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Modulators of platelet function in aging

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Abstract

Platelets are small, anucleated effector cells that play an important role in linking the hemostatic and inflammatory processes in the body. Platelet function is known to be altered under various inflammatory conditions including aging. A gain in platelet function during aging can increase the risk of thrombotic events, such as stroke and acute myocardial infarction. Anti-platelet therapy is designed to reduce risk of serious cerebrovascular and cardiovascular events, but the adverse consequences of therapy, such as risk for bleeding increases with aging as well. Age-associated comorbidities such as obesity, diabetes, and hyperlipidemia also contribute to increased platelet activity and thus can enhance the risk of thrombosis. Therefore, identification of unique mechanisms of platelet dysfunction in aging and in age-associated comorbidities is warranted to design novel antiplatelet drugs. This review outlines some of the current areas of research on aging-related mechanisms of platelet hyperactivity and addresses the clinical urgency for designing anti-platelet therapies toward novel molecular targets in the aging population.

Keywords

Aging; anti-platelets; platelet; thrombosis

Introduction

A greater life expectancy has led to an increasing proportion of elderly patients in the population that will pose a significant challenge to health-care systems in coming years. Thrombotic diseases, such as stroke and myocardial infarction (MI), are the leading causes of morbidity and mortality in the elderly [1–5]. Importantly, aging is associated with co-morbidities such as diabetes, hypertension, and hyperlipidemia, which are major triggers for thrombotic sequela [6,7]. Platelets play a crucial role in the initiation and progression of thrombosis. Anti-platelet drugs, such as aspirin and thienopyridine derivatives (clopidogrel and ticagrelor) are known to reduce the recurrence of ischemic stroke [8] and MI [9,10]. However, despite decades of use of anti-platelets for thrombotic diseases, controversy exists over their efficacy and safety, especially in the elderly [11,12]. Much of the controversy may be due to the knowledge gap between the molecular mechanisms of platelet activation and thrombosis across the ages and its modulation with other comorbidities.

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Declaration of interest statement

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In this critical review, we summarize findings from key studies that examined the effects of aging and age-associated comorbid factors on platelet function. We address how aging can affect the platelet micro-environment and interaction of platelets with other cells to increase the propensity for thrombosis. We discuss the challenges with current anti-platelet therapies in the aging population. Finally, with this foundation, we address the critical question of what key pathways may be altered in aging-associated platelet dysfunction, and that a mechanistic examination of these pathways may have potential to identify novel targets.

Aging and Platelet Function

The literature on the aspects of platelet function with increasing age is limited and the mechanisms of altered platelet activities are not well defined across the age-groups. Several studies beginning in the early 1980s reported changes in platelet function with age [13]. These studies used different measures of platelet activity, such as bleeding time [14], platelet aggregation [15,16], and plasma and urine markers of platelet activation [17,18], and suggested that platelet activity increases with age. However, these studies had several limitations, such as inadequate sample sizes [15,19], lack of rigorous exclusion of subjects with other comorbidities[16], and lack of consensus on what constitutes young, middle-aged, or elderly groups [15,16,19]. Overall, these early studies were descriptive and did not address the mechanisms of increased platelet activation. Secondly, several studies lacked platelet activity data from very elderly subjects such as those over 75 years of age [18,20]. Risk of bleeding increases in patients over age 75 on antiplatelet therapy [12]; therefore, this is a critical age where the effectiveness and safety of antiplatelet therapy needs to be improved. It is likely that mechanisms of platelet activation are different in this age-group and may represent an age-adjusted adaptation [21]. Therefore, a rigorous examination of critical pathways of platelet activation is needed across the age-groups and it is important to determine how they may modulate thrombotic outcomes in age-specific manner.

Effects of Aging-Mediated Inflammation on Platelet Function

A hallmark of the aging process is increased inflammation and oxidative stress [22]. Platelets are responsive to multiple circulating factors released from damaged or inflammatory cells and the current understanding is that platelet micro-environment of inflammation and oxidative stress can drive thrombotic phenotype. In this section, we discuss the inflammatory changes within platelets that may potentiate thrombotic conditions, and in the next section, we describe the role of oxidative stress pathways in platelet activation. Several of the findings discussed here and in subsequent sections were generated in aged mice or relatively younger mice challenged with age-associated comorbidities. It is pertinent to mention that considering the life-span of C57Bl6J mice is 27–29 months, the 4–6-, 12–14-, 18–20- and 24–27-month-old mice are roughly equivalent to young adults (20–30 years of age), middle aged (45–55 years of age), older (60–70 years of age) and very-old (>80 years of age) humans, respectively.

Platelets are known to serve an important role in hemostasis and inflammation[23]. Activated platelets secrete several procoagulant factors that are also inflammatory signals, such as platelet factor 4, plasminogen activator inhibitor (PAI-1), fibrinogen, and von

Willebrand factor (VWF), and many of which are known to increase with age [24–26]. Platelets also release soluble CD40L [27] and *P*-selectin [28], which serve a dual-purpose of activating inflammatory cells and promoting thrombus formation. Platelet *P*-selectin has been shown to bind PSGL-1 on leukocytes to promote fibrin deposition [28] and tissue factor release [29,30]. This platelet-leukocyte cross-talk is important for thrombus formation and stabilization: *P*-selectin/PSGL-1 binding upregulates the leukocyte beta-integrin, Mac-1, and mediates stable platelet–leukocyte interactions [31,32]. CD40L, which is expressed on platelets and secreted, is a strong inflammatory stimulus that also aids in platelet-leukocyte aggregate formation [33]. Furthermore, platelet-neutrophil and platelet-monocyte aggregates have been observed in elderly patients with varying inflammatory and thrombotic conditions, such as stroke [34], myocardial infarction [35] and venous thromboembolism [36] and portend poorer outcome [37]. It remains to be seen if platelet–leukocyte interactions are increased in aging as a by-product of an already heighted inflammatory state or is a mechanism independent of changes in aging-related inflammatory milieu [38].

Like immune sensing cells (dendritic and other phagocytic cells), platelet also express several subtypes of toll-like receptors (TLRs), such as TLR2 and TLR4, which aid in the surveillance of foreign pathogens or damaged cells during infection or inflammation[39]. Expression of certain TLRs on platelets has been linked to the propensity for arterial thrombosis in mice models of atherosclerosis [40,41]. While studies have not examined the alterations in age-dependent platelet TLR expression per se, a study in platelets from middle-aged and elderly subjects (aged 50–75) with elevated BMI and CV risk factors demonstrated that mRNA for several platelet TLR isoforms, such as TLR2, 4, and 9 positively correlated with CV risk factors and inflammatory markers, CRP and IL-6 [42]. Furthermore, Freedman et al. [43] observed age-related changes in platelet expression of inflammatory genes associated with the NF-kB pathway, such as IL-1, IL-6, ICAM-1, COX-2, and TLR-4. In their study, platelet inflammatory gene expression was a better predictor of age and associated CV risk factors compared to leukocyte inflammatory gene expression. For example, elderly (60–69 yrs) subjects had greater platelet inflammatory gene expression compared to the younger (<60 years) age group despite similar inflammatory gene expression in leukocytes [43]. Whether these observations are generalizable to the healthy aging population remains to be determined. So, in future, a rigorous study design should address sex and age differences in TLR expression and expression of other genes linked to inflammatory pathways using a broader cohort of young, middle-aged, and elderly subjects.

Yet another recent study by Davizon-Castillo and colleagues [44] studying platelets from aged mouse (>18 month of age) and humans (mean age 79.5 years) reported that elevated systemic levels of TNFα in aging promotes platelet hyperactivity and increased platelet–leukocyte interaction and blockade of TNFα reverses the adverse effect of inflammation. Their studies implied changes in megakaryocyte programming as a possible link for the TNFα driven platelet activation, but underlying mechanisms are not completely defined. Overall, age-induced inflammation can modulate interaction of platelets with other cell types and platelet activation with a potential to drive thrombosis; however, in-depth mechanistic studies are required to clarify which of the platelet-inflammatory pathways are

most critical and should be targeted for controlling thrombotic events in age-specific manner.

Aging, Oxidative Stress, and Pathways for Platelet Activation

While aging and oxidative stress have largely been studied in context of vascular inflammation [45], little is known about how platelets are affected by these interrelated mechanisms. What is known is that reactive oxygen species (ROS) production is critical for physiological platelet activation [46,47]. For example, intracellular ROS signaling is important for collagen and thrombin-induced platelet aggregation [48–50]. With increased oxidative stress in aging elevations of ROS can occur within platelets that can augment platelet activation and thrombotic susceptibility[51].

Several types of ROS including superoxide and hydrogen peroxide (H_2O_2) have been implicated in platelet activation. Superoxide, the key ROS is transient and is converted to H_2O_2 by the antioxidant enzyme superoxide dismutase (SOD1 or SOD2, expressed in platelet cytosol and mitochondria, respectively). In 18–20-month-old aged mice, we have demonstrated that mRNA for SOD1 is increased within platelets [51] suggesting that increased generation of platelet superoxide may be occurring during aging. Findings from past studies in humans and mice have suggested that platelet NADPH-oxidase containing Nox2 catalytic subunit is important for platelet superoxide generation and subsequent platelet activation [49,52–54]. Yet recent studies in our lab [55] and others [56,57] using young (3–4 month-old) mice deficient in Nox2 have observed that neither superoxide production and platelet activation, nor susceptibility to carotid artery thrombosis were different in these mice compared to wild type mice. While these studies suggest that Nox2-derived superoxide is not essential for platelet activation, other Nox-subunits or regulatory subunits of NADPH oxidase may be critical, particularly during aging. Consistent with this idea, in 18–20-month-old aged mice we have demonstrated upregulation of intra-platelet mRNA for a regulatory subunit p47Phox but not Nox2, and the increased activation of platelet was overcome by apocynin, an NADPH oxidase inhibitor [51]. Mitochondria are an alternative pathway for superoxide generation and thrombin is known to elicit a strong mitochondrial bioenergetics response in platelets [58], with the potential to generate mitochondrial ROS. Increased platelet-mitochondrial ROS is considered important in platelet activation in some disease state [59,60], but it is not known if mitochondrial superoxide is increased during aging and thus contribute to increased platelet activation.

Hydrogen peroxide, which serves as signaling molecule for several vascular process is also shown to trigger platelet activation [61,62]. A study from our lab in 18–20-month-old mice demonstrated an age-dependent increase in platelet H_2O_2 that drives platelet activation [51]. This harmful ROS is converted to water through the intracellular antioxidant, glutathione peroxidase (Gpx1). Overexpression of Gpx1 in 18–20-month-old mice reduced H_2O_2 levels within platelets and decreased the age-dependent platelet activation and thrombosis [51]. Studies in humans have also supported the role of Gpx1 in thrombotic cardiovascular (CV) events. A prospective study observed an inverse correlation between Gpx1 activity in red blood cells and risk for non-fatal MI or mortality due to CV causes, after adjusting for traditional CV risk factors[63]. Interestingly, SOD levels did not correlate with risk of

cardiovascular events [63]. Similarly, plasma Gpx3 deficiency has been shown to increase platelet-dependent thrombosis in mice [64] and clinically increase the risk of thrombotic events, such as stroke [65,66], but, whether Gpx3 is altered with age is not known. These studies corroborate the notion that the aging-associated increase in platelet reactivity may result due to an imbalance of antioxidants and pro-oxidants.

Age-associated Comorbid Risk Factors and their Effects on Platelet Function

So far, our discussion has been on the effects of aging alone on platelet function. However, the prevalence of comorbid risk factors, such as obesity-related type 2 diabetes, hyperlipidemia, and hypertension tend to increase with age, especially in those over age 65 (CDC Faststats:Diabetes 2011–14; CDC Faststats:Obesity 2013–16; CDC Faststats:Hypetension 2015–16). All of these co-morbid conditions are also associated with an increased risk of CV disease (MI, stroke). Little is known, however, how age interacts with these risk factors to exacerbate platelet activation or whether certain comorbidities pose a relatively higher risk for platelet activation than others for precipitating thrombotic events in aging population.

Metabolic conditions like diabetes and obesity can affect platelet function through alterations in inflammatory signaling and oxidative stress. Both obesity and diabetes are associated with increased expression of platelet pro-inflammatory markers, such as *P*-selectin and CD40L [67,68]. Also, platelet-mitochondrial superoxide has been shown to be increased in diabetes [69] and may be further elevated with aging under this disease condition. Studies have shown that mean platelet volume (MPV), a marker of platelet reactivity, increases with diabetes and obesity [70–72]. Hyperglycemia has also been shown to activate platelets directly: Increased glucose in the blood can result in nonspecific glycation of circulating proteins, which has been shown to activate platelets via CD36 leading to arterial thrombosis [73]. Uptake of glucose by platelets can also affect platelet metabolism and function [74]. A recent study by Fidler et al. demonstrated that murine platelets depend on GLUT1 and GLUT4 transporters for glucose uptake and platelet activation and streptozotocin-induced young diabetic mice had higher glucose uptake and platelet hyperactivity compared to control mice [75]. Similarly, a study in human platelets from middle-aged diabetic patients (aged 50–60 years) reported an increase in glucose-mediated inflammatory NF-kB gene expression and heightened sensitivity to the agonist, ADP[76], demonstrating the link between platelet metabolism, inflammatory signaling, and platelet reactivity. These biochemical and functional changes in platelets with hyperglycemia might explain the pro-thrombotic state of diabetic patients [77] and the findings that diabetics have increased platelet activation despite being on antiplatelet therapy [78].

Other commonly observed co-morbid conditions with aging, such as hypertension and hyperlipidemia, affect platelet function as well. Elevated platelet *P*-selectin expression and platelet activation is reported in patients with uncontrolled severe hypertension [79]. Elevations in intracellular calcium in platelets are observed in hypertensive patients, which may potentiate heightened responses to platelet agonists, such as serotonin and epinephrine

[80]. Another study in similar patient population reported that enhanced platelet superoxide production within platelets is mediated through AT1 receptors [81], and this increased superoxide generation has the potential to enhance platelet reactivity. In hyperlipidemia, elevated oxidized LDL (ox-LDL) can induce platelet aggregation via CD36 activation [82,83]. Hyperlipidemia is also associated with increased expression of platelet tissue factor, which is a potent pro-coagulant [84]. A recent study [21] demonstrated that age-associated increase in platelet activation is linked to decrease in platelet antioxidants in patients (age 40–79 years) with CV co-morbidities including diabetes, hypertension, and hyperlipidemia. This study suggested that diminishing antioxidant capacity with age leads to platelet activation under these conditions. Interestingly, they also reported that very elderly patients in the age group of 80–100 years developed adaptive increase in antioxidant levels and exhibited less severe platelet phenotype, which needs to be confirmed in other cohorts. Further studies are needed to determine how aging and one or more of the age-associated comorbidities affects the platelet-inflammatory micro-environment and exert imbalance between pro- and antioxidants.

Controversy Related to Beneficial Effects of Anti-platelet Therapy in Elderly

Current conventional anti-platelet therapies, such as aspirin (a cyclooxygenase inhibitor) and clopidogrel (an ADP-receptor antagonist), have been widely used in the treatment of CVDs, but their efficacy in the elderly for the prevention of CVDs has been recently called into question [11]. For example, it has been shown that use of low dose aspirin for the primary prevention of CV events, such as stroke or MI, led to a higher risk of major bleeding in patient's age >70 years, and did not decrease incidence of CV events compared to placebo group [11]. Efficacy and safety of other ADP-receptor antagonists such as prasugrel and ticagrelor has been also assessed in the elderly with acute coronary syndrome (ACS). There is a growing list of trials that have not found a clear benefit of prasugrel in the elderly (>74 years) compared to clopidogrel but it seems to confer a modest risk for bleeding [85–87]. Further, a substudy of the large PLATO trial showed no clear clinical benefit or difference in bleeding risk of ticagrelor over clopidogrel in the elderly [88] and head-to-head trial of prasugrel vs. ticagrelor showed similar bleeding risks [89]. Additional trials are underway comparing ticagrelor, prasugrel, and clopidogrel in patients with ACS > 70 years [90].

Elderly patients are often prescribed dual antiplatelet therapy (DAPT) after a stroke or stent procedure to target different platelet activation pathways: these combined treatments may also be ineffective and increase the risk of bleeding [91,92]. In older patient's age >65 years, long term (>12 months) use of clopidogrel with aspirin was associated with higher risk of major bleeding compared to clopidogrel alone [93]. Further, a higher percentage of residual platelet activity was observed in very elderly (>70 or 75 years) despite use of DAPT [94,95]. This suggests an unidentified age-related factor affecting platelet activity [96]. Recent studies by Jain et al. [21] observed that age-associated adaptation occurs within platelets in the very elderly, leading to paradoxical increase in antioxidant capacity and protection from platelet activation. Such adaptation may predispose the very elderly to higher risk for bleeding if anti-platelets are prescribed.

In an attempt to further reduce bleeding risk of conventional therapies, other FDA-approved drugs have been tested and shown promise in reducing stroke and major bleeding risk but studies in the elderly are scarce. A Cochrane review identified two RCTs (CASISP [97] and CSPS2 [98]) in the Asian population (mean age 60 years) that compared aspirin to cilostazol, a phosphodiesterase-3 inhibitor which increases cAMP levels to inhibit platelet aggregation. These studies found a lower recurrence of stroke and intracranial bleeding with cilostazol compared to aspirin. Furthermore, cilostazol, in combination with DAPT, reduced in-stent restenosis with no increase in major bleeding [99,100]. Future trials are required with a broader demographic group including elderly and very elderly (age >75) patients to assess the efficacy of cilostazol compared to conventional therapy. Combined treatment strategies with anti-platelets and anticoagulants (i.e., coagulation factor inhibitor) have been also explored. The potential benefit of rivaroxaban (factor Xa inhibitor) was previously studied in the ATLAS ACS2-TIMI trial which found a reduction in acute cardiovascular-related death in patients with acute coronary syndrome but patients had a higher rate of bleeding [101]. The COMPASS trial expanded on this to include patients with stable coronary artery disease and showed that the rivaroxaban + aspirin group had lower cardiovascular-related death, stroke or MI but a higher GI bleeding risk, particularly among the very elderly (age > 75), suggesting such combined therapies may have an age-appropriate window.

Novel strategies targeting other platelet-dependent hemostatic pathways are currently in clinical trials [102]. Inhibitors of protease-activating receptors (PAR1 and 4), thrombin binding receptors, and GPVI, a collagen binding receptor, have shown effective platelet inhibition [103] and reduced thrombi formation in animal models [104]; These novel inhibitors may offer attractive targets in aging since these receptors are modulated by inflammatory, oxidative and hemostatic signals, all of which are altered with aging (Figure 1). However, there are contraindications: Vorapaxer, a platelet PAR-1 inhibitor, has been evaluated in clinical trials (TRA2P and TRACER) in patients with stable ACS: Though it effectively lowered the rate of ischemic events, the incidence of hemorrhagic stroke was higher than placebo in the elderly patient [105]. Interestingly, these patients were already on DAPT with aspirin and ADP-receptor antagonist, suggesting an increased bleeding risk with triple therapy. In another study of patients with ACS prescribed vorapaxar as an add on to standard antiplatelet therapy (aspirin with and without clopidogrel) showed no difference in ischemic events, such as stroke, MI, or death and no difference in major intracranial bleeding risk [106], suggesting voraxpar as an alternative to clopidogrel may be as effective, but further head-to-head trials comparing vorapaxar with clopidogrel and other P2Y12 antagonists are needed.

Overall, a combined treatment with these novel drugs in addition to de-escalation or modification of conventional therapies after assessing individual risk, may offer a better alternative to conventional therapy alone in elderly.

Pathways of Platelet Activation in Aging and Consideration for Novel Targets

One of the future goals of studying mechanisms of platelet-dependent thrombosis in the elderly is to elucidate newer molecular pathways for targeted therapy. From studies in our lab and others, elevated platelet ROS has been implicated as a mediator of platelet function in aging [51,107]. Generalized anti-oxidant supplementation, such as with vitamin E, has been shown to reduce platelet aggregation in a dose-dependent manner [108] but clinical trials have not shown its effectiveness in reducing CV events [109] suggesting a more targeted anti-oxidant approach is needed. Our studies in aged mice have suggested that overexpression of the anti-oxidant enzyme Gpx 1 protects from aging-associated platelet activation and thrombosis [51]. Gpx is selenium (Se)-dependent enzyme and supplementation with Se has been shown to increase platelet Gpx activity in the healthy population [110], but whether it will reduce oxidative stress-mediated platelet activation in aging is not known. Another alternative is supplementation with N-acetyl cysteine (NAC), a potential donor of sulfydryl groups in the biosynthesis of glutathione, the critical substrate for Gpx activity. A study using NAC has demonstrated some benefit in improving vascular function in patients with coronary artery disease [111]. Similarly, high-dose intravenous NAC administered with low-dose intravenous nitroglycerin is associated with reduced infarct size in patients with MI undergoing percutaneous coronary intervention [112]. In platelets, NAC protects against oxidative stress-induced activation and apoptosis [55,113] and could be considered as a potential therapy in addition to conventional antiplatelet therapy. Trials are needed to determine whether NAC- or Sesupplementation will reduce platelet hyperactivity in the elderly and thus protect from platelet-mediated thrombosis.

In addition to increasing anti-oxidants, a clear understanding of oxidative-pathways that generate ROS within platelets might also provide a novel therapeutic target. We previously mentioned that mitochondria had been implicated as a source of ROS in healthy platelets [55] and in disease states [59,114], but its role in aging is not yet defined. A key regulator of mitochondrial oxidative stress is the family of sirtuins (SIRT1 and SIRT3) and p66shc adapter protein. Sirtuins are histone deacetylases that modify the function of various proteins, including those involved in mitochondrial oxidative stress [115]. Deficiency of SIRT1 is known to accelerate aging and oxidative stress [116] whereas loss of p66shc in mice has been shown to lower the levels of ROS in endothelial cells [117] and protect from atherosclerosis [118]. SIRT1 is also thought to regulate p66shc acetylation and thus modulate mitochondrial ROS and apoptosis [119]. In platelets, it has been shown that p66shc expression was increased in mice on high-fat diet and correlated with increased *P*-selectin expression and aggregation [120]. Suppression of p66shc with short-hairpin interference RNA blunted the pro-inflammatory, hyper-reactive platelet phenotype [120], suggesting that p66shc or its regulator sirtuin may be a target to modulate ROS production in platelets. In platelets, a predominant form of sirtuin is SIRT3 [121], which is a mitochondrial-specific sirtuin, and is known to deacetylate and activate transcription of mitochondrial genes, such as the antioxidant enzyme SOD2. Recently, SIRT3 loss of function was shown to accelerate arterial thrombosis in mouse models [122]. While this study focused on neutrophil SIRT3 and SOD2 levels, SIRT3 (or SIRT1) may be an attractive

target in platelets as it provides an important link to inflammatory and oxidative pathways for platelet activation.

Targeting mitochondrial metabolism within platelets is another growing area of interest. While resting platelets rely on oxidative phosphorylation and aerobic glycolysis to generate adenosine triphosphate, during activation platelets switch their energy metabolism to aerobic glycolysis, suggesting the existence of metabolic flexibility in platelets[58]. Two separate groups [123,124] recently showed that inhibitors of aerobic glycolysis attenuated the agonist-induced platelet responses. These studies suggested that reversing metabolic adaptations of platelets could be an effective alternative to conventional anti-platelet approaches. Though change in mitochondrial metabolism has been reported with aging in several tissues [125,126], data is lacking in platelets. A very recent study [44] did demonstrate increases in mitochondrial mass, oxygen consumption and ATP-linked respiration in platelets from mice over 18 months of age. It remains to be seen whether these changes mediate platelet activation and thrombosis and has distinct molecular pathway for targeted therapy.

Finally, aging is complicated by environmental and genetic factors that lead to cellular and molecular alterations. Many factors are modifiable, such as diet and lifestyle, but other aging-related factors, such as the presence of malignancy [127], menopause [128,129], and multiple medication use for other underlying conditions cannot be easily controlled and have an effect on platelet function (Figure 1). These factors may pose limitations while designing studies in the aging population and future work should consider these factors during examination of mechanistic pathways for platelet activation in human aging.

Summary

Platelets are key players in the thrombotic processes during aging. With the increase in aging population and prevalence of age-related comorbid conditions, such as diabetes, obesity, hyperlipidemia and hypertension, the thrombotic sequela such as stroke, MI, and deep vein thrombosis will continue to rise. Current literature provides minimal mechanistic insight in platelet activation at different stages of aging and its alteration with comorbidities. Therefore, incorporating aging populations for platelet studies in a broader age-groups and with varied comorbidities can help provide better mechanistic understanding of unique risk and protective factors at different stages of aging and help tailor age-appropriate anti-platelet therapies.

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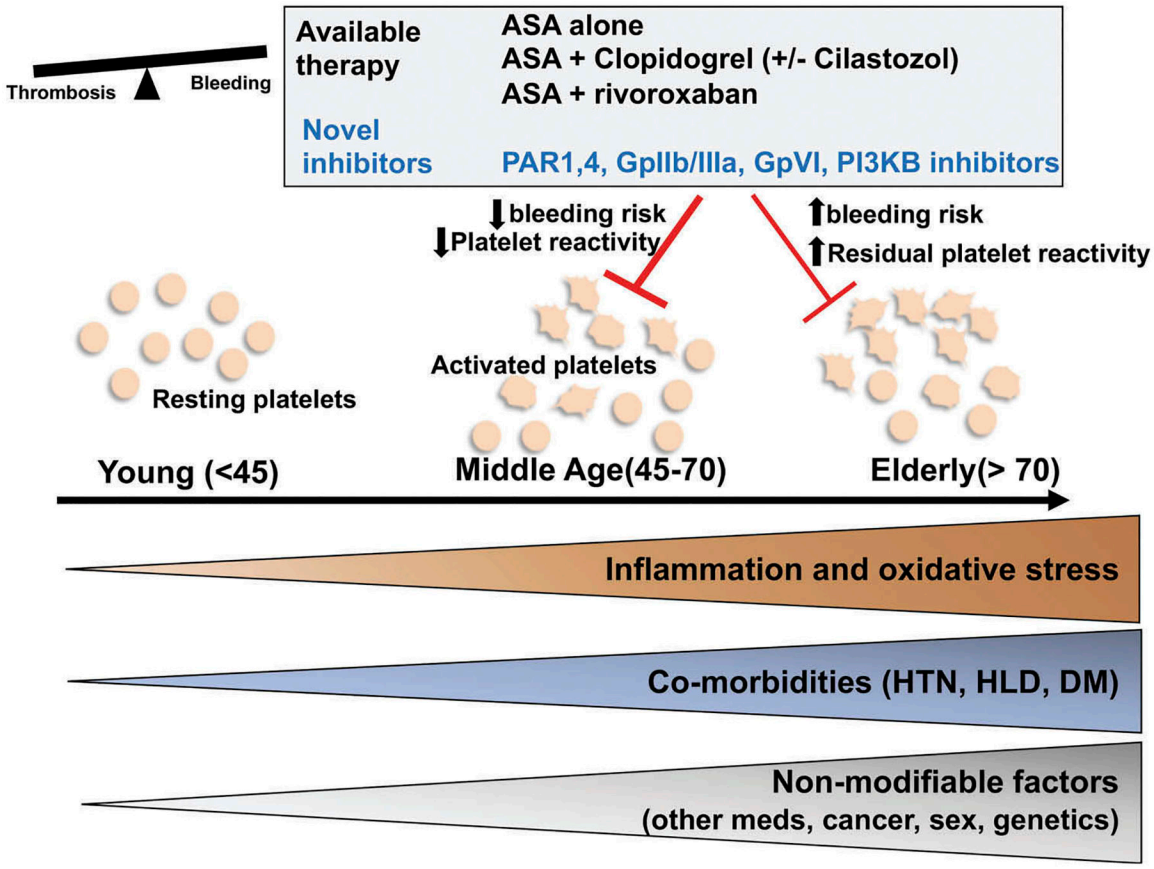

Figure 1.

Risk factors associated with aging driving platelet activation and increased thrombotic susceptibility: therapeutic alternatives. Aging is associated with increased inflammation and oxidative stress that can affect platelet activation and aggregation. Other age-associated co-morbidities, such as hypertension, diabetes, and hypercholesterolemia can affect platelet metabolism and can heighten the inflammatory micro-environment. Less modifiable risk factors, such as sex, presence of malignancy, genetics, and multiple medication use for age-associated comorbidities can affect platelets through yet undescribed mechanisms. This can culminate in a reduced threshold for platelet activation. The use of antiplatelet medications requires balancing the risk of bleeding with the risk of thrombosis. Current therapies, such as aspirin (ASA) and clopidogrel target the COX-2/thromboxane and ADP-mediated pathways, respectively. These may be ineffective in the elderly population as platelets become more sensitive to agonists and have a higher bleeding risk. Other approved but less studied treatments include combination of ASA and cilostazol or factor Xa inhibitors (rivaroxaban). Other novel inhibitors targeting other platelet activation pathways that focus on inflammatory and hemostatic signaling are in clinical trials and may offer more beneficial therapy options to the aging population. Future trials should focus on the elderly population where the risks of bleeding and anti-thrombotic benefits need careful assessment (HTN = hypertension, HLD = hyperlipidemia, DM = diabetes mellitus, PAR = protease-activating receptor, PI3KB = phosphoinositide 3 kinase, ASA = aspirin).