

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Diabetes and Aspirin Resistance

Subhashini Yaturu and Shaker Mousa

*Stratton VA Medical Center/Albany Medical College; Pharmacy Research Institute
Albany College of Pharmacy and Health Sciences
Albany, NY
USA*

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with diabetes mellitus (DM). DM is considered as a coronary artery disease equivalent for future risk of vascular events. There are 3 different classes of platelet-inhibiting drugs: cyclooxygenase-1 (COX-1) inhibitors (aspirin), ADP P2Y₁₂ receptor antagonists (thienopyridines), and platelet glycoprotein (GP) IIb/IIIa inhibitors, and these platelet inhibitors are mostly used for the prevention and treatment of atherothrombotic disorders.

Aspirin inhibits the COX-1 enzyme and therefore blocks platelet thromboxane A₂ synthesis. In 2007, the American Diabetes Association (ADA) and the American Heart Association (AHA) jointly recommended primary prevention strategy in those with diabetes, and that was modified by The U.S. Preventive Services Task Force recently; they did not differentiate their recommendations based on the presence or absence of diabetes. ADA recommends the use of low-dose aspirin (75–162 mg/day) for secondary prevention of cerebrovascular and cardiovascular events in all diabetic patients. In this chapter we discuss the cardiovascular risk in diabetes, what aspirin resistance means, the mechanism of aspirin resistance in diabetes including platelet activity, methods that are useful to identify aspirin resistance, and methods and management of aspirin resistance.

2. Diabetes and cardiovascular risk

Prevalence of diabetes is increasing rapidly worldwide. Diabetes is projected to affect 300 million people around the world by 2025. Type 2 diabetes is the most common form of diabetes. The prevalence of type 2 diabetes increases with age. Type 2 DM creates a prothrombotic state that is related to endothelial dysfunction, impaired fibrinolysis, increased levels of coagulation factors, and high platelet reactivity. (Carr 2001) Diabetes is considered as a coronary artery disease equivalent for future risk of vascular events <http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf>. Despite a decline in mortality from CVD over the past decade, DM remains a key risk factor for CVD. Individuals with diabetes are at a 2- to 4-fold increased risk of cardiovascular events compared with age- and sex-matched individuals without diabetes. In diabetic patients over the age of 65 years, 68% of deaths are from coronary heart disease (CHD) and 16% are from stroke. (Pignone, Alberts et al. 2010) National Health and Nutrition Examination Survey data

suggest that declines in all-cause mortality have occurred among men with DM but not women. Mortality rates among individuals with DM remain approximately 2-fold higher compared to individuals without DM.(Preis, Hwang et al. 2009) Mechanisms leading to prothrombotic state are shown in the Figure 1.

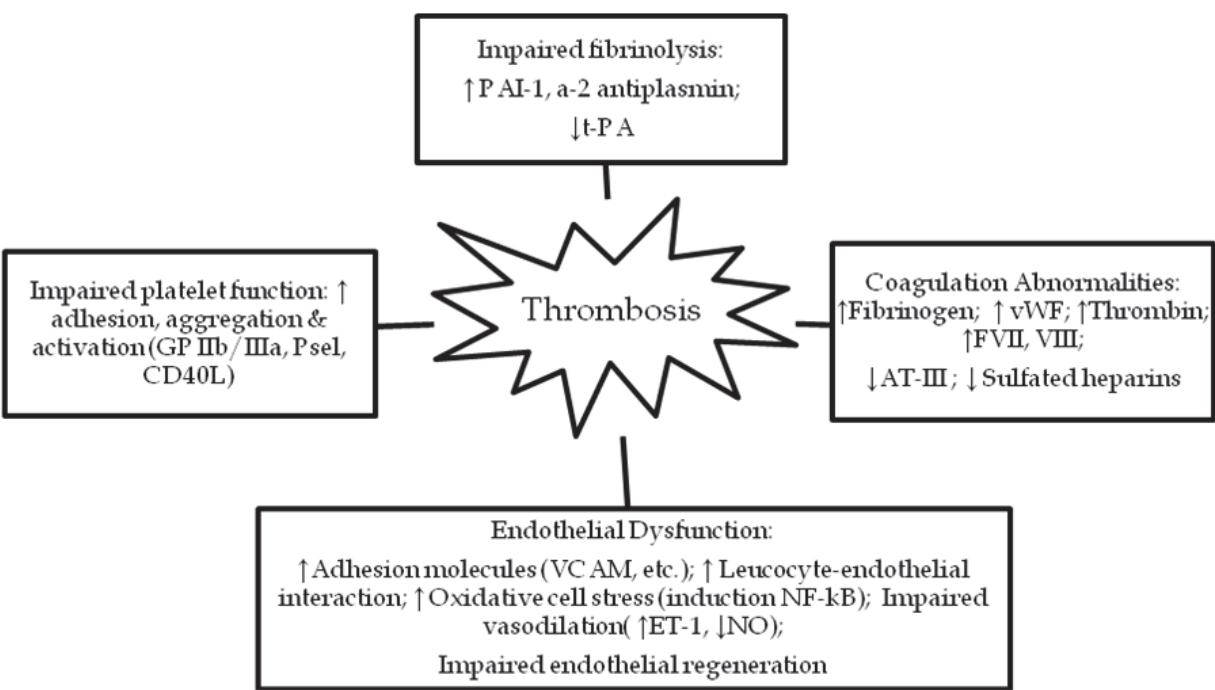


Fig. 1. Mechanisms leading to prothrombotic states in type 2 diabetes

3. Aspirin

Aspirin is one of the most important therapeutic agents used in the prevention of CVD (both primary and secondary) in patients with diabetes. Long-term aspirin administration in patients at high risk of occlusive vascular events reduced up to 34% of nonfatal myocardial infarction (MI), 25% of nonfatal stroke, and 18% of all-cause mortality. Low-dose aspirin (as low as 81 mg/day) irreversibly inhibits the COX-1 enzyme, by acetylating the serine residue at position 529, consequently impairing the transformation of arachidonic acid to prostaglandin (G2/H2), and TX A2, which is a potent mediator of platelet aggregation and activation. Aspirin's effect on COX-2 is minimal in doses <1200 mg per day.(Bucchi, Bodzenta et al. 1986; Frolich 1997) Equivalent doses of the enteric-coated aspirin are said to be as effective as plain aspirin.(Cox, Maree et al. 2006) Lower bioavailability of these preparations and poor absorption from the higher pH environment of the small intestine may result in inadequate platelet inhibition, particularly in heavier patients.(Cox, Maree et al. 2006)

3.1 Aspirin as a primary prevention strategy in diabetes mellitus

The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial (Ogawa, Nakayama et al. 2008) was the first prospectively designed trial to evaluate the use of aspirin (81 mg or 100 mg) in the primary prevention of cardiovascular events in patients

with type 2 diabetes ($n = 2,539$) aged 30–85 years in Japan, and reported that aspirin use was associated with a 32% reduction in the risk of the primary end point at 4.7 years of follow up. The ongoing trials that will provide insights into the appropriateness of aspirin usage in diabetic patients include the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D). (De Berardis, Sacco et al. 2007) Results of the Prevention Of Progression of Arterial Disease And Diabetes (POPADAD) trial have been reported, with no benefit with aspirin or antioxidants in primary prevention of cardiovascular events. (Belch, MacCuish et al. 2008) ADA recommends enteric-coated aspirin at a dosage of 81–325 mg to be used as a preventive strategy in high-risk diabetic individuals. (Pignone, Alberts et al. 2010) An important consideration is that patients may acquire additional risk factors over time, which would necessitate a reassessment of their overall risk profile. Several meta-analyses have explored the benefit of aspirin therapy in the primary prevention of major adverse cardiovascular events (MACE) among patients with diabetes. (Baigent, Blackwell et al. 2009; Calvin, Aggarwal et al. 2009; De Berardis, Sacco et al. 2009; Pignone, Alberts et al. 2010; Younis, Williams et al. 2010; Zhang, Sun et al. 2010) There are several tools to calculate the risk. Tools that can be used in patients with diabetes are available from several sources, for example: UKPDS Risk Engine: <http://www.dtu.ox.ac.uk/riskengine/index.php>; ARIC CHD Risk Calculator: <http://www.aricnews.net/riskcalc/html/RC1.html>; American Diabetes Association Risk Assessment Tool, Diabetes PHD: <http://www.diabetes.org/phd>. The AHA has issued similar guidelines and recommends 75–160 mg/day of aspirin as a primary prevention strategy in high-risk individuals, defined as those with a 10-year risk of coronary artery disease (CAD) over 10%.

3.2 Aspirin as a secondary prevention strategy in diabetes mellitus

Two large meta-analyses of major secondary prevention trials by the Antithrombotic Trialists' Collaboration (ATC) showed oral aspirin to be protective in patients at high risk for CVD, including those with diabetes (1994; 2002). The meta-analyses included 287 secondary prevention trials involving 212,000 high-risk patients with acute or prior vascular disease or another condition that increased their risk of vascular disease. Of note, a low dose of aspirin (75–150 mg/day) was found to be at least as effective as higher daily doses. In more than 4,500 diabetic patients studied in the ATC, the incidence of vascular events was also reduced from 23.5% in the control group to 19.3% in the group treated with antiplatelet therapy ($P < 0.01$) and from 17.2% to 13.7% in the ~42,000 nondiabetic patients ($P < 0.00001$). The ADA recommends the use of aspirin (81–325 mg/day) as a secondary prevention measure in diabetic patients with atherosclerotic disease. (Pignone, Alberts et al. 2010)

3.3 Aspirin resistance

Aspirin resistance, defined as failure of suppression of thromboxane generation, increases the risk of cardiovascular events in a high-risk population. (Eikelboom, Hirsh et al. 2002) Causes of aspirin resistance include concurrent use of nonsteroidal anti-inflammatory drugs such as ibuprofen that may compete with aspirin at the COX-1 receptor site, (Catella-Lawson, Reilly et al. 2001) polymorphisms in the COX-1 gene, (Eikelboom, Hirsh et al. 2002; Halushka and Halushka 2002) poor glucose control, body weight, and conditions associated with a high platelet turnover. (Zimmermann, Wenk et al. 2003; Zimmermann, Kurt et al. 2005; Guthikonda, Lev et al. 2007; Modica, Karlsson et al. 2007)

3.4 Terminology (Ben-Dor, Kleiman et al. 2009)

The lack of agreement on a standardized definition for “aspirin resistance” has contributed to the disparity in reports of its incidence among different studies. Whereas some use the term “aspirin treatment failure,” others like to call it “aspirin non responsiveness.” The term *aspirin resistance* has been used to describe the occurrence of cardiovascular events despite regular aspirin intake at recommended doses.

3.5 Diabetes and aspirin resistance

The benefit of aspirin in diabetic patients has been consistently documented in several trials. Aspirin is recommended for primary and secondary prevention in DM. Yet, in the meta-analysis of the ATC, the event rate of DM patients on treatment was similar to that of non-DM patients off treatment.(2002) In the Primary Prevention Project Trial, aspirin treatment reduced cardiovascular events and deaths in high-risk non-diabetic patients, but not in patients with type 2 DM (T2DM). Furthermore, in the recent Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Study,(Ogawa, Nakayama et al. 2008) a low dose of aspirin in primary prevention did not reduce the risk of cardiovascular events at 4 years in diabetic patients. Other studies in secondary prevention similarly suggested that aspirin might be less effective in T2DM, especially in patients with poor metabolic control, than in non-DM patients, the underlying mechanism being still debated. Since platelets play a key role in the development of atherothrombotic events, the dysfunctional status of platelets in DM patients may contribute to the enhanced atherothrombotic risk of these patients. It has been proposed that reduced sensitivity to aspirin in diabetic patients might be owing to accelerated thrombopoiesis,(DiMinno, Silver et al. 1986) or to reduced platelet permeability to aspirin caused by membrane glycosylation.(Winocour, Watala et al. 1992)

The mechanisms that lead to increased platelet reactivity observed in patients with DM can be grouped together into the following aetiopathogenic categories: a) hyperglycaemia, b) insulin deficiency and resistance, c) associated metabolic conditions, and d) other cellular abnormalities (as shown in Figure 2). Poor glucose control and body weight are also proposed to contribute to aspirin resistance. (Watala, Golanski et al. 2004; Singla, Antonino et al. 2009) Poorly controlled patients with diabetes have the greatest platelet reactivity. High platelet reactivity was defined as >46% for 5 micromol/L ADP-induced and >59% for 20 micromol/L ADP-induced platelet activity and may require alternative antiplatelet strategies, and further clinical investigations are warranted.(Singla, Antonino et al. 2009)

Platelets: Platelets play a key role in the development of atherothrombotic events. Platelets are essential for primary hemostasis and repair of the endothelium, but they also play a key role in the development of acute coronary syndromes and contribute to cerebrovascular events. Platelet adhesion is an essential function in response to vascular injury and is generally viewed as the first step during which single platelets bind through specific membrane receptors to cellular and extracellular matrix constituents of the vessel wall and tissues. Beyond acute activation as a consequence of vascular injury, circulating platelets are actively involved in all phases of the atherogenetic process, from atherosclerotic plaque formation to plaque inflammation and rupture. (Davi and Patrono 2007; Ruggeri and Mendolicchio 2007; Langer and Gawaz 2008)

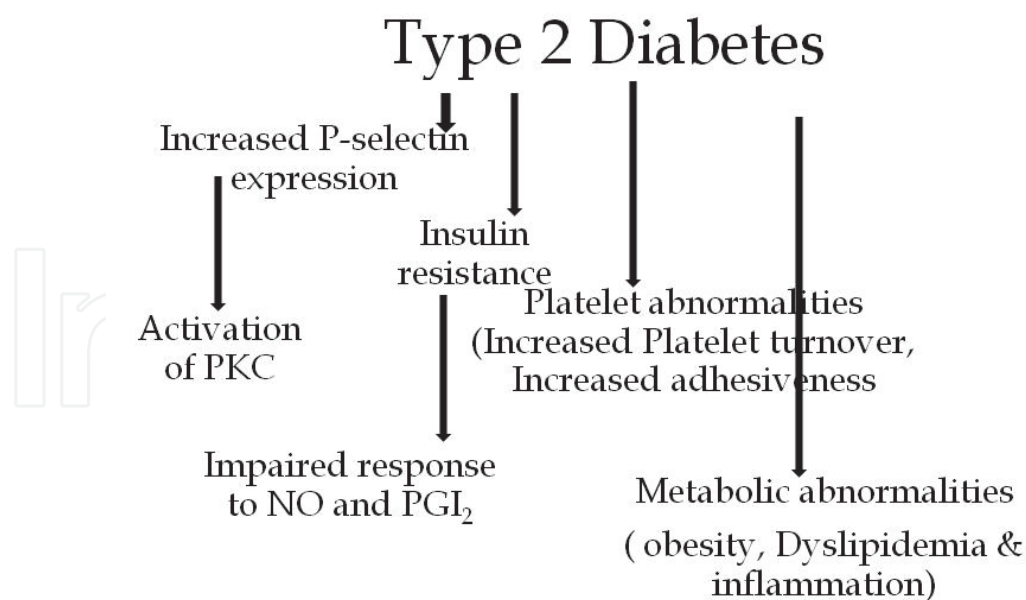


Figure 2 Mechanisms that lead to Platelet dysfunction in diabetes

Fig. 2. Mechanisms that lead to Platelet dysfunction in diabetes

Mechanism of aspirin resistance in diabetes: Increased platelet reactivity observed in patients with DM may be secondary to several factors. Acute hyperglycemia as well as poor control of diabetes is associated with increased platelet reactivity. Comparative studies of patients with good glycemic control show they have better response to aspirin compared to the patients with poor glycemic control. Although this might implicate that better glucose control leads to less incidence of aspirin non-responsiveness, the clinical significance of such findings should be carefully inspected, since in 2 of the largest trials assessing the role of aspirin on primary prevention of cardiovascular events in patients with type 2 diabetes, low-dose aspirin did not decrease the risk of cardiovascular events when compared to placebo. Insulin resistance, TNF- α and IL-6 are shown to affect platelet reactivity. The clinical determinants that help identify aspirin resistance in diabetes are suggested to be CVD, microalbuminuria, poor diabetes control, and increased waist circumference. (Yassine, Davis-Gorman et al. 2010)

Platelet abnormalities in Type 2 diabetes: The abnormalities described in patients with diabetes are listed here.

1. Increased production of thromboxane A₂ from arachidonic acid. (Halushka, Mayfield et al. 1981; Halushka, Rogers et al. 1981)
2. Increase in platelet-dependent thrombin generation.
3. Increased expression of platelet surface adhesion molecules such as CD31, CD49b, CD62P, and CD63, leading to increased platelet activation.
4. Increased platelet surface receptors such as P-selectin, GP Ib, and GP IIb/IIIa. (Gresele, Guglielmini et al. 2003)
5. Reduced vascular synthesis of the anti-aggregants PGI₂ and NO, shifting balance towards aggregation and vasoconstriction.
6. Disordered calcium homeostasis that affects platelet shape change, secretion, aggregation, and thromboxane formation (Halushka, Mayfield et al. 1981; Halushka, Rogers et al. 1981).

7. Decreased platelet insulin receptor number and affinity and failure to reduce platelet responses to the agonists ADP, collagen, thrombin, arachidonate, and PAF.
8. Glycation of circulating LDL rendering platelets hypersensitive. Glycated LDL causes an increase in intracellular calcium concentration and platelet NO production, as well as inhibition of the platelet membrane Na⁺/K⁺-ATPase activity.

Key: GP = glycoprotein; PGI₂ = prostacyclin; NO = nitric oxide; ADP = adenosine diphosphate; PAF = platelet-activating factor; LDL= low-density lipoprotein; Na⁺/K⁺-ATPase = Na⁺/K⁺-adenosine triphosphatase

An accelerated platelet turnover represented by the presence of a higher number of reticulated platelets has been observed in patients with DM.(Guthikonda, Alviar et al. 2008) The dysfunctional status of platelets in patients with DM may contribute to the enhanced atherothrombotic risk of these patients. Platelets obtained from diabetic patients show increased adhesiveness, hyperfunction both spontaneous as well as in response to agonists. These observed hyperfunctions are attributed to increased expression, activation or abundance of surface membrane receptors for agonists as well as cell matrix components, increased binding of fibrinogen, altered membrane fluidity, changes in activation mechanisms and signaling pathways. Changes in platelets in diabetes include enhanced GP receptor binding of agonists and adhesive proteins; decreased membrane fluidity; enhanced activation of the arachidonic acid pathway resulting in increased TxA₂ formation; altered PI turnover leading to changes in diacylglycerol and inositol triphosphate production, calcium mobilization, and protein phosphorylation; impaired responses to antiaggregants resulting in decreased PGI₂ receptor binding, cyclic nucleotide production and cyclic nucleotide-dependent protein phosphorylation; and reduced sensitivity to the inhibitory actions of insulin. These changes translate to impaired PGI₂ stimulation of cAMP and blindness to the inhibitory actions of both PGI₂ and NO. Platelet dysfunction coupled with decreased endothelial production of these antiaggregatory agents conspire to amplify the risk of CVD in patients with type 2 diabetes.(Vinik, Erbas et al. 2001)

Metabolic control and platelet reactivity

In the early 1960s Bridges *et al* showed that both *in vitro* as well as *in vivo* administration of glucose increased platelet stickiness.(Bridges, Dalby et al. 1965) Combined hyperinsulinemia and hyperglycemia in healthy volunteers increased circulating tissue factor, plasma thrombin generation, and coagulation factors VII and VIII activities, suggesting that the coagulation system had been activated.(Boden and Rao 2007) Chronic hyperglycemia has been identified as a causal factor for *in vivo* platelet activation and platelet hyperreactivity in DM patients as evidenced by enhanced TXA₂ biosynthesis.(Davi, Gresele et al. 1997; Davi, Ciabattini et al. 1999) Of note, T2DM platelets are characterized by enhanced thromboxane biosynthesis and tight metabolic control, shown to lead to a reduction of thromboxane levels.(Davi, Catalano et al. 1990) Acute, short-term hyperglycemia induces an increased activation of platelets exposed to high shear stress conditions *in vitro* (filtration method) or *in vivo* (bleeding time). *In vivo* platelet activation is reflected by an increased urinary excretion of 11-dehydro-TxB₂ (2).(Gresele, Guglielmini et al. 2003) This acute hyperglycemia-induced enhancement of platelet activation is resistant to aspirin: an NO -donating agent suppresses it.(Gresele, Marzotti et al. 2010) LDL, a circulating complex of lipids and proteins that is increased in hypercholesterolemia, enhances platelet function and sensitizes platelets via binding of apoB-100 to a receptor on the platelet membrane and via transfer of lipids to the platelet membrane.(Relou, Hackeng et al. 2003) Hyperglycemia also induces an increase

in nonenzymatic glycation of LDL (glycLDL), which renders them more susceptible to oxidative stress.(Angiolillo 2007)

Insulin and platelet reactivity

The T2DM patients had platelet aggregation and shear-induced platelet function significantly increased compared to nondiabetic patients using all assays. Platelet aggregation was increased in ITDM (n = 68) compared with NITDM (n = 133) patients after P2Y₁₂-specific stimuli. Insulin treatment was the strongest predictor of ADP-induced aggregation. Platelet function profiles were similar between ITDM and NITDM using assays non-specific to the P2Y₁₂ pathway. Platelet dysfunction was independent of glycemic control and inflammatory status.(Angiolillo, Bernardo et al. 2006)

NF- κ B is a transcription factor that stimulates numerous genes and activates inflammatory responses related to insulin resistance. Salicylates inhibit NF κ B activation. This inhibition was shown to be associated with a significant decrease in IL-6 and TNF- α release, mediated through inhibition of IKK β activity.

Platelet activity measures

A major urinary metabolite of thromboxane A₂ synthesized from extra renal sources is 11-dehydro thromboxane B₂. A major portion of this metabolite is believed to come from the platelet, but there are additional cellular sources. In the Heart Outcomes Prevention Evaluation (HOPE) trial, patients whose urinary 11-dehydro thromboxane B₂ levels were in the highest quartile had an odds ratio of 2 for having a myocardial infarction and an odds ratio of 3.5 for a risk of having a cardiovascular-related death compared to those patients in the lowest quartile. Serum aspirin esterase (AE) activity may account for part of aspirin pharmacokinetics and has been proposed as one source of variation in aspirin effectiveness.(Adebayo, Williams et al. 2007) Elevated MPV values are associated with a shortened bleeding time and increased thromboxane B₂ plasma levels. Thus, MPV could be considered an indicator of platelet function.(Vizioli, Muscari et al. 2009) Diabetic patients with coronary heart disease have significantly higher MPV values compared to control patients.(Tavil, Sen et al. 2010)

Methods that directly measure the capacity of platelets to synthesize TxA₂ are certainly preferable. Of these, the urinary levels of the TxB₂ metabolite, 11-dehydrothromboxane B₂, represent a time-integrated index of TxA₂ biosynthesis *in vivo*.(Patrono, Ciabattini et al. 1986) 11-dehydro-TxB₂ is the most abundant urinary metabolite of TxB₂. Detection in the urine of this metabolite, which is not formed in the kidney, reflects systemic TxA₂ formation, which largely, albeit not exclusively, occurs in the platelets. It has been calculated that about 30% of the urinary metabolite derives from extra-platelet sources, as in inflammatory diseases, the contribution of extra-platelet sources may increase in atherosclerosis and inflammatory conditions.(Catella and FitzGerald 1987) Test measures consider the end products of the TxA₂ pathway such as serum TxB₂, or urine 11-dehydro-TxB₂, for assessing aspirin activity.(Eikelboom, Hirsh et al. 2002) In fact, these 2 tests may better reflect the amount of TxA₂ derived from sources other than platelets such as macrophages and monocytes, and on the COX-2 linked pathway of arachidonic acid, which is blocked by aspirin at very high doses (1200 mg/ day) only.(Bucchi, Bodzenta et al. 1986) Urinary 11-dehydro- TxB₂ concentration is affected by renal production of this substance. However, measurement of this metabolite is still commonly used in trials assessing aspirin resistance, due to its low cost and ease of measurement.(Eikelboom, Hirsh et al. 2002)

In aspirin-treated patients, elevated urinary 11-dehydro thromboxane B₂ levels identify patients who are relatively resistant to aspirin and who may benefit from additional antiplatelet therapies or treatments that more effectively block *in vivo* thromboxane production or activity.(Eikelboom, Hirsh et al. 2002)

Clinical implications

The clinical implication of aspirin resistance as measured *in vitro* by the inability of aspirin to reduce platelet activation and aggregation by failure to suppress the platelet production of TXA has not yet been elucidated via prospective trials that have controlled for confounders, such as hypertension, and dyslipidemia. Large meta-analyses have found low-dose aspirin to be as effective as high-dose aspirin in preventing vascular events, making a dose-dependent improvement in laboratory response clinically irrelevant. Causes of aspirin resistance include poor compliance, inadequate dose, drug interactions, genetic polymorphisms of cyclooxygenase-1, increased platelet turnover, and upregulation of nonplatelet pathways of thromboxane production. At present, there is no standardized approach to the diagnosis and no proven effective treatment for aspirin resistance. Further research exploring the mechanisms of aspirin resistance is needed in order to better define aspirin resistance, as well as to develop a standardized laboratory test that is specific and reliable, and can correlate with the clinical risk of vascular events.

Management

Factors that need to be considered in the approach to patients with suspected treatment failure include: compliance with aspirin use, ensure the optimal dose and drug form (avoid use of enteric-coated aspirin formulations), evaluate concomitant infections or inflammatory conditions, and assess possible drug-drug interactions. Several approaches have been evaluated for treatment failure and some of these approaches are based on laboratory testing for evidence of resistance. The role of testing in directing management is still controversial. Management strategies are currently limited to dosing alteration and introduction of other anti platelet agents. However, these measures have not met the expected efficacy or safety.

Increased aspirin doses: The idea of increasing aspirin dose has been assayed in many studies, as there is some evidence that response to aspirin may be dose dependent.(ten Berg, Gerritsen et al. 2002) Because patients with diabetes exhibit a higher prevalence of aspirin resistance on standard aspirin doses (81 mg/day) and have significantly higher ADP- and collagen-induced platelet aggregation, 11-dehydro- TxB₂ levels and the aspirin resistance may be partially overcome by higher aspirin doses.(DiChiara, Bliden et al. 2007) Laboratory and genetic inconsistency, as well as dose dependence, is seen when agonists other than arachidonic acid (the most specific in assessing aspirin resistance), such as ADP, collagen, and epinephrine, are used for *in vitro* assessment of platelet inhibition by aspirin.(McCabe, Harrison et al. 2005; Assadian, Lax et al. 2007; Gurbel, Bliden et al. 2007). The Clopidogrel vs Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial compared the efficacy for secondary prevention of clopidogrel (75 mg daily) versus aspirin (325 mg daily) in a high-risk population (n = 19,185) consisting of patients with a history of recent MI, recent ischaemic stroke, or established peripheral artery disease.(Diener, Bogousslavsky et al. 2004) The benefit of clopidogrel therapy was higher (15.6% vs. 17.7%; *P* = 0.042) in DM patients, despite the increased incidence of ischaemic outcomes in this subgroup. The absolute reduction in events was highest among diabetic patients requiring insulin therapy.(Diener,

Bogousslavsky et al. 2004) In large, well-designed multicentre trials, such as CURE, COMMIT, and CLARITY-TIMI 28, the addition of clopidogrel to aspirin therapy improved outcomes in patients with acute coronary syndromes.(Plosker and Lyseng-Williamson 2007) *Addition of other antiplatelet agents:* Dual antiplatelet therapy using acetylsalicylic acid and clopidogrel is of great importance following coronary stenting. Clopidogrel, a thienopyridine, works by irreversibly inhibiting ADP binding to the P2Y₁₂ receptors on the platelet surface, and ultimately interfering with platelet-fibrinogen binding. The PLATO (PLATelet Inhibition and Patient Outcomes) study has shown that ticagrelor, an agent with a similar mechanism of action to clopidogrel and still in phase III trials, showed a significant reduction of a combined endpoint of cardiovascular death, myocardial infarction, or stroke as compared with clopidogrel (hazard ratio 0.84; 95%CI 0.75, 0.94; $P = 0.0025$). (Cannon, Harrington et al. 2010) In the subgroup of patients undergoing coronary artery bypass graft (CABG) within 7 days after the last study drug intake, ticagrelor compared with clopidogrel was associated with a substantial reduction in total and cardiovascular mortality without excess risk of CABG-related bleeding. (Held, Asenblad et al. 2011) Addition of dipyridamole to aspirin can lead to significant platelet inhibition in aspirin-resistant patients. The addition of dipyridamole to aspirin appears to be more effective than aspirin alone in the prevention of secondary vascular events in stroke patients and does not cause an increase in haemorrhagic events compared to aspirin alone in an identical dose. (Diener, Darius et al. 2001; Diener, Darius et al. 2001) There is also a suggestion that dipyridamole may partially compensate for aspirin resistance in patients with ischaemic stroke via an alternative antithrombotic mechanism. (Serebruany, Malinin et al. 2005; Serebruany, Malinin et al. 2006) In a study to determine whether treatment with dipyridamole or clopidogrel, in addition to aspirin, is more effective at reducing embolization and transient ischemic attacks, King and associates have shown that both dipyridamole and clopidogrel reduced embolization to a similar extent. (King, Bath et al. 2011) Other antiplatelet agents that may be more potent via alternative pathways are under investigation.

Statins to improve aspirin resistance: There is evidence that statins may be useful in treating aspirin resistance. Tirnaksiz and associates reported that in a study of patients with stable coronary artery disease, 11.2% were found to be aspirin resistant as measured by PFA-100, with a closure time of <186 seconds with collagen/adrenaline cartridges. (Tirnaksiz, Pamukcu et al. 2009) After 3 months of statin therapy (atorvastatin 10 mg/day), 65% of the aspirin-resistant patients became aspirin sensitive by PFA-100 measurements ($P < 0.0001$). (Tirnaksiz, Pamukcu et al. 2009) Tekten and his colleagues have shown that statins reduced platelet aggregation. (Tekten, Ceyhan et al. 2004)

Another recommendation is that because saturated fat ingestion increases *in vivo* thromboxane production despite aspirin therapy, diabetic patients on ASA therapy should have low dietary saturated fat intake and aggressive lipid management. (Yassine, Davis-Gorman et al. 2010)

4. Conclusion

Aspirin is recommended for primary prevention and secondary prevention of CVD in patients with type 2 diabetes. Aspirin resistance is common in patients with type 2 diabetes. Further studies are required to answer the question, will improving glycemic control in patients with poor glycemic control cause a change in responsiveness to aspirin? The relationship of the adipokines TNF- α and IL-6 to aspirin non-responsiveness needs

further evaluation. Prospective randomized trials are needed to prove the clinical benefits of adapting the dosing of clopidogrel or switching to alternative compounds in high-risk patients with impaired antiplatelet effectiveness according to the result of platelet function assays.

5. References

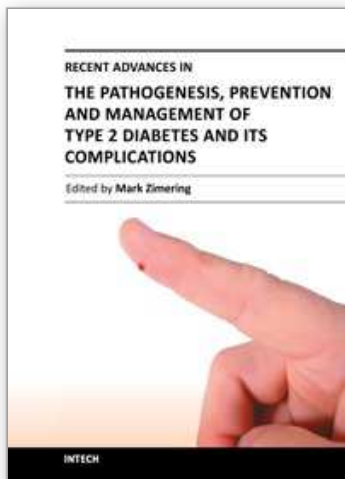
- (1994). "Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration." *BMJ* 308(6921): 81-106.
- (2002). "Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients." *BMJ* 324(7329): 71-86.
- Adebayo, G. I., J. Williams, et al. (2007). "Aspirin esterase activity - Evidence for skewed distribution in healthy volunteers." *Eur J Intern Med* 18(4): 299-303.
- Angiolillo, D. J. (2007). "Antiplatelet therapy in type 2 diabetes mellitus." *Curr Opin Endocrinol Diabetes Obes* 14(2): 124-131.
- Angiolillo, D. J., E. Bernardo, et al. (2006). "Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment." *J Am Coll Cardiol* 48(2): 298-304.
- Assadian, A., J. Lax, et al. (2007). "Aspirin resistance among long-term aspirin users after carotid endarterectomy and controls: flow cytometric measurement of aspirin-induced platelet inhibition." *J Vasc Surg* 45(6): 1142-1147; discussion 1147.
- Baigent, C., L. Blackwell, et al. (2009). "Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials." *Lancet* 373(9678): 1849-1860.
- Belch, J., A. MacCuish, et al. (2008). "The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease." *BMJ* 337: a1840.
- Ben-Dor, I., N. S. Kleiman, et al. (2009). "Assessment, mechanisms, and clinical implication of variability in platelet response to aspirin and clopidogrel therapy." *Am J Cardiol* 104(2): 227-233.
- Boden, G. and A. K. Rao (2007). "Effects of hyperglycemia and hyperinsulinemia on the tissue factor pathway of blood coagulation." *Curr Diab Rep* 7(3): 223-227.
- Bridges, J. M., A. M. Dalby, et al. (1965). "An Effect of D-Glucose on Platelet Stickiness." *Lancet* 1(7376): 75-77.
- Bucchi, F., A. Bodzenta, et al. (1986). "Effects of 1 gram oral or intravenous aspirin on urinary excretion of thromboxane B2 and 6-keto-PGF1 alpha in healthy subjects." *Prostaglandins* 32(5): 691-701.
- Calvin, A. D., N. R. Aggarwal, et al. (2009). "Aspirin for the primary prevention of cardiovascular events: a systematic review and meta-analysis comparing patients with and without diabetes." *Diabetes Care* 32(12): 2300-2306.
- Cannon, C. P., R. A. Harrington, et al. (2010). "Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study." *Lancet* 375(9711): 283-293.

- Carr, M. E. (2001). "Diabetes mellitus: a hypercoagulable state." *J Diabetes Complications* 15(1): 44-54.
- Catella-Lawson, F., M. P. Reilly, et al. (2001). "Cyclooxygenase inhibitors and the antiplatelet effects of aspirin." *N Engl J Med* 345(25): 1809-1817.
- Catella, F. and G. A. FitzGerald (1987). "Paired analysis of urinary thromboxane B2 metabolites in humans." *Thromb Res* 47(6): 647-656.
- Cox, D., A. O. Maree, et al. (2006). "Effect of enteric coating on antiplatelet activity of low-dose aspirin in healthy volunteers." *Stroke* 37(8): 2153-2158.
- Davi, G., I. Catalano, et al. (1990). "Thromboxane biosynthesis and platelet function in type II diabetes mellitus." *N Engl J Med* 322(25): 1769-1774.
- Davi, G., G. Ciabattini, et al. (1999). "In vivo formation of 8-iso-prostaglandin f2alpha and platelet activation in diabetes mellitus: effects of improved metabolic control and vitamin E supplementation." *Circulation* 99(2): 224-229.
- Davi, G., P. Gresele, et al. (1997). "Diabetes mellitus, hypercholesterolemia, and hypertension but not vascular disease per se are associated with persistent platelet activation in vivo. Evidence derived from the study of peripheral arterial disease." *Circulation* 96(1): 69-75.
- Davi, G. and C. Patrono (2007). "Platelet activation and atherothrombosis." *N Engl J Med* 357(24): 2482-2494.
- De Berardis, G., M. Sacco, et al. (2007). "Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins." *Trials* 8: 21.
- De Berardis, G., M. Sacco, et al. (2009). "Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials." *BMJ* 339: b4531.
- DiChiara, J., K. P. Bliden, et al. (2007). "The effect of aspirin dosing on platelet function in diabetic and nondiabetic patients: an analysis from the aspirin-induced platelet effect (ASPECT) study." *Diabetes* 56(12): 3014-3019.
- Diener, H. C., J. Bogousslavsky, et al. (2004). "Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial." *Lancet* 364(9431): 331-337.
- Diener, H. C., H. Darius, et al. (2001). "Cardiac safety in the European Stroke Prevention Study 2 (ESPS2)." *Int J Clin Pract* 55(3): 162-163.
- Diener, H. C., H. Darius, et al. (2001). "[Does early high dosage dipyridamole in prevention of secondary stroke induce cardiac events?]." *Z Kardiol* 90(5): 348-351.
- DiMinno, G., M. J. Silver, et al. (1986). "Trial of repeated low-dose aspirin in diabetic angiopathy." *Blood* 68(4): 886-891.
- Eikelboom, J. W., J. Hirsh, et al. (2002). "Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events." *Circulation* 105(14): 1650-1655.
- Frolich, J. C. (1997). "A classification of NSAIDs according to the relative inhibition of cyclooxygenase isoenzymes." *Trends Pharmacol Sci* 18(1): 30-34.

- Gresele, P., G. Guglielmini, et al. (2003). "Acute, short-term hyperglycemia enhances shear stress-induced platelet activation in patients with type II diabetes mellitus." *J Am Coll Cardiol* 41(6): 1013-1020.
- Gresele, P., S. Marzotti, et al. (2010). "Hyperglycemia-induced platelet activation in type 2 diabetes is resistant to aspirin but not to a nitric oxide-donating agent." *Diabetes Care* 33(6): 1262-1268.
- Gurbel, P. A., K. P. Bliden, et al. (2007). "Evaluation of dose-related effects of aspirin on platelet function: results from the Aspirin-Induced Platelet Effect (ASPECT) study." *Circulation* 115(25): 3156-3164.
- Guthikonda, S., C. L. Alviar, et al. (2008). "Role of reticulated platelets and platelet size heterogeneity on platelet activity after dual antiplatelet therapy with aspirin and clopidogrel in patients with stable coronary artery disease." *J Am Coll Cardiol* 52(9): 743-749.
- Guthikonda, S., E. I. Lev, et al. (2007). "Reticulated platelets and uninhibited COX-1 and COX-2 decrease the antiplatelet effects of aspirin." *J Thromb Haemost* 5(3): 490-496.
- Halushka, M. K. and P. V. Halushka (2002). "Why are some individuals resistant to the cardioprotective effects of aspirin? Could it be thromboxane A₂?" *Circulation* 105(14): 1620-1622.
- Halushka, P. V., R. Mayfield, et al. (1981). "Increased platelet arachidonic acid metabolism in diabetes mellitus." *Diabetes* 30(Suppl 2): 44-48.
- Halushka, P. V., R. C. Rogers, et al. (1981). "Increased platelet thromboxane synthesis in diabetes mellitus." *J Lab Clin Med* 97(1): 87-96.
- Held, C., N. Asenblad, et al. (2011). "Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial." *J Am Coll Cardiol* 57(6): 672-684.
- King, A., P. M. Bath, et al. (2011). "Clopidogrel versus dipyridamole in addition to aspirin in reducing embolization detected with ambulatory transcranial Doppler: a randomized trial." *Stroke* 42(3): 650-655.
- Langer, H. F. and M. Gawaz (2008). "Platelet-vessel wall interactions in atherosclerotic disease." *Thromb Haemost* 99(3): 480-486.
- McCabe, D. J., P. Harrison, et al. (2005). "Assessment of the antiplatelet effects of low to medium dose aspirin in the early and late phases after ischaemic stroke and TIA." *Platelets* 16(5): 269-280.
- Modica, A., F. Karlsson, et al. (2007). "Platelet aggregation and aspirin non-responsiveness increase when an acute coronary syndrome is complicated by an infection." *J Thromb Haemost* 5(3): 507-511.
- Ogawa, H., M. Nakayama, et al. (2008). "Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial." *JAMA* 300(18): 2134-2141.
- Patrono, C., G. Ciabattoni, et al. (1986). "Estimated rate of thromboxane secretion into the circulation of normal humans." *J Clin Invest* 77(2): 590-594.
- Pignone, M., M. J. Alberts, et al. (2010). "Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert

- consensus document of the American College of Cardiology Foundation." *Diabetes Care* 33(6): 1395-1402.
- Plosker, G. L. and K. A. Lyseng-Williamson (2007). "Clopidogrel: a review of its use in the prevention of thrombosis." *Drugs* 67(4): 613-646.
- Preis, S. R., S. J. Hwang, et al. (2009). "Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005." *Circulation* 119(13): 1728-1735.
- Relou, I. A., C. M. Hackeng, et al. (2003). "Low-density lipoprotein and its effect on human blood platelets." *Cell Mol Life Sci* 60(5): 961-971.
- Ruggeri, Z. M. and G. L. Mendolicchio (2007). "Adhesion mechanisms in platelet function." *Circ Res* 100(12): 1673-1685.
- Serebruany, V., A. Malinin, et al. (2006). "Dipyridamole decreases protease-activated receptor and annexin-v binding on platelets of post stroke patients with aspirin nonresponsiveness." *Cerebrovasc Dis* 21(1-2): 98-105.
- Serebruany, V. L., A. I. Malinin, et al. (2005). "Effects of clopidogrel and aspirin in combination versus aspirin alone on platelet activation and major receptor expression in patients after recent ischemic stroke: for the Plavix Use for Treatment of Stroke (PLUTO-Stroke) trial." *Stroke* 36(10): 2289-2292.
- Singla, A., M. J. Antonino, et al. (2009). "The relation between platelet reactivity and glycemic control in diabetic patients with cardiovascular disease on maintenance aspirin and clopidogrel therapy." *Am Heart J* 158(5): 784 e781-786.
- Tavil, Y., N. Sen, et al. (2010). "Coronary heart disease is associated with mean platelet volume in type 2 diabetic patients." *Platelets* 21(5): 368-372.
- Tekten, T., C. Ceyhan, et al. (2004). "The effect of atorvastatin on platelet function in patients with coronary artery disease." *Acta Cardiol* 59(3): 311-315.
- ten Berg, J. M., W. B. Gerritsen, et al. (2002). "High-dose aspirin in addition to daily low-dose aspirin decreases platelet activation in patients before and after percutaneous coronary intervention." *Thromb Res* 105(5): 385-390.
- Tirnaksiz, E., B. Pamukcu, et al. (2009). "Effect of high dose statin therapy on platelet function; statins reduce aspirin-resistant platelet aggregation in patients with coronary heart disease." *J Thromb Thrombolysis* 27(1): 24-28.
- Vinik, A. I., T. Erbas, et al. (2001). "Platelet dysfunction in type 2 diabetes." *Diabetes Care* 24(8): 1476-1485.
- Vizioli, L., S. Muscari, et al. (2009). "The relationship of mean platelet volume with the risk and prognosis of cardiovascular diseases." *Int J Clin Pract* 63(10): 1509-1515.
- Watala, C., J. Golanski, et al. (2004). "Reduced sensitivity of platelets from type 2 diabetic patients to acetylsalicylic acid (aspirin)-its relation to metabolic control." *Thromb Res* 113(2): 101-113.
- Winocour, P. D., C. Watala, et al. (1992). "Decreased platelet membrane fluidity due to glycation or acetylation of membrane proteins." *Thromb Haemost* 68(5): 577-582.
- Yassine, H. N., G. Davis-Gorman, et al. (2010). "Clinical determinants of aspirin resistance in diabetes." *Diabetes Res Clin Pract* 90(1): e19-21.
- Yassine, H. N., G. Davis-Gorman, et al. (2010). "Effect of glucose or fat challenge on aspirin resistance in diabetes." *Int J Endocrinol* 2010: 820876.

- Younis, N., S. Williams, et al. (2010). "Role of aspirin in the primary prevention of cardiovascular disease in diabetes mellitus: a meta-analysis." *Expert Opin Pharmacother* 11(9): 1459-1466.
- Zhang, C., A. Sun, et al. (2010). "Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis." *Diabetes Res Clin Pract* 87(2): 211-218.
- Zimmermann, N., M. Kurt, et al. (2005). "Is cardiopulmonary bypass a reason for aspirin resistance after coronary artery bypass grafting?" *Eur J Cardiothorac Surg* 27(4): 606-610.
- Zimmermann, N., A. Wenk, et al. (2003). "Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery." *Circulation* 108(5): 542-547.



Recent Advances in the Pathogenesis, Prevention and Management of Type 2 Diabetes and its Complications

Edited by Prof. Mark Zimring

ISBN 978-953-307-597-6

Hard cover, 442 pages

Publisher InTech

Published online 29, August, 2011

Published in print edition August, 2011

Type 2 diabetes “œmellitus” affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Subhashini Yaturu and Shaker Mousa (2011). Diabetes and Aspirin Resistance, Recent Advances in the Pathogenesis, Prevention and Management of Type 2 Diabetes and its Complications, Prof. Mark Zimring (Ed.), ISBN: 978-953-307-597-6, InTech, Available from: <http://www.intechopen.com/books/recent-advances-in-the-pathogenesis-prevention-and-management-of-type-2-diabetes-and-its-complications/diabetes-and-aspirin-resistance>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](https://creativecommons.org/licenses/by-nc-sa/3.0/), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen