Thrombosis Research 136 (2015) 712–716

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Obesity and Antiplatelets-Does One Size Fit All?

Craig J. Beavers [a,b,*], Paula Heron [c], Susan S. Smyth [c], Jonathan A. Bain [d], Tracy E. Macaulay [c]

[a] TriStar Centennial Medical Center, Nashville, TN, USA
[b] University of Tennessee College of Pharmacy, USA
[c] Gill Heart Institute, University of Kentucky HealthCare, Lexington, KY, USA
[d] Cedars Sinai Medical Center, Los Angeles, CA, USA

ARTICLE INFO

Article history:
Received 24 April 2015
Received in revised form 6 July 2015
Accepted 14 July 2015
Available online 16 July 2015

Keywords:
Antiplatelets
Obesity
Platelets
Clopidogrel
Reactivity

ABSTRACT

Antiplatelet therapy has become a cornerstone in the management of many vascular diseases. With growing antiplatelet options, attention has focused on their comparative effectiveness in specific patient populations. Perhaps one of the least defined factors influencing efficacy of these agents is body mass and obesity. Evidence from preclinical models established that obesity promotes inflammation that in turn enhances platelet reactivity. Thus, adiposity has the potential to diminish or alter the therapeutic effect of antiplatelet therapy. Pharmacodynamic analyses suggest a potential need for dose adjustments of antiplatelet therapy in obese patients. Yet, obese patients paradoxically have better outcomes after acute coronary syndromes. In this review, we identify a critical need for clinical studies with outcome data to enable the development of recommendations for optimal antiplatelet regimens in obese individuals. Until such data exists, healthcare providers should be aware of the potential impact of obesity on the efficacy of anti-platelet therapy.

Contents

Abbreviations: MI, myocardial infarction; SCD, sudden cardiac death; CV, cardiovascular; GP, glycoprotein; IL-6, interleukin-6; CRP, C-reactive protein; BMI, body mass index; WHO, World Health Organization; ASA, aspirin; CI, confidence interval; PFA, platelet function assay; kg, kilogram; m^2, meters squared; mg, milligram; AA, arachidonic acid; LTA, light transmittance aggregometry; μM, micromolar; CAD, coronary artery disease; PCI, percutaneous coronary intervention; ADP, adenosine diphosphate; mL, milliliter; μg, microgram; HTPR, high on-treatment platelet reactivity; STEMI, ST-segment elevation myocardial infarction; NYHA, New York Heart Association; VASP, vasodilator phosphoprotein; LD, loading dose; NSTEMI, non-ST segment elevation myocardial infarction; UA, unstable angina; ACS, acute coronary syndrome; OR, odds ratio; MACE, major adverse cardiovascular event.

* Corresponding author at: TriStar Centennial Medical Center, University of Tennessee College of Pharmacy, 2300 Patterson Street, Nashville, Tennessee 37203, USA.
E-mail addresses: craig.beaverspharmd@gmail.com (C.J. Beavers), pmhero2@uky.edu (P. Heron), susan.smyth@uky.edu (S.S. Smyth), jonabain@gmail.com (J.A. Bain), temaca2@uky.edu (T.E. Macaulay).

http://dx.doi.org/10.1016/j.thromres.2015.07.015
0049-3848/

1. Introduction and Background

Complications of atherothrombosis such as myocardial infarction (MI), stroke, and sudden cardiac death (SCD) are the leading cause of mortality among adults in the United States [1]. One of the common causes of these events is a direct consequence of localized vascular inflammation and thrombosis. Great strides have been made in the reduction of cardiovascular (CV) morbidity and mortality through risk factor modification and preventative therapies. This progress is at risk of being halted by the growing epidemic of obesity. The National Health and Nutrition Examination Survey (NHANES) demonstrated the prevalence of obesity has increased by nearly 50% in the last decade with almost one-third of Americans now classified as obese [2]. While obesity is linked to several metabolic derangements associated with known cardiovascular disease, such as hypertension, hyperlipidemia, hyperinsulinemia, and glucose intolerance; it remains an independent predictor of disease [3]. Obesity leads to a systemic inflammatory state as well as a pro-thrombotic milieu that is likely to contribute to its CV consequences. It is well known that platelets play a central role in arterial thrombosis and vascular inflammation and that they undergo alterations in function with obesity that may affect normal vascular physiology and possibly response to antiplatelet therapy [4].

1.1. Normal Platelet Activity

Platelets are small fragments of bone marrow-resident megakaryocytes whose principle function is to facilitate thrombus formation by adhesion to damaged blood vessels, aggregation with other platelets, and generation of thrombin. These actions contribute to hemostasis by producing a platelet plug and then reinforcement of the plug by the action of thrombin converting fibrinogen to fibrin strands. Platelets accomplish these tasks through the coordinated actions of signaling receptors and adhesive glycoproteins (GP) on their surface. Platelet adhesion is initiated by damage to or loss of endothelial cells. After platelets adhere and aggregate, they initiate coagulation in part through the exposure of phospholipids on their surface and release of procoagulant microparticles.

1.2. Platelets as Modulators of Inflammation

The role of platelets in thrombosis and hemostasis is well characterized and they play a role in inflammation, vascular and lymphatic development and barrier function, fibrinolysis, and wound healing. Platelets act as storehouses for a variety of molecules that affect their own function while also impacting inflammation, vascular and lymphatic development and barrier function, fibrinolysis, and wound healing.

One of the most robust markers of platelet activation is the expression of the integral membrane protein P-selectin on the platelet surface. P-selectin mediates the initial interactions of platelets with leukocytes while also contributing to platelet-endothelial interactions. Thus, exposure of P-selectin on the platelet surface is an important step in local vascular inflammatory responses. Platelet α-granules also contain a number of chemokines that are released upon platelet activation and affect leukocyte and endothelial function [5]. These chemokine-promoted-interactions between leukocytes and endothelial cells result in the accumulation of platelets along the endothelial surface, which in turn allows for leukocyte arrest and eventual monocyte recruitment. Intravital microscopy in obese mice revealed endothelial cell – platelet – leukocyte interactions along the microcirculation in fat tissue, with up-regulation of endothelial adhesion molecules, local platelet activation, P-selectin expression, and the development of platelet – leukocyte heterotypic cell aggregates [6]. Thus, thromboinflammation is a hallmark feature of adipose tissue in obese animals; whether a similar response occurs in humans is not known, although the *ex vivo* analyses described below are consistent with *in vivo* observations in mice.

1.3. Platelets in Obesity

In comparison to normal weight counterparts, obese individuals display higher platelet reactivity in a number of *ex vivo* assays of platelet function, including platelet aggregation, sCD40L levels, and mean platelet volumes [7]. While not fully understood, adipose tissue produces multiple bioactive substances and hormones such as leptin, adiponectin, TNF-α, interleukin-6 (IL-6), and resistin all of which may directly or indirectly effect platelet function. The leptin receptor is present on platelets and potentiates aggregation in response to agonists, suggesting a potential direct link between hyperleptinemia of obesity and heightened platelet function. Farb and colleagues demonstrated that individuals with adipose tissue inflammation in subcutaneous abdominal fat biopsy samples were more likely to have impairments in vascular function, as measured by flow-mediated vasodilatation, than individuals who lacked evidence of tissue inflammation [8]. Therefore, it is reasonable to speculate that the systemic inflammation in obesity might also alter platelet function. In the Framingham Offspring cohort analysis of more than 1800 participants, platelet mRNA levels for multiple inflammatory transcripts (ICAM1, IFNG, IL1R1, IL6, MPO, COX2, TNF, TLR2, and TLR4) were significantly associated with a higher body mass index (BMI) [9,10].

2. Antiplatelet Agents and Obesity

Pharmacodynamic observations from a number of clinical studies indicate that obese individuals have higher platelet reactivity and display lower response to antiplatelet agents. In multiple large clinical studies, poor responsiveness to the platelet P2Y12 antagonist clopidogrel was consistently associated with several co-morbidities including diabetes, renal dysfunction, and obesity [11]. Likewise, obese individuals may not receive adequate protection from aspirin (ASA) alone as demonstrated in a study of over 2000 patients where obese individuals had higher platelet reactivity at baseline and after 81 mg of ASA than the non-obese controls [12]. Table 1 provides an overview of studies in which an interaction between antiplatelet agents and obesity was reported.

2.1. Aspirin

The lack of response to aspirin is a complex phenomenon with many potential mechanisms, from decreased platelet response to medication non-adherence. A substudy of the Genetic Study of Aspirin Responsiveness (GENESTAR), evaluated platelet responsiveness following administration of aspirin in obese (BMI > 30 kg/m^2) compared to non-obese patients ($n = 830$ and 1184 respectively) with a family history of premature coronary artery disease [12]. The results indicated obese patients had higher baseline reactivity in response to arachidonic acid (AA) and significantly higher residual response following the administration of ASA 81 mg. Therefore, as the authors concluded, this data may suggest that ASA 81 mg was not sufficient to overcome the higher baseline reactivity, perhaps due to an increased volume of distribution. At the time of this publication there have been no large clinical trials to determine if there is a clinical impact of obesity on aspirin response.

2.2. Clopidogrel

Studies investigating the relationship between clopidogrel and platelet aggregation in obese patients indicate that platelet aggregation is higher in obese versus nonobese patients. Obesity also emerged as a predictor of high on-treatment platelet reactivity (HTPR) in a 2009 study by Bonello-Palot and colleagues [13]. The authors observed that patients who had HTPR often were diabetic (44% vs 20%, $p = 0.01$) and had a higher BMI (28.1 ± 3.6 versus 25.6 ± 4.2 kg/m^2, $p = 0.01$) compared to good responders. Gaglia and colleagues published an investigation that used VASP, LTA, and the VerifyNow P2Y12 and ASA