Pharmacological Modulation of Platelet Function in Hypertension

Andrew D. Blann, Sunil Nadar, Gregory Y.H. Lip

Abstract—Platelets exert a considerable influence on human morbidity and mortality. The rationale for their study in hypertension follows the observation that the major consequences of hypertension are stroke and myocardial infarction. However, the etiology of these consequences in hypertension is, paradoxically, not hemorrhagic (as might be expected from the effects of high blood pressure), but occlusive, with thrombus being the culprit lesion. Mechanisms of platelet activation include high shear force, activation of the renin-angiotensin system, endothelial changes, and the presence of comorbidity, such as atrial fibrillation. The treatment of high blood pressure brings about a reversal of the changes seen in the cell. This could be in part due to the direct effect of the drug on the megakaryocyte and/or the platelets themselves, or it might simply be due to the reduction in blood pressure. Some drugs, such as calcium channel antagonists and angiotensin II receptor blockers, however, might have direct effects on platelet biochemistry other than reducing blood pressure. Finally, antiplatelet drugs are becoming an important part of the management of high-risk hypertensives, which aim to minimize vascular complications. (Hypertension. 2003;42:оШоЩоШоШоШо)

Key Words: platelet activation ■ hypertension, chronic ■ antihypertensive therapy

Hypertension, a common ailment, affects ≈15% to 20% of persons older than 40 years,1 a proportion that rises with age2 and varies in different ethnic/racial groups.3 Its importance in cardiovascular disease is undisputed, being associated with a higher incidence of myocardial infarction, atrial fibrillation, and stroke, and numerous studies confirm the benefit achieved with blood pressure reduction.4–6 Because cardiovascular pathophysiology involves thrombosis, the possibility of a causal relationship with hypertension exists. It is indeed interesting that a condition characterized by hemodynamic vascular stress and abnormal blood flow under high pressure is associated with complications that are, paradoxically, thrombotic rather than hemorrhagic.7,8 The Figure illustrates some of the possible pathways connecting platelets, hypertension, and atherothrombotic disease. Studying the mechanisms underlying platelet activation in hypertensive patients will therefore be helpful in understanding the pathogenesis of various thrombotic complications and thus, help to devise alternative pharmacologic strategies to prevent activation rather than treat it once present.

Evidence of Platelet Activation in Hypertension

The importance of platelets in hypertension can be illustrated by the presence of spontaneous platelet aggregation (long known to be present in hypertension)9 that predicts vascular occlusions.10 Similarly, increased platelet aggregation in response to endothelin could contribute to thrombosis.11 As a result of activation, platelets change from the normal disc shape to a sphere with long, dendritic extensions that facilitate adhesion. With the release of granule contents, there is additional aggregation and adhesion of the platelets, leading to autoactivation and acceleration of the thrombotic process.12,13

At the biochemical level, there are several different pathways by which activation causes a shape change, metabolite secretion, changes in membrane glycoproteins, and a maximal, irreversible, aggregatory response. A formal discourse into platelet signaling pathways is beyond the scope of this review, but, for example, the availability of arachidonic acid is the rate-limiting step in the formation of vasoconstrictor and proaggregant thromboxane A2. The former, released from membrane phospholipids mainly by the enzyme phospholipase A2, is itself activated after stimulation of receptors, such as those for collagen and thrombin.13,14

Thus, platelet function and/or activation can be assessed by various methods, such as morphology, function, and plasma markers. Platelets from hypertensive patients have an increased tendency to aggregate,15–17 an increased release of plasma β-thromboglobulin,18 high soluble and membrane expression of P-selectin,19–21 and increased intraplatelet calcium22,23 (Table 1). However, the relationship between the levels of these markers and the degree of hypertension or responses to therapy remains unclear.24–26 Lower platelet nitric oxide (NO) might be important, as this potent inhibitor of platelet aggregation could be, in part, responsible for autocrine and/or paracrine platelet activation.27,28 This will be discussed later.
Platelet microparticles, released after activation, have procoagulant effects, might promote platelet adhesion to the vessel wall, might promote thrombin generation, and are implicated in many disease processes, including the atherosclerotic complications of diabetes. Although there are few reports of raised platelet microparticles in hypertension, they could play a role in thrombotic complications, being produced when platelets are exposed to increased shear force seen in hypertension. In one report, the number of platelet microparticles was correlated with blood pressure.

Mechanisms of Platelet Activation in Hypertension

Hemodynamic and Vascular Factors
The increased shear force that platelets are exposed to as a result of the high blood pressure could, in itself, lead to platelet activation. In vitro studies have shown that platelets exposed to high-pressure flows exhibit enhanced degranulation. Increased hematocrit and whole-blood viscosity in patients with hypertension (the latter a risk factor for adverse cardiovascular events) might also contribute to platelet activation. Atherosclerotic lesions might also contribute to platelet activation, possibly because such atheromas seem likely to have a dysfunctional (ie, procoagulant) endothelium, (eg, in expressing tissue factor) and generating local flow disturbances.

Endothelial activation/dysfunction has been well documented in hypertension, and there is considerable evidence of endothelium/platelet cross-talk. After vascular damage in which the collagen-rich subendothelium is exposed, tissue factor and von Willebrand factor are upregulated by the dysfunctional endothelium, events that contribute to thrombosis. A further consequence of endothelial damage might be decreased production of endothelial NO. An effective platelet inhibitor, this reduction of NO in hypertension could therefore lead to increased platelet activation. Whether or not a dysfunctional endothelium produces less prostacyclin is unclear, as is whether or not this influences platelets. There is also a decrease in the production of bradykinins, other potent stimulators of NO production.

Neuroendocrine Activation
Enhanced platelet sensitivity in hypertension has also been attributed to both increased endogenous production of catecholamines and potentiated sensitivity to them. Platelet aggregation ex vivo in response to epinephrine is an important laboratory tool. In hypertension, the number of platelet \( \alpha_2\)-adrenoceptors is increased, and this could facilitate greater catecholamine response. Catecholamines, the \( \beta \)-adrenoreceptor agonist isoprenaline, and angiotensin II themselves promote platelet activation and aggregation and have also been shown to increase the intracellular calcium content in platelets and could also account for their activation in hypertension. There is also evidence that genetic polymorphism of the \( \alpha_2\)-adrenoceptors associated with hypertension relates to increased adrenaline-mediated platelet aggregation. These interactions might explain the success of certain classes of antihypertensive drugs in reducing platelet activity (see below).

Comorbidity
Comorbidities and risk factors commonly associated with hypertension could be responsible for some of the platelet changes, independent of high blood pressure. For example, atrial fibrillation is common in hypertensives and induces a hypercoagulable state with increased platelet activation, possibly because of intra-atrial turbulence. Diabetes and renal impairment are also often associated with hypertension, and
diabetics also have platelets in various states of activation,49 as suggested by increased plasma P-selectin.50

Reversal of Platelet Activation in Hypertension

It follows from the aforementioned evidence that numerous metabolic and physiologic changes in platelet function in hypertension might be targets for appropriate pharmacologic treatments. Indeed, many studies51–55 have shown that various parameters of platelet activation are normalized with the treatment of hypertension. Tables 2 through 4 summarize studies performed with the different classes of drugs. Because the literature is extensive, we show only a small but representative sample. Although results are variable, with the same drug showing different effects on different parameters of platelet activation, most classes of antihypertensive agents have some degree of antiplatelet activity. Although numerous studies have shown alterations in the physiology of circulating platelets, it is unclear whether or not the megakaryocyte is also affected. It is also debatable whether or not this action is entirely due to the blood pressure reduction itself or whether or not there is some direct action(s) of the drug on the platelet.

### TABLE 2. \(\beta\)-Blockers, \(\alpha\)-Blockers, and Platelet Function

<table>
<thead>
<tr>
<th>Drug</th>
<th>Authors</th>
<th>Platelet Function Studied</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(\beta)-Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol 80 mg BID</td>
<td>Hansen et al51</td>
<td>ADP-induced aggregation</td>
<td>Increased</td>
</tr>
<tr>
<td>Propranolol 40–120 mg</td>
<td>Ding et al50</td>
<td>(\beta) thromboglobulin</td>
<td>Reduced</td>
</tr>
<tr>
<td>Propranolol 80 mg BID</td>
<td>Winther et al52</td>
<td>ADP-induced aggregation</td>
<td>Increased</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Larsson et al44</td>
<td>Aggregability</td>
<td>No change</td>
</tr>
<tr>
<td>Bopindolol 1 mg BID</td>
<td>Winther et al52</td>
<td>ADP-induced aggregation</td>
<td>No change</td>
</tr>
<tr>
<td>Metoprolol 100 mg BID</td>
<td>Winther et al53</td>
<td>ADP-induced aggregation</td>
<td>No change</td>
</tr>
<tr>
<td>Atenolol 100 mg</td>
<td>Gleeup et al70</td>
<td>(\beta) thromboglobulin</td>
<td>Reduced</td>
</tr>
<tr>
<td>Atenolol 80 mg</td>
<td>Smith et al71</td>
<td>(\beta) thromboglobulin</td>
<td>Reduced</td>
</tr>
<tr>
<td>Atenolol 50 mg</td>
<td>Knight et al72</td>
<td>Multiple aggregations</td>
<td>No change</td>
</tr>
<tr>
<td><strong>(\alpha)-Blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin 2–8 mg</td>
<td>Okrucka et al64</td>
<td>ADP-induced aggregation</td>
<td>No change</td>
</tr>
<tr>
<td>Urapidil</td>
<td>Spah et al65</td>
<td>ADP-induced aggregation</td>
<td>Decrease</td>
</tr>
<tr>
<td>Terazosin 1–4 mg</td>
<td>Hernandez et al64</td>
<td>ADP-induced aggregation</td>
<td>No change</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>Hernandez et al67</td>
<td>ADP-induced aggregation</td>
<td>Decreased</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>Hernandez et al68</td>
<td>ADP-induced aggregation</td>
<td>Decreased</td>
</tr>
<tr>
<td>Phenotolamine</td>
<td>Kimura and Okuda59</td>
<td>Epinephrine-induced calcium flux</td>
<td>Inhibition</td>
</tr>
</tbody>
</table>

ADP indicates adenosine diphosphate.

### TABLE 3. ACE Inhibitors, Angiotensin II Antagonists, and Platelet Function

<table>
<thead>
<tr>
<th>Drug</th>
<th>Authors</th>
<th>Platelet Function Studied</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril 25 mg BID</td>
<td>Someya et al78</td>
<td>ADP-induced aggregation</td>
<td>Decreased</td>
</tr>
<tr>
<td>Captopril 25–50 mg BID</td>
<td>Birkebaek et al79</td>
<td>ADP-induced aggregation, PF4</td>
<td>No change</td>
</tr>
<tr>
<td>Quinalapril 20 mg BID</td>
<td>Gupta et al90</td>
<td>ADP-induced aggregation, PF4</td>
<td>No change</td>
</tr>
<tr>
<td>Enalapril 10–20 mg</td>
<td>Li-Saw-Hee et al81</td>
<td>ADP-induced aggregation, PF4</td>
<td>No change</td>
</tr>
<tr>
<td>Captopril 25–50 mg</td>
<td>Muller et al82</td>
<td>Platelet (\alpha)-adrenoceptors</td>
<td>Decreased</td>
</tr>
<tr>
<td>Enalapril 20 mg</td>
<td>Hernandez-Hernandez et al83</td>
<td>ADP-induced aggregation</td>
<td>Increased</td>
</tr>
<tr>
<td><strong>Angiotensin II antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan 50–100 mg</td>
<td>Li-Saw-Hee et al81</td>
<td>Soluble P-selectin</td>
<td>No change</td>
</tr>
<tr>
<td>Losartan 50–100 mg</td>
<td>Pathansali et al81</td>
<td>Megakaryocyte size and ploidy</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bleeding time</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aggregation</td>
<td>No effect</td>
</tr>
<tr>
<td>Losartan 100 mg</td>
<td>Levy et al84</td>
<td>Platelet aggregation</td>
<td>Decreased</td>
</tr>
<tr>
<td>Losartan and valsartan</td>
<td>Kalinowski et al77</td>
<td>NO release in vitro</td>
<td>Increased</td>
</tr>
</tbody>
</table>

PF4 indicates platelet factor 4; NO, nitric oxide.
**TABLE 4. Calcium Channel Antagonists and Platelet Function**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Authors</th>
<th>Platelet Function Studied</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine 20–40 mg</td>
<td>Birkebaek et al^79</td>
<td>Platelet factor 4</td>
<td>No change</td>
</tr>
<tr>
<td>Isradipine 2.5 mg</td>
<td>Gleerup et al^15</td>
<td>ADP-induced aggregation</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Gleerup et al^10</td>
<td>β thromboglobulin</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Platelet factor 4</td>
<td>Decreased</td>
</tr>
<tr>
<td>Diltiazem 60–180 mg</td>
<td>Pechan et al^90</td>
<td>ADP-induced aggregation</td>
<td>Decreased</td>
</tr>
<tr>
<td>Nitrendipine 10–20 mg</td>
<td>Muller et al^82</td>
<td>Platelet α adrenoceptors</td>
<td>No change</td>
</tr>
<tr>
<td>Felodipine</td>
<td>Sengelov et al^102</td>
<td>Platelet factor 4</td>
<td>Decreased</td>
</tr>
<tr>
<td>Amlodipine 10 mg</td>
<td>Hernandez-Hernandez et al^85</td>
<td>ADP-induced aggregation</td>
<td>Decreased</td>
</tr>
<tr>
<td>Verapamil 80–200 mg</td>
<td>Ding et al^89</td>
<td>β thromboglobulin</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple aggregations</td>
<td>No effect</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Addonizio et al^103</td>
<td>ADP-induced aggregation</td>
<td>Decreased</td>
</tr>
<tr>
<td>Ef nadipine 40 mg</td>
<td>Nomura et al^101</td>
<td>Soluble P-selectin, CD62⁺ platelets, microparticles</td>
<td>All decreased</td>
</tr>
</tbody>
</table>

**Blockers of the Adrenergic System**

Because this class of drugs was one of the first to be widely used clinically, there is a large literature, and, as mentioned previously, it has been established that hypertension is associated with changes in platelet α- and β-adrenoceptors. Interfering with these receptors with their respective blockers has been shown to influence platelet function, (mostly) as defined by ADP-induced aggregation in vitro and in vivo. However, it has also been suggested that these agents act on calcium metabolism and by inhibiting signal transduction via the phospholipase C/protein kinase C pathway.

Table 2 also shows the variability in effects reported by different groups, some of whom studied purified platelets ex vivo. There appears to be little consensus of an effect on aggregation, although other pathophysiological mechanisms (such as fibrinolysis) might be influenced by these classes of drugs. Gleerup et al^70 showed that treatment with both atenolol and isradipine was associated with reduced plasminogen activator inhibitor, a molecule involved in fibrinolysis, and this effect was correlated with the 70% greater potency in NO release in platelets than in endothelial cells, and this effect was correlated with the degree of inhibition of platelet adhesion and aggregation.

However, despite laboratory and animal evidence of the efficacy of these possible mechanisms, in the clinical setting, there is little consensus, due as much to differences in study designs and the types of patients enrolled. Table 3 illustrates the relative discrepancies between the clinical and laboratory effects of the different ACEIs and ARBs. Other reasons for these differences could be because in hypertensive patients, there is frequently a significant degree of endothelial dysfunction, which might reduce the effect of angiotensin II on platelets, that they prevent its formation. The ARBs, on the other hand, directly block the angiotensin receptors and therefore have a direct antiplatelet effect. For example, a direct antiplatelet action in vitro might be mediated mainly through thromboxane A₂ receptor antagonism, rather than inhibition of synthesis. Of unique interest is the report that a 6-week course of losartan reduced megakaryocyte size and ploidy and lengthened bleeding time, although low power (n=8 hypertensive patients) demands caution.

**Calcium Channel Blockers**

The rationale for an effect of calcium channel blockers (CCBs) is evident from the role of this ion in cell metabolism. Indeed, an increase in cytosolic calcium concentration is a major signal underlying platelet activation. This is mediated via calcium channels that open mainly in response to "classic" agonist receptors such as adrenaline, thrombin, and ADP, although the major receptor concerned with calcium transport is the ionotropic P₂X₇ purinoceptor. Further evidence of the possible involvement of the calcium ion in hypertension include reports of its correlation with blood pressure and reduction with successful treatment. Theoretically, therefore, blocking these and other calcium gates should prevent platelet activation through a wide variety of stimuli.

Unsurprisingly therefore, CCBs have indeed been shown to be effective at blocking platelet activation, both in vitro and in vivo. One group concluded that verapamil and nisoldipine inhibit platelet aggregation mechanisms other than by α₂-adrenoceptor blockade, while others reported that felodipine reduced α-degranulation in healthy young men at rest and after exercise, although there was no effect on platelet aggregation or thromboxane release. However, also unsurprisingly, there are alternative data.
Some\textsuperscript{70} reported that amlopidine enhanced P-selectin expression (implying increased platelet activation) and enhanced degranulation, while others\textsuperscript{103} used in vitro data to conclude that verapamil was relatively ineffective as an inhibitor of ADP-induced aggregation and that it failed to alter calcium ionophore–induced platelet aggregation. However, the same group\textsuperscript{104} later reported that both therapeutic verapamil and diltiazem are specific inhibitors of epinephrine-induced platelet activation and that verapamil exhibits greater antiplatelet potency than diltiazem.

Conclusions
Platelet involvement in the pathogenesis of the thrombosis-related complications associated with hypertension is now undisputed. However, is platelet activation in hypertension the main mechanism promoting stroke and myocardial infarction, or merely a bystander?

For convenience, we have grouped antihypertensive drugs into \( \alpha \)- and \( \beta \)-blockers (Table 2), ACEIs, ARBs (Table 3), and CCBs (Table 4). However, given the diversity of study design and the doses of the drugs concerned, consensus is poor, and we find it impossible to determine whether any particular agent in superior to another. We have cited selected but representative clinically orientated literature, focusing on single-class treatment, showing the effect (or lack thereof) of various types of antihypertensive therapy on this cell, although several articles attempt to compare different groups of these drugs.\textsuperscript{25,69–72} However, most patients need more than one class of drug to control their hypertension, and some workers have used subjects on dual therapy to dissect the pathophysiologic process in a more genuine clinical setting that, of course, obscures the effects of any single drug.\textsuperscript{20,105} Indeed, in animal models, the combination of an ACEI and an ARB mediates greater increases in coronary blood flow and more potent cardioprotection than either drug alone.\textsuperscript{106,107}

Future research should be directed to elucidating the different mechanisms of the activation of platelets in hypertension and thus developing different means of addressing this activation, although it is notable that two of the oldest pharmaceuticals in cardiovascular disease (aspirin and nitroglycerin) have antiplatelet activity.\textsuperscript{108,109} However, these are far from perfect, and it is clear that other antiplatelet drugs are becoming considered as part of the management of well-controlled high-risk hypertensives in preventing further vascular complications.

Acknowledgment
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References


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