more likely to present with multi-vessel involvement, higher Gensini scores, and high-risk plaque features such as thin-cap fibroatheromas, suggesting a relationship between telomere shortening and both the extent and instability of coronary atherosclerosis [53–55]. Mechanistically, telomere shortening directly affects the biology of vascular wall cells. In vitro studies indicate that shortened telomeres restrict smooth muscle cell replication and increase apoptosis, thereby weakening fibrous cap integrity and reducing plaque stability [37]. Endothelial cells with shortened telomeres also tend to synthesize and secrete pro-inflammatory mediators, exacerbating the local inflammatory microenvironment and further promoting plaque progression and rupture [56].

Cross-sectional studies reveal a gradient relationship between telomere length and CAD clinical subtypes. LTL is the shortest in patients with acute myocardial infarction (AMI), intermediate in those with unstable angina pectoris (UAP), and relatively longer in patients with stable angina pectoris (SAP), indicating a significant inverse correlation between telomere length and CAD clinical instability [15]. This supports the notion that telomere shortening reflects accumulated biological damage and may lower the threshold for acute ischemic events.

Beyond assessing the severity of disease, telomere length is increasingly recognized for its prognostic value in CAD. A follow-up study of patients with 40–70% coronary stenosis found that individuals with shorter telomeres experienced a significantly higher risk of major adverse cardiovascular events (MACE, including death, rehospitalization, recurrent infarction, cardiogenic shock, and new-onset heart failure) within six months [15]. Another prospective study in patients with stable CAD demonstrated that telomere shortening was significantly associated with all-cause mortality and heart failure hospitalization, independent of conventional clinical measures, inflammatory markers, and echocardiographic parameters. This finding suggests that telomere length captures long-term biological damage not reflected by traditional assessments.[16]. In patients with acute coronary syndrome, the risk stratification value of telomere length is even more pronounced: individuals in the lowest tertile of telomere length had approximately 7.7% higher risk of composite endpoints (including death, recurrent ischemia, revascularization, and heart failure) than those in the highest tertile, highlighting its additional utility in post-acute risk stratification [17].

Despite the substantial evidence supporting LTL as a biomarker for CAD risk and prognosis, several challenges remain for clinical application. Telomere length is strongly influenced by genetic background, resulting in substantial inter-individual baseline variation. Moreover, methodological differences (e.g., qPCR, Southern blot, Flow-FISH) limit measurement consistency and standardization across studies, affecting comparability [57–59]. Most studies are observational, and whether telomere shortening is a causal factor, or a consequence, or both in CAD remains to be elucidated through mechanistic research and causal inference models.

Overall, telomere length represents a key molecular marker of BA with unique value in CAD research. It reflects cellular-level damage accumulated from traditional risk factors and may aid in early identification of high-risk individuals, disease stratification, and prediction of adverse outcomes. However, compared with clinical composite BA measures, telomere length assessment is highly dependent on experimental conditions and technical platforms, with limited standardization, posing obstacles for routine clinical implementation. Future studies should employ standardized telomere measurement strategies in larger, multi-center cohorts, integrating genetic and epigenetic information to clarify causal relationships between telomere shortening and CAD. In parallel, interventions targeting telomere maintenance, such as antioxidant therapy, lifestyle modification, or telomerase-targeted approaches, warrant further investigation in rigorously designed clinical trials [60,61].

2.3. Epigenetic Clocks

Epigenetic clocks have emerged as a rapidly evolving approach for estimating BA by measuring DNA methylation levels, also referred to as DNA methylation age (DNAmAge) [62]. Unlike age assessment methods based on physiological or clinical indicators, epigenetic clocks capture molecular-level aging signatures by analyzing methylation patterns at specific genomic loci [63]. Increasing evidence shows that epigenetic clocks not only provide accurate estimates of BA but are also closely associated with the risk of multiple chronic diseases, including CVD [63]. Commonly used epigenetic clocks include the Horvath clock, Hannum clock, DNAm PhenoAge, and DNAm GrimAge [62,64], each with distinct CpG site selections, algorithmic structures, and predictive targets, reflecting different aspects of the aging process. Given that CAD is a prototypical age-related disorder, systematically reviewing the applications of epigenetic clocks in CAD research is essential for understanding their underlying mechanisms and potential clinical utility [62,65,66].

2.3.1. Principles and Types of Epigenetic Clocks

Epigenetic clocks estimate BA by analyzing DNA methylation patterns. DNA methylation, one of the most prominent epigenetic modifications, occurs mainly at CpG dinucleotides, where methyl groups attach to cytosine residues [67]. During aging, methylation patterns change at specific genomic regions, including age-associated CpG sites and promoter CpG islands, which can serve as biomarkers of aging and disease progression [68,69].

The first-generation epigenetic clocks include the Horvath and Hannum clocks. The Horvath clock is based on 353 CpG sites and demonstrates cross-tissue applicability, allowing stable BA estimation in blood, skin, saliva, and other sample types [70]. In contrast, the Hannum clock relies on 71 blood-specific CpG sites, providing robust performance in peripheral blood samples but limited applicability in non-blood tissues [71,72].

Second-generation epigenetic clocks integrate information related to health status and mortality risk. DNAm PhenoAge combines DNA methylation features with multiple clinical indicators, such as blood glucose and inflammatory markers, emphasizing "healthy aging" [30,73,74]. This model has shown enhanced predictive performance for aging-related diseases, including CAD and metabolic disorders [73–75]. GrimAge integrates seven DNA methylation-based plasma protein surrogates and smoking history and is considered among the most accurate epigenetic clocks for predicting lifespan and mortality risk [76].

2.3.2. Epigenetic Clocks and CAD

In recent years, epigenetic clocks have gained attention as tools for assessing biological aging in CAD research [77]. Epidemiological and clinical studies consistently show that epigenetic age acceleration (EAA), wherein BA exceeds chronological age, is closely associated with CAD incidence, progression, and adverse outcomes [78,79]. Positive EAA values indicate accelerated aging and identify individuals at higher risk [80].

Depending on the model and its sensitivity to blood cell composition, EAA can be subdivided into multiple subtypes. Extrinsic EAA (EEAA), derived from the Hannum clock and incorporating blood cell counts, better reflects immune system–related aging. Intrinsic EAA (IEAA), based on the Horvath clock, is independent of blood cell composition and reflects cell-intrinsic aging processes [81]. Second-generation clocks yield PhenoAge acceleration (PhenoAA) and GrimAge acceleration (GrimAA), which exhibit higher sensitivity and stability for predicting disease risk and mortality [82].

The predictive performance of different epigenetic clocks for CAD varies. Comparative studies indicate that GrimAge generally outperforms first-generation clocks [76,83]. By integrating lifestyle factors such as smoking, GrimAge significantly improves CAD risk prediction compared to Hannum or Horvath clocks, likely due to the inclusion of multiple proteins closely associated with atherosclerosis and inflammation [76,83,84]. Even after adjusting for age, body mass index, diabetes, and other conventional risk factors, GrimAge acceleration retains independent predictive value [76].

However, the predictive utility of epigenetic clocks is not uniform across populations. In postmenopausal women, EAA's ability to predict CAD is limited [85]. After gender stratification, some studies observed that associations between EAA and coronary stenosis became nonsignificant, suggesting a potential modulatory role of sex-specific lifestyle factors, such as smoking and diet [83]. Additionally, IEAA and EEAA derived from the Horvath clock show weaker correlations with traditional CAD risk factors (e.g., dyslipidemia and inflammation), limiting their predictive performance [83]. In contrast, GrimAA demonstrates high sensitivity in predicting all-cause mortality and cardiovascular events, maintaining stability after adjusting for multiple confounders [86].

Mechanistically, EAA is thought to reflect a state of chronic low-grade inflammation in the cardiovascular system. Individuals with higher EAA often exhibit systemic inflammatory features, including elevated platelet and leukocyte counts, increased C-reactive protein, fibrinogen, and neutrophil-to-lymphocyte ratios [87]. Multi-omics analyses further reveal strong correlations between inflammatory markers such as hsCRP and GlycA and accelerated DNA methylation age, highlighting inflammation as a key driver of epigenetic aging [82]. Moreover, single-cell sequencing and in vitro studies suggest that endothelial-to-mesenchymal transition may contribute to EAA, providing mechanistic insights into its role in atherosclerosis progression [88].

Despite the promising potential of epigenetic clocks in assessing biological aging and predicting chronic disease risk, clinical application in CAD remains limited. Large-scale, long-term prospective studies are scarce, restricting the ability to fully evaluate the independent prognostic value of epigenetic age in CAD. Furthermore, the measurement of epigenetic age typically relies on high-throughput methylation platforms, which are technically complex and costly, limiting their adoption in routine clinical practice. Future research should systematically evaluate the predictive performance of various epigenetic clocks in larger, multi-center cohorts and explore their feasible applications in early CAD screening, risk stratification, and clinical decision-making.

3. Discussion and Perspectives

From a hierarchical perspective, current BA markers in CAD research can be broadly categorized into clinical, cellular, and molecular levels. At each of these levels, distinct yet complementary aspects of aging relevant to CAD risk and progression are captured. Collectively, current evidence indicates that leukocyte telomere length, epigenetic clocks, and composite clinical BA each provide valuable insights into aging in the context of CAD. Telomere length, as a cellular-level aging marker, reflects the replicative history of chromosomes and the cumulative burden of oxidative stress, with shorter telomeres associated with increased risk of CAD and other cardiovascular events. For example, genetic analyses have shown that longer telomeres are linked to lower coronary artery disease risk, supporting their role as an indicator of chronic physiological burden [89].

Epigenetic clocks, by capturing age-related molecular regulation through DNA methylation, have also been linked to various cardiovascular risk factors and clinical outcomes. In the MESA cohort, GrimAge was significantly associated with composite cardiovascular events, stroke, and heart failure, highlighting its potential utility in risk characterization [18]. Similarly, DNAm PhenoAge has been used in epidemiological studies to explore how environmental and behavioral factors, such as smoking, influence cardiovascular risk via epigenetic mechanisms, further supporting the mechanistic relevance of methylation-based age [90].

In comparison, composite clinical BA metrics (e.g., PhenoAge, KDM-BA), which integrate conventional clinical indicators of metabolism, inflammation, renal function, and immunity, offer dynamic quantification of aging that aligns closely with clinical risk assessment and monitoring needs. Large-scale studies, including the UK Biobank, have demonstrated that accelerated clinical BA is significantly associated with future cardiovascular events, and incorporation of clinical BA into traditional risk models (e.g., Framingham risk score) improves risk discrimination, indicating that composite clinical BA can complement conventional approaches [13]. Among hypertensive populations, accelerated phenotypic age has been linked to higher all-cause and cardiovascular mortality, supporting its practical utility in clinical risk stratification [91].

3.1. Clinical Application of BA Markers in CAD

From the perspective of temporal dynamics and clinical feasibility, composite clinical BA, relying on routinely collected clinical data, low-cost measurements, and repeatable assessments, is well suited to serve as the core BA metric in CAD research and clinical practice. It can dynamically reflect the continuous progression of individuals from healthy states to high-risk profiles and eventually to CAD and adverse outcomes, offering directly translatable value for routine risk assessment, disease monitoring, and evaluation of intervention efficacy. Telomere length, with its slower rate of change, is more suitable as a background marker of long-term susceptibility and cumulative physiological burden. Epigenetic clocks, sensitive to environmental and metabolic perturbations, provide detailed molecular-level information on aging regulation and critical inflection points.

3.2. Challenges in Clinical Translation

Before composite clinical BA markers such as KDM-BA and PhenoAge can be more widely applied in routine CAD risk assessment, several practical issues still need to be addressed. Greater standardization in biomarker selection, measurement units, and data collection procedures would likely improve comparability across studies and clinical settings [92,93]. More consistent handling of missing values, outliers, and algorithm implementation may also help improve reproducibility [92,94]. In addition, external validation in independent CAD cohorts, and recalibration when necessary, will be important for broader clinical application [92,94].

The applicability of BA markers across different CAD subgroups is another issue that deserves attention. Some existing studies have suggested that the performance of these markers may not be identical across different populations. For example, KDM-BA has been reported to show better stability in younger populations [25], whereas some epigenetic age measures showed limited predictive value for coronary heart disease in postmenopausal women and became nonsignificant after sex-stratified analyses in some studies [83,85]. In addition, a recent large-scale analysis found that PhenoAge acceleration showed a significant interaction with age, with stronger associations in younger participants, whereas KDM-BA acceleration did not show the same pattern [13]. Epigenetic clock studies have also suggested that aging patterns may vary by sex and ethnicity; for example, men generally showed higher epigenetic aging rates than women, and differences in extrinsic epigenetic aging rates were also reported across ethnic groups [85,86]. Evidence from specific clinical settings, such as hypertension, further indicates that BA markers may also show different associations across disease backgrounds. In hypertensive populations, both PhenoAge and PhenoAge acceleration were significantly associated with all-cause and CVD-related mortality, and these associations were not entirely uniform across different clinical subgroups [91]. Taken together, these findings suggest that the same BA marker may not carry exactly the same implications across different CAD-related populations.

Possible reasons include differences in baseline biomarker distributions, hormonal and metabolic milieu, chronic inflammatory burden, environmental exposures, and the populations in which individual BA algorithms were originally developed. Therefore, in practice, BA markers still need to be interpreted and validated in the context of specific populations, and further recalibration may be needed when appropriate, rather than simply applying a single uniform standard. However, most available studies have mainly focused on subgroup differences or stratified associations, and studies specifically developing dedicated BA models for particular CAD subgroups remain limited. Although population-specific BA model development has been reported in non-CAD settings [25], truly optimized BA models for specific CAD subgroups are still scarce at present.

3.3. Therapeutic Implications and Future Directions

Beyond risk stratification, BA assessment may also have potential value in guiding preventive and therapeutic strategies for CAD. At present, the most realistic intervention pathway is still lifestyle modification, including regular aerobic and resistance exercise, dietary optimization, caloric restriction or weight control, smoking cessation, and sleep improvement, which may also represent the most feasible and safest strategy in current clinical practice. These measures may attenuate biological aging processes by reducing chronic inflammation, oxidative stress, and metabolic dysregulation, all of which are closely linked to vascular aging and CAD progression [95,96]. Recent human interventional studies further suggest that caloric restriction and selected nutritional interventions such as omega-3 supplementation may modestly slow biological aging trajectories, although the available evidence remains limited and the observed effects are relatively small [97,98].

In parallel, pharmacological therapies already used in CAD management, particularly lipid-lowering and anti-inflammatory treatment, may also influence BA-related pathways indirectly through improvement of vascular inflammation, endothelial dysfunction, and cardiometabolic risk profiles. For example, anti-inflammatory agents such as colchicine and lipid-lowering therapies including statins and PCSK9 inhibitors may contribute to reducing residual inflammatory and lipid-related risk, although current evidence is stronger for improving CAD prognosis than for directly reversing BA acceleration itself [99–101].

From a marker-specific perspective, telomere-related intervention strategies have mainly focused on reducing telomere attrition or enhancing telomerase activity, whereas interventions targeting epigenetic aging remain largely exploratory [60,102]. By comparison, composite clinical BA markers such as KDM-BA and PhenoAge may currently be more practical in clinical settings, not because they are direct therapeutic targets, but because they may serve as composite indicators of overall biological vulnerability and its changes over time [103–105]. Recent evidence from three prospective cohorts further showed that, compared with persistent accelerated aging, recovery from accelerated aging, delayed accelerated aging, or maintenance of non-accelerated aging was associated with lower risks of CVD and mortality, and these patterns were observed for both PhenoAge and KDM-BA [29]. This finding further supports the potential clinical relevance of interventions aimed at preventing, delaying, or reversing accelerated aging. However, the current evidence remains largely observational, and further studies are still needed to determine the effectiveness and safety of different intervention strategies in reversing BA acceleration and improving CAD outcomes.

At the same time, current evidence remains insufficient to conclude that modifying BA markers themselves can directly alter CAD occurrence or progression. Mendelian randomization studies provide relatively stronger support for a causal relationship between telomere biology and coronary heart disease, with genetically determined longer telomere length being associated with lower risks of myocardial infarction, angina pectoris, unstable angina pectoris, and coronary atherosclerosis [47,89]. In contrast, the causal evidence for epigenetic age acceleration appears much less consistent in CAD [89]. For composite clinical BA metrics such as KDM-BA and clinical PhenoAge, direct causal evidence remains limited, and most currently available findings are still based on observational associations. Although some interventional studies suggest that lifestyle or nutritional interventions may influence telomere attrition or epigenetic aging measures, these findings do not yet establish that modifying BA markers themselves can directly improve CAD prognosis [106,107]. Overall, current evidence more strongly supports BA markers as indicators of biological vulnerability and treatment response than as confirmed causal mediators or fully established therapeutic targets in CAD. Therefore, under current clinical research conditions, composite clinical BA can serve as the primary tool for biological age assessment and risk stratification, while telomere length and epigenetic clocks can be employed as complementary measures when available, providing insight into long-term risk backgrounds and mechanistic understanding. Given its clinical feasibility, future studies should further strengthen the evidence base for composite clinical BA, especially regarding its prognostic value and applicability across different CAD populations. Future studies may also explore whether these BA markers can be integrated or selected using statistical methods such as weighted scores, regression-based approaches, or

machine-learning models, although the value of such integrated models beyond composite clinical BA alone still requires further validation.

4. Conclusions

In the management of coronary artery disease and other chronic conditions, BA provides a more refined measure of risk than chronological age. Composite clinical BA, by integrating multi-system indicators and offering ease of measurement as well as dynamic tracking, represents the most clinically applicable tool for clinical risk assessment, disease progression monitoring, and individualized intervention. Telomere length and epigenetic clocks, while providing unique insights into cumulative physiological burden and molecular mechanisms, are primarily valuable in basic research and mechanistic studies, with more limited clinical accessibility. Given these considerations, future studies should further strengthen the evidence base for composite clinical BA, especially regarding its prognostic value, external validation, and applicability across different CAD populations. Further exploration of integrated models combining clinical and molecular BA markers may also be warranted.

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