Review Article

Off-Label Uses of Medications

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ABSTRACT

The term Off-Label Drug Use (OLDU) is utilized broadly in the medical literature. It is a polarizing term since it may be related with incredible advantage or harm to patients. OLDU is defined as drug uses that not included in the indications or dosage regimens listed in the Food and Drug Administration (FDA)-approved labeling. There are many drugs with various off-label uses such as indomethacin that considered as effective alternative for surgery in neonates suffering from patent ductus arteriosus. Using of atorvastatin in Chronic Heart Failure (CHF) can be one of the most important off-label use due to its pleiotropic action also it can show significant reduction in the frequency of hospitalization due to CHF exacerbation. Off-label use of anti-platelet agents especially aspirin, have since quite a while ago filled in as the foundation in the management of patients with Peripheral Vascular Disease PVD and its recommended by both American College of Cardiology (ACC)/American Heart Association (AHA).

Keywords: Off-label drug use; Indomethacin; Atorvastatin; Aspirin

Introduction

The term Off-label Drug Use (OLDU) is utilized broadly in the medical literature. It is a polarizing term since it may be related with incredible advantage or harm to patients [1]. OLDU is defined as drug uses that not included in the indications or dosage regimens listed in the Food and Drug Administration (FDA)-approved labeling. Unlabeled use remembers the utilization of a drug product in doses, patient populations, indications, or routes of administration that are not reflected in FDA-approved product labeling. OLDU use is regular in numerous clinical areas such as psychiatry, pediatrics, oncology and intensive care unit. Sometimes off-label drug use is the only option available for the patient's treatment [2]. When a drug is available on the market, all the information about it depends on pre-marketing studies: during the development of the molecule, experimental studies on its effect sand toxicity are conducted in animals (pre-clinical studies). If no inadmissible toxic effects are watched, the first clinical trials in humans are conducted. These are termed phase I, II, and III studies, which investigate aspects of the pharmacokinetics, toxicity, and efficacy in humans. In clinical trials, several factors may meddle with the outcomes, such as inclusion and exclusion criteria, sample sizes, and apparently ethical, completely defended in the beginning of the assessment of a new drug, preclude scientific study in specific populaces [3]. Children and pregnant women are well on the way to be prescribed off-label drugs because most trials are never acted in this subset of population for ethical reasons. Offlabel use of drugs, such as antibiotics, is life-saving in children and pregnant women. Numerous diseases do not have approved drugs, partly because the diseases are rare or conducting clinical trials and marketing the drug for such diseases may not be gainful [4]. Off-label use is considered as legal except if it disregards ethical guidelines or other safety regulations. It is ethical and justifiable to use drugs in an off-label fashion provided such use depends on sound data and evidence. Several prescription drugs and over-the-counter drugs are used in off-label ways to great effect [5]. The main issue with off-label use is that there is insufficient information

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support the use of the drug. Whereas on-label use is based on scientifically valid and statistically significant evidence indicating that the potential benefits of a drug. On the other hand, off-label drug use is a vital tool for treat various diseases. It allows physicians to treat patients for whom off-label drug use may be the only therapy available, including patients for whom on-label use has failed [6].

■ Examples of Off-label Uses of Drugs

■ Indomethacin

Indomethacin is a Non-steroidal Anti-inflammatory Drug (NSAID) that displays antipyretic and pain relieving properties. Its mechanism of action, like that of other non-steroidal anti-inflammatory drugs [7]. IV form of indomethacin can be used as alternative to surgery for closure of Patent Ductus Arteriosus (PDA) in neonates as off-label use [8]. Not-with-standing, indomethacin can cause several side effect such as increasing the risk of developing necrotizing enterocolitis and renal impairment, so the safer alternative to indomethacin is ibuprofen was approved for the treatment of PDA. Ibuprofen has likewise as of late been associated with spontaneous intestinal perforation, leading to vulnerability over which drug has the better safety profile. However, spontaneous intestinal perforation due to ibuprofen forced many physician to using indomethacin for treatment of PDA [9].

■ Atorvastatin

It Inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme which is responsible for catalyzing an early step in the synthesis of cholesterol. Its therapeutic effects include: Lowering of total and Low Density Lipoprotein (LDL) cholesterol and triglycerides. Slightly increases High Density Lipoprotein (HDL) cholesterol [10]. There is a wide range off-label uses of atorvastatin:

Rheumatoid Arthritis (RA): The disease is also associated with an increased risk of death from cardiovascular disease, specifically quickened atherogenesis. Similarities exist between inflammation present in atherogenic lesions in the cardiovascular vessel and inflammation found in the chronic synovitis of RA. Thus, the use of statins to improve markers of cardiovascular disease, as well as to promote control of RA, has been suggested. Atorvastatin may influence markers for cardiac disease, as well as some parameters for clinical inflammatory changes, in patients with RA. However, larger, controlled trials with stricter controls for disease state assessment and adjunctive therapy are required before this treatment is set up as viable [11].

Prevention of Atrial Fibrillation (AF): Atorvastatin treatment is essentially associated with a decreased risk of AF in selected population. Ongoing studies propose that those with higher CHADS2 and CHA2DS2VASc scores will benefit most from statin use for the prevention of AF. Statins give restricted advantages in primary prevention of AF in patients with low CHADS2 and CHA2DS2-VASc scores. The CHADS2 and CHA2DS2VASc scoring are helpful for recognizing the patients who will benefit most from statins for AF prevention [12].

Diabetic Retinopathy (DR): use of atorvastatin could reduce the risk in progression of DR but they did not have protective effects on vision acuity and hard exudates. These findings provided important evidence that intensive control of blood lipid levels at early stage of DR potentially represented a novel therapeutic strategy for delaying DR development [13].

Chronic Heart Failure (CHF): The benefit of using atorvastatin in CHF likely result from its pleiotropic action, including the improvement of endothelial function, the inhibition of neurohormonal activation, and the inhibition of proinflammatory activation. Meta-analysis of several clinical studies show that patients suffering from CHF and using atorvastatin leading to reducing the rates of all-cause cardiovascular mortality and sudden cardiac death. Also there is significant reduction in the frequency of hospitalization due to CHF exacerbation among the patients using atorvastatin [14].

■ Aspirin

Aspirin consider as one of the non-steroidal anti-inflammatory drugs (NSAIDs), that has salicylic acid as the active agent. The mechanism of action of aspirin mainly by inhibition of cyclooxygenase, but also there is characteristic effect for aspirin due to its reactive acetate group [15]. There are many off- label uses of aspirin like:

Esophageal cancer: condition associated with increased risk for esophageal cancer, aspirin use was associated with reduced risk of esophageal adenocarcinoma or high grade dysplasia [16].

Colorectal cancer: using aspirin at low dose for patients suffering from colorectal cancer can decrease the risk of Stages B-D colorectal cancer recommending a role for low-dose aspirin in the progression of established colorectal cancer. The hypothesis that aspirin has a chemo-preventive effect early in the adenoma sequence in colorectal cancer development [17].

Non-cardiac surgery and most intrusive strategies increase the risk of stent thrombosis, particularly when the procedure is performed before endothelial re-growth is established. This happens primarily because antiplatelet therapy is often discontinued in the perioperative period and because surgery creates a pro-thrombotic state, leading to most cases of stent thrombosis happening in the quick or early postoperative period because this antiplatelet therapy like aspirin should be used in cardiac postoperative [18].

Peripheral Vascular Disease (PVD): Anti-platelet agents especially aspirin, have since quite a while ago filled in as the foundation in the management of patients with PVD. Both American College of Cardiology (ACC)/ American Heart Association (AHA) was endorsed the use of aspirin in the treatment of PVD, PVD guidelines in both symptomatic (Class I, level of evidence A recommendation) and asymptomatic (Class IIa, level of evidence C) patients [19].

Kawasaki disease (KD): It is an acute systemic vasculitis of unknown origin that happens prevalently in children who are 5 years old. The most significant complication is coronary arteritis, and aneurysm development happens in 20% to 25% of untreated children. Aspirin should be used in KD but the role and appropriate dose of aspirin during the acute phase is still unclear [20].

Preeclampsia: The use of aspirin at low doses are successful in secondary prevention of preeclampsia in high risk patients, especially for those with a history of preeclampsia. In preeclampsia, platelet TXA2 increases significantly and prostacyclin drops forcefully. TXA2/PGI2 imbalance can be turned around by about fourteen days of treatment with low-dose aspirin, which inhibits TXA2 secretion, and thus platelet aggregation, without altering secretion of endothelial prostacyclin (PGI2), there by preferring systemic vasodilatation [21].

Hypertension: It is one of the major risk factors for atherothrombosis especially stroke. At present, the incidence of hypertension is continuously increasing. Complications such as stroke are significantly reduced if blood pressure is controllable. Aspirin therapy as primary prevention is successfully introduced in high-risk diabetic patients [22].

***In Vitro* Fertilization (IVF):** Low-dose aspirin may improve clinical pregnancy rate in IVF. Aspirin can effectively inhibit platelet aggregation the mechanism is through selective acetylation of COX a serine hydroxyl, irreversible inhibition of the Cyclooxygenase (COX) enzyme, reducing activity of thromboxane A2 (TXA2) and Prostaglandin Synthesis (PGs), inflammatory reaction, thus inhibiting platelet activity, and preventing the formation of blood clots, as well as reducing resistance in the blood vessels and increasing tissue perfusion [23].

Niacin-induced flushing: it is described by redness and warmth because of vasodilation of dermal blood vessels and it is associated with a sensation of tingling and burning. It appears to be likely that niacin-induced flushing is enhanced by prostaglandins produced initially by bone marrow-derived cells such as platelets and dendritic cells, perhaps contributing to subsequent induction of COX-2-dependent lipids by dermal or epidermal cells. During chronic drug administration, niacin-induced flushing and prostaglandin release are subject to tachy-phylaxis within a seven days. So we can decrease the risk of niacin-induced flushing by pretreatment with aspirin [24].

■ Propranolol

Propranolol is belongs to group of medicines called β-blockers a nonselective β-blocker. If β receptor sites is blocked by propranolol, the inotropic, chronotropic, and vasodilator responses to β-adrenergic stimulation are decreased proportionately. However, propranolol should be stopped gradually, if it stopped suddenly may cause chest pain or heart attack in some patients [25]. Off label uses of propranolol:

Anxiety: Propranolol now consider as first line pharmacological treatment for anxiety disorders have probably contributed to a step by step declining consideration for the specialist as a potential treatment of anxiety related conditions. However, propranolol use in anxiety due to its

ability to reduce some peripheral symptoms of anxiety, such as tachycardia and sweating.

Post-burn hypermetabolic response: The burn induced stress response stimulates secretion of endogenous catecholamines such as dopamine, norepinephrine and epinephrine, which are believed to be the main mediators of hypermetabolism after severe burns. Overproduction of catecholamines induces a hyperdynamic circulation, enhance protein catabolism in skeletal muscle and augments energy expenditure. Medications that prevent the action of catecholamine on the receptor site such as propranolol is effective at reducing the risk of catecholamine induced sequelae after severe burns. Propranolol, a non-selective β blocker has been studied extensively and shown promise result for decrease the post-burn hypermetabolic response.

Gastrointestinal hemorrhage: Propranolol can markedly reduce the risks of both primary and recurrent gastrointestinal hemorrhage, and also the total mortality.

Tetralogy of fallot: It's a type of heart defect present at birth lead to episodic central cyanosis due to total occlusion of right ventricle outflow in a patient with a congenital heart disease. Propranolol by its blocking beta receptor effect on the heart which will lead to reduction in the cardiac contractility may decrease infundibular obstruction of right ventricular outflow. However, propranolol will be used at dose 0.1 mg/kg slow IV push and may be repeated in 15 minutes. When used chronically, have the beneficial effect of stabilizing peripheral vascular reactivity.

Thyroid storm: Thyroid storm is a deadly form of hyperthyroidism that associated with untreated hyperthyroidism. 1 mg-2 mg of propranolol can be used intravenously in the treatment of thyroid storm also it can be used orally usually begins at 20 mg-120 mg per dose, or 160 mg/day-320 mg/day in divided doses, the dose should be increased gradually until symptoms are controlled. Propranolol has ability to relief the adrenergic symptoms of hyperthyroidism such as tremor, palpitations, heat intolerance, and nervousness. However, the most widely used β-blockers is propranolol because it has ability to block conversion of T4 to T3 and has more direct effect on hypermetabolism.

■ Gabapentin

Gabapentin is structurally related to the neurotransmitter GABA (Gamma-Aminobutyric Acid) but it does not modify GABAA or GABAB radioligand binding, it is not converted metabolically into GABAA or GABAB agonist, and it is not an inhibitor of GABA uptake or degradation. Off label uses of gabapentin:

Diabetic Peripheral Neuropathy (DPN): DPN is nerve damage caused by chronic high blood sugar. Gabapentin is structurally related to GABA and has the similar therapeutic target the α2-δ subunit of voltage gated calcium channels. The exact mechanism of action responsible for the analgesic effects of gabapentin is still not understood. However animal studies suggest that analgesic properties may be due to the release of GABA in spinal cord pathways that change pain perception.

Fibromyalgia: Fibromyalgia is a chronic disorder that lead to pain in the body muscle and mental distress. Clinical study show the adequacy of gabapentin in fibromyalgia at doses of 2400 mg was compared with placebo in 150 participants in a single placebo controlled parallel-group. The outcome is noticeable reduction in pain over baseline was reported, 49% for gabapentin and 31% for placebo.

Pruritus in hemodialysis: Gabapentin is likely effective for uremic pruritus but adverse events are common. Starting at a low dose of 100 mg orally after hemodialysis and titrating to effect may best provide effective and safe outcomes.

Hot flushes: Women whom hormone therapy is not effective or when hot flashes do not respond to medications, daily use of gabapentin at dose 300 mg can be helpful to relieve hot flashes. Nevertheless, side effects such as drowsiness, dizziness, ataxia, and withdrawal syndrome are of concern with larger doses of Gabapentin but with lower doses (300 mg/day) only GI discomfort may appear.

Acute postoperative pain: Pre-operative gabapentin at dose 600 mg-1200 mg has ability to reduce postoperative pain scores, decreases narcotic requirement, and decreases narcotic-related side effects such as nausea, and ileus.

■ Imipramine

Tricyclic antidepressants (TCAs) acts primarily

as a serotonin norepinephrine reuptake inhibitor, with more strong action on the serotonin transporter than norepinephrine transporter. Off label uses of imipramine:

Binge Eating Disorder (BED): BED is a dietary problem described by recurrent, distressing binge eating episodes without the unseemly compensatory weight loss behaviors of bulimia nervosa. Controlled combination treatment studies have had differentiating results. In one, diet guiding with psychological support in addition to imipramine was better than diet counseling and psychological support in addition to placebo.

Diabetic neuropathy: There is one study on 12 patients with serious, painful diabetic neuropathy in the lower extremities were treated with imipramine and placebo in a fixed-dose. The rating of specific symptoms at the end of each treatment period showed a beneficial effect of imipramine on pain, paresthesia, dysesthesia, numbness, and nocturnal aggravation.

Panic Disorder (PD): PD is a disabling condition which exerts a negative impact on social, family and working lives of patients and imipramine was the first drug used in the treatment of PD.

Urinary incontinence: Imipramine, among several other pharmacological effects, inhibits the re-uptake of noradrenaline in adrenergic nerve endings. In the urethra, this can be expected to enhance the contractile effects of noradrenaline urethral smooth muscle.

■ Clomipramine

Off label uses of Clomipramine:

Autism: Clinical studies shown that repetitive behaviors and stereotypies in patients with autism can be treated effectively by clomipramine also can be effective for aggression and hyperactivity. However, adverse effects due to clomipramine can be serious especially in children and adolescents. One case report of a twelve year old male with autism shown that clomipramine 75 mg daily has ability to reduce worsening of self-mutilation, sensitivity to loud noises irritability, irritability. Furthermore, a case series of 5 patients with autism, after using clomipramine shown significant improvements in obsessive compulsive symptoms, aggression, and impulsive behavior.

Premature ejaculation: Multiple studies has been found that clomipramine at a daily dose of 25 mg or 50 mg for premature ejaculation can be effective. Furthermore, premature ejaculation in men can be treated with clomipramine with initial dose (25 mg or less), clomipramine can be taken as needed before sexual intercourse, however if this treatment is not effective, daily clomipramine with initially 10 mg and increasing to 30 mg gradually may be helpful.

Panic disorder: Clomipramine at low dose without additional therapeutic measure, appears highly effective in treatment of panic disorder.

■ Acetylcysteine

Off label uses of Acetylcysteine (NAC):

Acute Respiratory Distress Syndrome (ARDS): There is one meta analysis study showed that the clinical benefits of NAC for ARDS are limited. The application of NAC did not significantly reduce short term mortality. But analysis of the pooled data indicated that NAC reduced the duration of intensive care unit stay also there is no side effects were reported in all of the trials, which means that NAC is at least safe for use.

Non-acetaminophen-induced acute liver failure: In non-acetaminophen induced acute liver failure the issue isn't one of depleted glutathione. A major complication is abnormal oxygen transport and utilization. Oxygen delivery (D_{O2}) increases, but the oxygen extraction ratio and consumption (V_{o2}) decrease. The resulting tissue hypoxia leads to anaerobic metabolism and ultimately to lactic acidosis. Acetylcysteine has certain pharmacologic properties that could be of benefit in this patient population. It is a scavenger of free radicals, which have been associated with cellular damage. In replenishing glutathione, acetylcysteine may improve antioxidant defenses. Acetylcysteine acts as a vasodilator and may improve hepatosplanchnic blood flow, DO2, and oxygen extraction. All of these properties have prompted interest in using this agent as a treatment for acute liver failure.

Obsessive-compulsive disorders: Obsessive compulsive disorder is a debilitating illness that can severely affect patients' quality of life. The development of this condition has long been associated with the dysfunction in the availability of serotonin transporter in the brain. More recently, the role of the neurotransmitter glutamate has also been implicated in its pathogenesis. However, Increase of glutamate

level in the cerebrospinal fluid has been noted in patients suffering from obsessive compulsive disorder. NAC has been proposed as a successful pharmacological option for this condition due to its ability to inhibit the synaptic glutamate release through the glial cysteine-glutamate exchange. Furthermore, other related disorders such as trichotillomania, onychophagia, Tourette syndrome, and excoriation can be treated with NAC as a glutamate-modulating agent.

Organophosphate poisoning: NAC is safe and it can be used as an adjuvant to treatment in patients suffering from organophosphate poisoning, also there is no adverse effects were reported with its use. However, NAC had no significant effect on length of hospitalization and its use may provide an extra benefit through reduction of atropine requirements and hence the proposed adverse effects resulting from large dose of atropine used in these cases of poisonings.

Prevention of contrast-induced nephropathy: One randomized double-blind study shown that oral NAC 600 mg twice daily on the day before and the day of the CT scan compare to placebo indicate that acute renal failure occurred in 21% of placebo subjects compared with 2% in the NAC group. This dramatic reduction in risk with NAC drew great attention and led recommend it as appropriate option to preventing contrast induced nephropathy.

Skin picking disorder: Glutamatergic agents have shown early promising result in case reports for the treatment of skin picking disorder and the commonest glutamatergic agents is NAC which has an excellent benefit in treating skin picking disorder, trichotillomania, and nail biting.

■ Sildenafil

The mechanism of sildenafil responsible for erection of penis is inhibiting phosphodiesterase type V, which is responsible for the degradation of cGMP in the corpus cavernosum. Off label uses of sildenafil:

Female Sexual Arousal Disorder (FSAD): A double blind, placebo controlled trial assessed the adequacy of sildenafil at dose 25 mg to 100 mg, 1 h before sexual intercourse during a 3 month period in 202 postmenopausal or post-hysterectomy women with FSAD. Postmenopausal subjects were required to be on a stable dose of hormone replacement therapy for at least 3 months. Most had at least one additional sexual dysfunction. Efficacy was assessed by means of the sexual function questionnaire. However, both sildenafil and placebo groups noted improvement in outcome measures, but sildenafil group has significantly greater improvement was noted compare to placebo group.

Persistent Pulmonary Hypertension of the Neonate (PPHN): Multiple clinical studies suggested that sildenafil is an excellent pharmacological option as adjuvant therapy for treat infants suffering from pulmonary hypertension in centers lacking inhaled nitric oxide and extracorporeal membrane oxygenation.

Raynaud's Phenomenon (RP): RP is the transient digital ischemia that happens upon exposure to cold temperature or emotional distress and it usually affects the fingers. The utilization of PDE5 inhibitors such as sildenafil is being investigated in patients with RP because of their potential effects on both microvascular and macrovascular circulation. A randomized, double-blind, crossover study compared the physiologic effects of single-dose sildenafil and alpha tocopherol in 15 patients with RP. The result showed that sildenafil group cause significant increase of basal forearm blood flow and plasma cGMP, and reduced systolic and diastolic blood pressure. However, alpha tocopherol group had no effect on any of these parameters.

Conclusion

While on-label use of medications is based on scientifically valid and statistically significant evidence indicating that the potential benefits of a drug. However, off-label drug use is a vital tool for treat various diseases. It allows physicians to treat patients for whom off-label drug use may be the only therapy available.

References

1. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. Mayo Clin Proc 87, 982-990 (2012).
2. Zheng Z, Yang M, Wu J. Ethical off-label drug-use: Need for a rethink? Indian Pediatr 54, 447-450 (2017).
3. Carvalho ML. Challenges on off label medicine use. Revista Paulista de Pediatria 34, 1-2 (2016).
4. Narayanan R, Honavar SG. A tale of two drugs: Off and on-label. Indian J Ophthalmol 65, 549-550 (2017).
5. Gota V, Divatia JV. Off-label use of drugs: An evil or a necessity? Indian J Anaesth 59, 767-768 (2015).
6. Abbott R, Ayres I. Evidence and extrapolation: Mechanisms for regulating off-label uses of drugs and devices. Duke LJ 64, 377-435 (2014).
7. Stolfi C, De Simone V, Pallone F, et al. Mechanisms of action of non-steroidal anti-inflammatory drugs (NSAIDs) and mesalazine in the chemoprevention of colorectal cancer. Int J Mol Sci 14, 17972-17985 (2013).
8. Sekar KC, Corff KE. Treatment of patent ductus arteriosus: Indomethacin or ibuprofen? Cochrane Lib 28, S60-S62 (2008).
9. Gulack BC, Laughon MM, Clark RH, et al. Comparative effectiveness and safety of indomethacin versus ibuprofen for the treatment of patent ductus arteriosus. Early Hum Dev 91, 725-729 (2015).
10. Stancu C, Sima A. Statins: Mechanism of action and effects. J Cell Mol Med 5, 378-387 (2001).
11. Generali JA, Cada DJ. Atorvastatin: Rheumatoid Arthritis. Hospital Pharmacy 44, 232-233 (2009).
12. Hung CY, Hsieh YC, Huang JL, et al. Statin therapy for primary prevention of atrial fibrillation: Guided by CHADS2/CHA2DS2VASc score. Korean Circ J 44, 205-209 (2014).
13. Shi R, Zhao L, Wang F, et al. Effects of lipid-lowering agents on diabetic retinopathy: a meta-analysis and systematic review. Int J Ophthalmol 11, 287 (2018).
14. Szyguła-Jurkiewicz B, Szczurek W, Krol B, et al. The role of statins in chronic heart failure. Kardiochir Torakochirurgia Pol 11, 301-305 (2014).
15. Cadavid AP. Aspirin: The mechanism of action revisited in the context of pregnancy complications. Frontiers in immunology 8, 261 (2017).
16. Pasche B, Wang M, Pennison M, et al. Prevention and treatment of cancer with aspirin: Where do we stand? Semin Oncol 41, 397-401 (2014).
17. Rodríguez LAG, Soriano-Gabarro M, Bromley S, et al. New use of low-dose aspirin and risk of colorectal cancer by stage at diagnosis: A nested case-control study in UK general practice. BMC Cancer 17, 637 (2017).
18. Michael PD. Antiplatelet drugs, coronary stents, and non-cardiac surgery. BJA Edu 10, 187-191 (2010).
19. Mahmoud AN, Elgendy AY, Rambarat C, et al. Efficacy and safety of aspirin in patients with peripheral vascular disease: An updated systematic review and meta-analysis of randomized controlled trials. PloS One 12, e0175283 (2017).
20. Hsieh KS, Weng KP, Lin CC, et al. Treatment of acute Kawasaki disease: Aspirin's role in the febrile stage revisited. Pediatrics 114, e689-e693 (2014).
21. Atallah A, Lecarpentier E, Goffinet F, et al. Aspirin for prevention of preeclampsia. Drugs 77, 1819-1831 (2017).
22. Sawanyawisuth K, Limpawattana P, Bumrerraj S, et al. Aspirin therapy as primary prevention in hypertensive patients at Srinagarind hospital. J Med Assoc Thail 88, 1797 (2005).
23. Wang L, Huang X, Li X, et al. Efficacy evaluation of low-dose aspirin in IVF/ICSI patients evidence from 13 RCTs: A systematic review and meta-analysis. Medicine 96, e7720 (2017).
24. Kamanna VS, Ganji SH, Kashyap ML, et al. The mechanism and mitigation of niacin-induced flushing. Int J Clin Pract 63, 1369-1377 (2009).
25. Gorre F, Vandekerckhove H. Beta-blockers: Focus on mechanism of action which beta-blocker, when and why? Acta Cardiol 65, 565-570 (2010).