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Combination of Antidiabetic drugs and Antilipidemic drugs for better clinical outcomes

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Abstract: This abstract provides an overview of the combination of antidiabetic drugs and antilipidemic drugs as a synergistic approach to achieving better clinical outcomes in individuals with coexisting diabetes and elevated lipid levels. Combining these two classes of medications provides a comprehensive approach to managing patients with diabetes and dyslipidemia. Individualized treatment plans are essential, considering patient-specific risk factors and response to therapy. The primary objective of combining antidiabetic and antilipidemic drugs is to reduce cardiovascular risk, given the heightened susceptibility of individuals with diabetes to heart disease. This abstract underscores the importance of evidence-based practices and adherence to clinical guidelines in tailoring treatment regimens for patients with diabetes and dyslipidemia. As cardiovascular disease continues to be a leading cause of morbidity and mortality worldwide, the combination of antidiabetic and antilipidemic drugs offers a promising strategy for mitigating risk and improving the overall health of affected individuals.

INTRODUCTION

Diabetes mellitus, or simply diabetes, is a set of endocrine illnesses characterised by persistently elevated blood sugar levels.**[1]** Diabetes is caused by either the pancreas not producing enough insulin or the body's cells being resistant to the hormone's effects**.[2]** Thirst, polyuria, weight loss, and blurred eyesight are common complaints. If left untreated, the condition can cause a variety of health problems, including problems with the cardiovascular system, eyes, kidneys, and nerves. **[3]** Diabetes kills around 1.5 million people each year because it is untreated or poorly treated.

Gestational diabetes, which occurs in some women during pregnancy, usually resolves shortly after birth. Globally, a projected 537 million adults (10.5% of the adult population) have diabetes as of 2021, with type 2 diabetes accounting for around 90% of all cases. **[4]** The disease is becoming more common, and this trend is most pronounced in low- and middle-income countries**. [5]** Diabetes is the seventh-leading

cause of death worldwide, with rates being comparable in men and women. **[6]** Type 1 diabetes is a chronic disease in which the pancreas produces little or no insulin. It is also known as insulin-dependent diabetes or juvenile diabetes **[7].** This type of diabetes is thought to be caused by an autoimmune reaction in which the body's immune system erroneously targets the insulin-producing beta cells in the pancreas this process can take months or perhaps years before any diabetes symptoms appear **[8].** Although certain genes may raise the risk of developing type 1 diabetes, it is considered that an environmental trigger, such as a viral infection, initiates the autoimmune response **[9].** Individuals with type 1 diabetes must constantly monitor their blood sugar levels, eat a balanced diet, engage in regular physical activity, and receive on going medical treatment to avoid complications and properly manage their condition **[10].** Type 2 diabetes is a chronic disease in which the body is unable to utilise insulin efficiently or make enough insulin to control blood sugar levels **[11].** It is the most prevalent type of diabetes, accounting for roughly 90-95% of all diagnosed cases **[12].** Type 2 diabetes occurs when the body's cells grow resistant to the action of insulin, resulting in high blood glucose (sugar) levels. This can lead to a variety of health consequences over time, including cardiovascular disease, renal damage, nerve damage, and eye problems. Although type 2 diabetes is most often associated with adults, it is increasingly being diagnosed in children **[13].** Monitoring blood sugar, cholesterol, and blood pressure levels, as well as obtaining frequent medical check-ups, are critical for effectively treating the illness and avoiding consequences **[14].** Antidiabetic drugs are medications used to lower abnormally high glucose levels in the blood, which are characteristic of diabetes mellitus 1 they aim to reduce blood sugar levels to an acceptable range and relieve symptoms of diabetes such as thirst, excessive urination, and ketoacidosis. Oral antidiabetic agents work in various ways to reduce blood sugar levels in people with type 2 diabetes, including stimulating insulin secretion by the pancreas, improving the responsiveness of cells to insulin, or preventing glucose production by the liver.

Antilipidemic drugs are pharmaceuticals that are used to lower blood lipid levels. These medications are often used to treat hyperlipidemia, a disorder marked by high levels of lipids such as cholesterol and triglycerides **[15].**Antilipidemic medicines are classified into several classes, each with its own mode of action and specific targets in lipid metabolism. Some commonly used antilipidemic drugs include statins, fibrates, bile acid

sequestrants, ezetimibe, proprotein convertase subtilisin/kexin type 9, niacin and omega 3 fatty acids. ***Statins,*** also known as HMG-CoA reductase inhibitors, work by inhibiting an enzyme involved in cholesterol synthesis in the liver. By reducing cholesterol production, statins help lower LDL (bad) cholesterol levels and reduce the risk of cardiovascular events **[16].** ***Fibrates*** act primarily on triglyceride metabolism by activating enzymes involved in their breakdown. They can also help raise HDL (good) cholesterol levels to some extent **[17].** ***Bile acid sequestrants*** bind to bile acids in the intestine, reducing their reabsorption. This stimulates the liver to use more cholesterol to produce new bile acids, leading to a decrease in LDL cholesterol levels **[18-19].** ***Ezetimibe*** works by inhibiting the absorption of cholesterol from the intestine. It can be used alone or in combination with other antilipidemic drugs to further lower LDL cholesterol levels **[20].** ***Proprotein convertase subtilisin/kexin type 9 (PCSK9)*** relatively new drugs target an enzyme involved in cholesterol metabolism, PCSK9. By inhibiting PCSK9, these drugs help increase the clearance of LDL cholesterol from the blood, leading to reduced LDL levels **[21].** ***Niacin (Nicotinic Acid)*** is a B-vitamin that can raise HDL cholesterol levels and lower LDL and triglyceride levels. It is available both as a prescription medication and as an over-the-counter supplement **[22].** ***Omega-3 Fatty Acids*** often obtained from fish oil supplements, can help lower triglyceride levels **[23].**

Using combination of antidiabetic and antilipidemic drugs for better clinical outcomes

The combination of antidiabetic drugs and antilipidemic drugs can be beneficial for individuals with type 2 diabetes, as they often have abnormal lipid metabolism along with hyperglycemia **[24].** This combination therapy can lead to better clinical outcomes and reduce the risk of other associated diseases and conditions with diabetes such as *cardiovascular diseases*, which are the most common causes of morbidity and mortality in individuals with type 2 diabetes **[25],** *polycystic ovary disease/syndrome (PCOD)*, Antidiabetic drugs such as metformin, sulfonylureas, incretin mimetics, and SGLT2 inhibitors can improve glycemic control and reduce the risk of cardiovascular diseases when used alone or in combination **[26].** However, these drugs may have different effects on lipid metabolism.

Antilipidemic drugs such as statins, fibrates, and bile acid sequestrants can improve lipid levels and reduce cardiovascular risks in individuals with or without diabetes **[27].**

Combination therapy with antidiabetic and antilipidemic drugs can improve glycemic and lipid control, respectively, which can lead to better outcomes.

Various clinical trials have demonstrated the benefits of combination therapy with antidiabetic and antilipidemic drugs in individuals with type 2 diabetes. For example, a study conducted in individuals with type 2 diabetes who had a history of cardiovascular diseases found that the combination of a statin and a fibrate reduced the risk of major cardiovascular events **[28]**. Another study showed that the combination of a statin and metformin reduced the incidence of cardiovascular events compared to treatment with either drug alone **[29].**

Overall, it is important to note that the combination of antidiabetic and antilipidemic drugs should be guided by a healthcare professional and tailored based on the individual patient's needs and comorbidities. Close monitoring of glucose and lipid levels, as well as potential side effects and drug interactions, is essential for optimizing outcomes.

CLINICAL OUTCOMES

The combination of antidiabetic and antilipidemic drugs is often used to manage patients with type 2 diabetes who also have dyslipidemia (abnormal lipid levels). This combination therapy aims to address both high blood sugar levels (hyperglycemia) and abnormal lipid profiles (dyslipidemia) to reduce the risk of cardiovascular events and improve overall health. Clinical outcomes for this combination therapy includes

Cardiovascular Risk Reduction:

Bulcao et al. (2007) **[30]** examined how metformin and simvastatin impacted insulin sensitivity and inflammation markers in overweight individuals with impaired glucose tolerance. Metformin reduced body weight, fasting glucose, and insulin resistance, while simvastatin lowered cholesterol. Both drugs independently decreased inflammation markers like CRP and IL-6 over 16 weeks, indicating their potential in reducing low-grade inflammation beyond glucose and lipid control. The study highlights the importance of early treatment in individuals at risk of diabetes or metabolic issues based on these positive effects.

Bala et al. (2008) **[31]** evaluated a fixed-dose combination of atorvastatin 10 mg + metformin SR 500 mg in Indian adults with diabetic dyslipidemia. Among 213 patients,

the 12-week treatment significantly improved fasting and postprandial glucose levels, notably reducing HbA1c. It also lowered total, LDL, and VLDL cholesterol while increasing HDL cholesterol, with a positive trend in reducing atherosclerosis. The combination was well-tolerated, primarily causing mild to moderate gastrointestinal adverse events. Overall, it demonstrated efficacy and tolerability, presenting as a convenient and beneficial therapeutic option for managing diabetic dyslipidemia.

Tousoulis et al. (2010) **[32]** studied metformin and atorvastatin treatments in newly diagnosed type 2 diabetes patients. In a six-week trial, patients receiving both medications showed partial prevention of glucose-induced endothelial dysfunction compared to those on metformin alone. The combination therapy also partly prevented glucose elevation at one hour after loading, a benefit not seen with metformin alone. This suggests that the combined use of metformin and atorvastatin had a more positive impact on glucose-induced endothelial dysfunction in these patients.

Kandhwal et al. (2011) **[33]** aimed to establish the bioequivalence of a fixed-dose combination (FDC) tablet of atorvastatin 10 mg and metformin 500 mg extended release (ER) against separate administration of these medications. In a study with 40 Asian male subjects, the FDC tablet showed comparable bioavailability to individual tablets. Safety and tolerability profiles were similar between the FDC and separate components, indicating potential use to reduce pill burden and improve patient compliance in clinical settings.

Tousoulis et al. (2011) **[34]** studied newly diagnosed type 2 diabetes patients, dividing them into two groups: one receiving metformin alone and the other receiving metformin with atorvastatin. After 12 weeks of treatment and glucose loading tests, they found that the metformin + atorvastatin group showed reduced serum TNF-α levels compared to the metformin-alone group. The combination therapy also partially prevented glucose-induced elevation, especially at 1 hour post-glucose intake, indicating a potentially better response compared to metformin alone in managing TNF-α levels after glucose loading.

Tousoulis et al.'s 2011 **[35]** study on newly diagnosed type 2 diabetes patients, they split participants into groups: one received metformin alone, the other metformin with

atorvastatin. After 12 weeks, the combination therapy showed partial prevention of glucose-induced elevation at 1 hour, indicating a better response to glucose intake compared to metformin alone. Moreover, the combined treatment reduced post-glucose loading TNF-α levels compared to metformin monotherapy, suggesting potential benefits in managing inflammatory markers in these patients.

Islam et al. (2012) **[36]** investigated combining metformin and atorvastatin in rats with long-term alloxan-induced diabetes and cardiovascular disease (CVD). Short-term diabetic rats showed metformin reduced blood glucose, while atorvastatin improved lipid profiles without heart-related changes. In long-term diabetic rats, atorvastatin, alone or combined with metformin, notably decreased left ventricular hypertrophy, cardiomyocyte size, total cholesterol, triglycerides, and LDL-C while increasing HDL-C. The combination therapy exhibited more effectiveness than monotherapy in preventing diabetes-related cardiovascular complications in these rats, alongside significant DPPH free radical scavenging activity.

Krysiak et al (2012) **[37]** simvastatin-treated patients with impaired fasting glucose, 41 participants were randomly assigned to either metformin (3 g daily) or a placebo. After 90 days, the study evaluated various haemostatic risk factors. Metformin treatment notably reduced plasma levels/activity of these risk factors and showed a correlation with improved insulin sensitivity. These findings suggest that high-dose metformin has a beneficial, multifaceted impact on coagulation and fibrinolysis in individuals with impaired fasting glucose already receiving statin therapy. This effect on haemostasis might contribute to preventing atherosclerosis-related complications and acute vascular events in this pre-diabetic state.

Another study of ***Krysiak et al.*** (2012) **[38]** studied subjects with impaired fasting glucose already on simvastatin treatment. Divided into groups receiving metformin or a placebo for 90 days, those receiving metformin alongside simvastatin showed reduced plasma inflammation markers like C-reactive protein and intercellular adhesion molecule-1. Metformin also notably lowered lymphocyte release of pro inflammatory cytokines, linked to improved insulin sensitivity and reduced free fatty acid levels. The combination therapy's impact on inflammation and lymphocyte activity may help

prevent and treat atherosclerosis and its complications in individuals with early glucose metabolism issues.

In 2013 another study of ***Krysiak et al*** **[39]** study on patients with impaired fasting glucose on chronic statin therapy, they explored metformin's impact versus a placebo on monocyte secretory function. Over 90 days, those on metformin alongside statin treatment showed reduced release of inflammatory markers from monocytes, including TNF-α, interleukins, and other markers. This decrease aligned with lower plasma C-reactive protein levels and improved insulin sensitivity. The findings suggest metformin might inhibit monocyte function, reducing systemic inflammation in those with prediabetes on statin therapy, potentially benefiting individuals at high cardiovascular risk.

Singh et al. (2015) **[40]** conducted a study using rats with streptozotocin-induced diabetes. These rats showed various adverse changes including altered body weight, blood pressure, increased glucose and lipid levels, decreased insulin, HDL, and pancreatic antioxidants, along with pancreatic tissue changes. Administering metformin with atorvastatin for 14 days significantly improved these parameters, displaying antioxidant properties and offering substantial protection against streptozotocin-induced diabetes mellitus, as confirmed by both biochemical and histopathological evaluations.

Ramadan et al. (2015) **[41]** reviewed Juvisync™, a combination drug containing sitagliptin and simvastatin, approved by the US FDA in 2011. Sitagliptin showed comparable efficacy to other diabetic medications, with lower hypoglycemia rates and weight gain. Simvastatin, the statin component, effectively reduced cardiovascular risk in diabetic patients, regardless of initial lipid levels or heart conditions. Both components demonstrated acceptable safety profiles, but caution was advised regarding coadministering drugs that could increase simvastatin levels, to mitigate the risk of myopathy and rhabdomyolysis. Overall, Juvisync was recommended for patients needing both sitagliptin and simvastatin due to their efficacy and favourable safety profiles. Sitagliptin, in particular, was highlighted for its beneficial effects on glycemic control with reduced hypoglycemia and weight gain risk.

Oh et al. (2016) **[42]** developed a once-daily bilayer tablet combining metformin and atorvastatin for type 2 diabetes and dyslipidemia patients. The tablet included sustained-release metformin (500 mg) and immediate-release atorvastatin (10 mg) using specific polymers to mimic reference drugs' release patterns. In vitro studies matched Glucophage XR and Lipitor release patterns. In beagle dog studies, the formulation showed sustained metformin absorption and immediate atorvastatin absorption, similar to reference drugs. The bilayer tablet formulation aims to improve patient compliance and therapeutic outcomes for metabolic diseases.

Hao et al. (2016) **[43]** conducted a study comparing atorvastatin alone to a combination of atorvastatin and metformin in individuals with dyslipidemia and overweight/obesity. After an 8-week period, both groups showed improvements, but the combination therapy group had more significant reductions in obesity rates, Hs-CRP levels, leukocyte ROCK2 concentration, and higher serum NO concentrations compared to the atorvastatin-only group. The combination therapy was associated with increased serum NO concentration and decreased leukocyte ROCK2 concentration, indicating potential additional benefits for these individuals.

Fei Luo et al. (2017) **[44]** studied rabbits on a high-cholesterol diet, investigating metformin and atorvastatin combined. The combination notably reduced atherosclerotic plaques compared to atorvastatin alone, without extra lipid-lowering effects. It increased larger HDL particles, improved glucose control, and enhanced cholesterol efflux from macrophages. This suggests that combining atorvastatin and metformin may provide added anti-atherosclerotic benefits by boosting cholesterol efflux from macrophages.

The study was examined through research by ***Graaf et al*** **[45]** in 2018 use of combination therapy involving metformin (an anti-diabetic drug) and statins (cholesterol-lowering medications). In patients with type 2 diabetes and dyslipidemia, a condition characterized by abnormal lipid levels. The study was aimed to understand the potential interactions and effects of these drugs when used together. It critically evaluated the molecular mechanisms through which statins and metformin individually impact glucose and lipid metabolism. Furthermore, the review develops a hypothesis to explain how these drugs might interact when administered together in combination therapy. This research is vital for improving our understanding on the benefits and

potential risks associated while using both drugs concurrently in diabetic patients at risk of cardiovascular disease.

Jia et al. (2021) **[46]** investigated metformin and atorvastatin's combined effects on diabetic cardiomyopathy in db/db mice and H9C2 cardiomyocytes under diabetic conditions. They studied four groups of db/db mice: receiving metformin alone, atorvastatin alone, both combined, or a control. The combination therapy showed superior efficacy in protecting cardiac tissue from diabetes-induced damage, inhibiting oxidative stress, reducing inflammation-related proteins, and decreasing apoptosis in cardiomyocytes. It notably upregulated AMPK and SIRT1 expression, suggesting their involvement in the therapy's anti-inflammatory and anti-apoptotic effects.

Hasymi et al. (2021) **[47]** investigated the impact of combining simvastatin and metformin in male Wistar rats on an atherogenic diet. Rats were divided into groups receiving simvastatin alone, simvastatin with metformin, or no treatment. After four weeks, the combination group showed significant differences in aortic organ weight and cholesterol levels compared to other groups. Body weight, BMI, and Lee index also exhibited significant changes after the diet in each group. The study suggests a potential association between the combination treatment of simvastatin and metformin in male Wistar rats subjected to an atherogenic diet.

Polycystic ovarian syndrome

In ***Banaszewska et al.'s*** 2009 **[48]** study on women with PCOS, simvastatin, metformin, and their combination led to significant reductions in testosterone levels, BMI, CRP, and soluble VCAM-1. Simvastatin outperformed metformin in reducing DHEAS, total cholesterol, and LDL cholesterol. However, combining simvastatin with metformin didn't offer significant advantages over simvastatin alone. While simvastatin was more effective than metformin alone in improving certain PCOS markers, the combination didn't show added benefits compared to using simvastatin alone.

In ***Talieh et al.'s*** 2010 **[49]** study on women with PCOS, combining metformin and simvastatin showed significant improvements compared to metformin plus placebo. The combination therapy led to greater reductions in serum testosterone and LH levels,

improved LH/FSH ratio, and notably lowered total cholesterol, LDL, and triglycerides while increasing HDL levels. This suggests that combining metformin and simvastatin may effectively address hormonal imbalances, lipid profiles, and insulin resistance in PCOS patients, offering a promising management option for both hormonal and metabolic aspects of the condition.

In ***Banaszewska et al.'s*** 2011 **[50]** study on PCOS in women, both simvastatin and metformin notably decreased total testosterone levels, improved menstrual cycles, and reduced hirsutism and acne symptoms. Simvastatin demonstrated superiority in reducing dehydroepiandrosterone sulfate, total cholesterol, and LDL cholesterol. Ovarian volume reduction and improvements in hirsutism, acne, and testosterone levels were sustained throughout the study. However, improvements in lipid profile and inflammatory markers were prominent in the initial three months and showed less change afterward. Overall, both treatments were well-tolerated, but long-term simvastatin treatment was more effective than metformin in addressing ovarian hyperandrogenism in PCOS.

Celik et al. (2012) **[51]** compared metformin alone to a combination of metformin and rosuvastatin therapies in PCOS patients with hyperlipidemia and impaired glucose tolerance. After 12 weeks, both groups showed similar improvements in BMI, insulin, glucose levels, and insulin resistance. However, the combination therapy group exhibited greater reductions in testosterone levels, DHEAS, hsCRP, triglycerides, total, and LDL cholesterol compared to the metformin-only group. The combination therapy demonstrated enhanced efficacy in reducing hyperandrogenism and atherosclerosis-related factors while improving lipid parameters in PCOS patients.

According to ***Hamdy et al.*** (2012), **[52]** in a study involving PCOS patients with metabolic syndrome, comparing metformin alone to a combination of simvastatin and metformin for three months, the combination therapy (Group II) showed superior results. Group II displayed greater improvements in lowering fasting blood sugar, insulin levels, and insulin resistance compared to metformin alone (Group I). Additionally, Group II demonstrated more significant reductions in total and free testosterone levels, alongside notable improvements in lipid profiles with decreased LDL cholesterol and increased HDL cholesterol, surpassing the effects observed in Group I. Overall, the combination therapy of simvastatin and metformin proved more

effective in reducing insulin resistance, enhancing lipid profiles, and lowering testosterone levels in PCOS patients than metformin alone.

In ***Karakas et al.'s*** 2013 **[53]** study involving untreated women with PCOS, therapies including metformin, simvastatin, or their combination for three months did not impact serum FABP4 or RBP4 levels. Initially, FABP4 correlated with obesity, insulin resistance, and inflammation, while RBP4 correlated with lipid profiles. However, none of the treatments affected these biomarkers associated with PCOS, indicating that insulin-sensitizing or lipid-lowering therapies did not alter FABP4 or RBP4 levels in these patients.

Sun et al. (2015) **[54]** studied the effects of statins alone, metformin alone, and their combination in women with PCOS. Trials comparing statin and metformin together versus metformin alone showed the combined therapy reduced inflammation markers, triglycerides, total cholesterol, and LDL cholesterol. However, it didn't notably improve insulin sensitivity or reduce high androgen levels. Statin therapy alone, compared to placebo, effectively reduced LDL cholesterol, triglycerides, and total cholesterol levels. Combining statins with metformin improved lipid and inflammation markers but didn't significantly enhance insulin sensitivity or reduce high androgen levels in women with PCOS. More extensive studies are necessary for understanding the long-term effects of this therapy in PCOS.

In ***Pourmatroud et al.'s*** 2015 **[55]** study on PCOS women preparing for intra-cytoplasmic sperm injection (ICSI), comparing metformin and simvastatin as pretreatment for eight weeks before the cycle, both drugs improved hirsutism symptoms. Simvastatin notably reduced hormonal and lipid markers better than metformin. However, pregnancy rates and ICSI cycle outcomes were similar between the two groups. While simvastatin effectively improved hyperandrogenism symptoms, it didn't yield significantly different ICSI cycle outcomes compared to metformin when used as pretreatment.

In ***Enas Hefzy et al.'s*** 2018 **[56]** study on 200 women with PCOS, comparing the effects of combining simvastatin and metformin versus using each medication separately for 12 months, the combined treatment (Group A) showed substantial improvements. Hormonal balance saw reductions in testosterone by 37%, LH by 51%, and LH/FSH ratio by 53%. Insulin resistance improved in Groups A and C, while lipid

profile notably decreased in Groups A and B. Menstrual regularity and hormonal symptoms improved in Groups A and C, with Group C showing slightly better outcomes. Group A had confirmed spontaneous ovulation over the study period. Overall, the combined simvastatin and metformin treatment demonstrated significant improvements in hormonal balance, insulin resistance, lipid profile, menstrual regularity, and ovulation, offering comprehensive benefits for managing PCOS in young women.

In ***Malik et al.'s*** 2018 **[57]** study on PCOS treatment, comparing metformin alone versus a combination of metformin and simvastatin in 108 patients, the combination therapy proved significantly more effective. 66.7% of patients on metformin alone showed efficacy, while 92.6% in the combination therapy group achieved efficacy, highlighting a notable difference in effectiveness (p=0.001). This suggests that combining metformin and simvastatin holds greater promise for managing PCOS in females compared to using metformin alone.

In ***Mohsin Shah et al.'s*** 2019 **[58]** study on PCOS treatment comparing metformin alone versus a combination of metformin and pioglitazone in 106 women, both groups showed improvements. However, the combination therapy demonstrated a more significant decrease in inflammatory markers IL-6 and IL-8, indicating reduced inflammation. Both groups improved insulin resistance and hormonal levels, but the combination therapy was notably more effective in reducing LH levels. Overall, the combined metformin and pioglitazone therapy appeared more effective in addressing inflammation and improving insulin resistance in PCOS, suggesting a comprehensive approach targeting both metabolic and inflammatory aspects may offer greater benefits for individuals with this condition.

In 2020 ***Al Mohammad et al*** **[59]** performed a study through a network meta-analysis of randomized clinical trials for comparative study on efficacy of statins, metformin spironolactone in reducing testosterone levels in women with polycystic ovarian syndrome**.** According to the study atorvastatin life style changes and placebo (-3.04{-3.56; -2.53}) showed better efficacy in reducing the testosterone in women. However, combination of simvastatin with metformin (-2.93 {-3.79; -2.06}) too showed better result in comparison to simvastatin alone (-2.88{-3.85; -1.92}) or spirolactone (-2.90{-

3.77; -2.02}) or combination of metformin with spirolactone (-2.83{-3.80; -1.87}) or combined oral contraceptives (-2.78{-3.60; -1.97}) alone.

In their 2021 meta-analysis, ***Liu et al.*** **[60]** found that combining metformin and simvastatin was more effective than metformin alone in reducing cholesterol, triglycerides, LDL, testosterone, and fasting insulin levels in PCOS patients. However, there were no significant differences in HDL, LH, FSH, prolactin, blood sugar, or insulin sensitivity index between the groups. Larger studies are needed to assess its safety in clinical use.

In their 2021 meta-analysis, **Meng et al. [61]** found that combining simvastatin with metformin for treating PCOS showed significant benefits over metformin alone. The combination therapy notably reduced total testosterone, LH:FSH ratio, and LDL cholesterol levels, but other factors like menses frequency, ovarian volume, BMI, and fasting glucose remained similar between the groups.

Prevention/cure for cancer

In ***Nakai et al.'s*** 2013 **[62]** study on advanced pancreatic cancer and diabetes, they found that while diabetes itself didn't strongly impact survival, those with diabetes taking statins for cholesterol seemed to have better survival rates. Medications used to treat diabetes didn't show a direct influence on survival. Other factors like cancer stage, overall health, specific chemotherapy, and certain blood pressure drugs were also linked to survival outcomes.

In their 2014 study on castration-resistant prostate cancer (CRPC), ***MA Babcook et al.*** **[63]** explored the combination of simvastatin (SIM) and metformin (MET) as a potential treatment strategy. This combination showed promise by correcting metabolic abnormalities linked to the Warburg effect, reducing CRPC cell viability and metastatic potential more effectively than standard chemotherapy. The treatment induced cell cycle arrest, primarily in the G1 phase, and increased autophagic activity. Surprisingly, inhibiting autophagy didn't rescue cell viability but triggered a form of cell death known as necrosis, suggesting the potential effectiveness of SIM and MET in treating metastatic CRPC cells resistant to traditional chemotherapy.

In their 2014 study, ***Babcook et al.*** **[64]** examined the impact of metformin and statin use on mortality in high-risk prostate cancer (PCa) patients. Analyzing data from the

SEER-Medicare linked database involving 12,700 patients, they found that both statin use alone and in combination with metformin were associated with reduced all-cause and PCa-specific mortality. Specifically, the metformin/statin combination showed significant reductions in all-cause mortality by 32% and PCa mortality by 54% among post-diagnosis users, while metformin alone didn't show significant associations with mortality outcomes. These findings suggest potential benefits in using statins, particularly in combination with metformin, for reducing mortality in high-risk PCa patients, especially post-diagnosis.

In 2015, ***Hsin-Hung Chen et al.*** [67] explored combining metformin and statins to reduce hepatocellular carcinoma (HCC) risk in newly diagnosed type 2 diabetes patients. They found that statin use alone reduced HCC risk by 63%, especially simvastatin, atorvastatin, and rosuvastatin. Combining metformin with these statins further lowered HCC risk, with metformin and simvastatin showing particularly effective results. However, the effectiveness varied among different statin combinations, emphasizing their potential in reducing HCC incidence in diabetic patients.

In 2014, ***Danzig et al.*** **[66]** observed a potential synergy between statins and metformin in reducing the risk of biochemical recurrence (BCR) in diabetic men post-prostatectomy. Analysing data from 767 men, they noted that while statins or metformin alone didn't show significant associations with BCR-free survival, using both drugs together exhibited a trend toward improved BCR-free survival rates at 2 and 5 years, though not statistically significant. However, the combined use of statins and metformin demonstrated a synergistic effect, significantly lowering BCR risk compared to each drug's independent effects. This suggests a potential biologically plausible synergy between statins and metformin in reducing BCR risk, urging further investigation in clinical trials for prostate cancer patients.

In 2015, ***Chen et al.*** **[67]** investigated the impact of statin and metformin use on cancer incidence in individuals with hepatitis B virus (HBV) infection. Analysing data from 71,847 patients, they found that both statin and metformin use independently reduced cancer incidence. Specifically, statin use showed a more pronounced effect on liver cancer, while metformin use had a significant effect on overall cancer reduction. Combining statin and metformin demonstrated the most substantial reduction in cancer risk, indicating an additive or synergistic effect. Both medications exhibited a dose-

dependent relationship in preventing cancer, with statin use showing a dose-response effect for various cancers, and metformin showing similar trends without dose stratification for statin use. Overall, the study highlighted the potential of statin and metformin as chemo preventive agents, especially when used together, in reducing cancer incidence in HBV-infected individuals.

In 2016, ***Pennanen et al.*** **[68]** investigated the effects of metformin and simvastatin, both individually and in combination, on prostate cancer cells (LNCaP) and normal prostate epithelial cells (RWPE-1). Metformin induced G1 cell cycle arrest, autophagy, and apoptosis in LNCaP cells but had little impact on RWPE-1 cells. Simvastatin induced effects in RWPE-1 cells, causing G2 cell cycle arrest, autophagy, apoptosis, and increased ATP levels without significant effects on LNCaP cells. Combining metformin and simvastatin synergistically reduced ATP levels, increased autophagy, and induced necrosis specifically in LNCaP cells without impacting RWPE-1 cells. This suggests that the combination of these drugs may be a promising strategy for targeting prostate cancer cells while sparing normal cells.

In 2016, ***Kozak et al.*** **[69]** studied 171 patients with pancreatic ductal adenocarcinoma (PDAC) who had undergone surgical resection. They found that both statin and metformin use were associated with improved overall survival (OS) in these patients. However, upon multivariate analysis, only statin use remained significantly linked to better OS, while the significance of metformin use diminished. The study suggested potential benefits of these medications in enhancing survival rates among PDAC patients after surgery, warranting further research into their long-term use for this population.

In 2017, ***Wang et al.*** **[70]** highlighted the potential synergy between metformin and atorvastatin in battling prostate cancer. Their laboratory experiments demonstrated that the combination markedly inhibited the growth of prostate cancer cells (PC-3) more effectively than either drug alone. This combination hindered cancer cell proliferation, promoted cell death, and suppressed tumor sphere formation by targeting key regulators of cell survival and inflammation. In mouse studies, the combination significantly suppressed tumor growth, suggesting its potential as a promising strategy for prostate cancer treatment, warranting further clinical investigation.

In 2017, ***Nimako et al.*** **[71]** found that in patients with diabetes and gastrointestinal cancer, using statins or metformin alone improved overall and disease-free survival. However, combining metformin and statins showed a synergistic advantage, particularly benefiting those with upper gastrointestinal cancers, leading to enhanced cancer-related outcomes compared to using either drug alone. Using statins without metformin or metformin without statins did not significantly improve outcomes in this context.

In 2018, ***Jose A. Del Campo et al.*** [72] found that the combination of metformin and simvastatin inhibited liver cell growth and Hepatitis C virus infection in laboratory experiments. In non-infected cells, simvastatin increased tumor control proteins, while metformin inhibited a protein linked to cancer growth. Together, they down regulated cancer-related factors and increased proteins associated with reduced cancer risk. In HCV-infected cells, this combination increased markers linked to lower cancer risk. These results suggest that using metformin and simvastatin together might help prevent liver cancer in individuals with HCV-related liver disease.

In 2019, ***Josephine et al.*** **[73]** discovered that combining metformin and simvastatin significantly inhibited the growth of endometrial cancer cells more effectively than either drug alone. This synergy induced programmed cell death (apoptosis) and suppressed the mTOR pathway, critical for cancer cell proliferation. Blocking a specific protein called Bim partially reversed this effect, emphasizing the role of apoptosis. These preclinical findings suggest potential for clinical research into using this drug combination as a treatment for endometrial cancer.

In 2020 ***Liu et al*** **[74]** conducted the study for better treatment for pancreatic cancer, a group used a platform to combine FDA-approved drugs that target specific genes in pancreatic cancer cells. By focusing on PDX1 and BIRC5 genes, they screened an FDA drug library and found metformin, simvastatin, and digoxin (C3) as a promising combination. This blend effectively targeted these genes in human pancreatic cancer tumors in mice without causing any toxic effects. This discovery holds potential for advancing treatment options for pancreatic cancer.

In a retrospective study of 12,700 high-risk prostate cancer patients, ***Tan et al.*** (2020) **[75]** found that using statins, either alone or combined with metformin, was associated with reduced all-cause and prostate cancer-specific mortality. The combination of metformin and statins notably decreased all-cause mortality by 32% and prostate cancer

mortality by 54% among post-diagnosis users. However, using metformin alone did not show a significant association with mortality outcomes. These findings highlight the potential benefit of combining statins and metformin, particularly after a prostate cancer diagnosis, though further research is advised to confirm these results.

In 2020, ***Liu et al.*** **[76]** sought more effective pancreatic adenocarcinoma treatments and screened an FDA-approved drug library to target PDX1 and BIRC5 genes in PDAC. They discovered a promising combination of metformin, simvastatin, and digoxin (C3) that effectively targeted these genes in PDAC tumors in mice without causing toxicity. This finding suggests a potential precision-targeted therapy for PDAC, offering hope for improved treatment outcomes.

In their 2021 study, ***Antonio et al.*** **[77]** explored the potential of drugs like insulin, metformin, and statins in managing endocrine-related cancers. While evidence is not conclusive for all drugs, metformin shows promise as a chemo preventive and adjuvant agent, affecting tumor cell metabolism and the tumor microenvironment through multiple pathways. Combining metformin with statins seems promising in slowing endocrine-related tumor progression, but further research is needed to confirm their clinical significance in cancer treatment. Overall, these medications offer intriguing potential in fighting these cancers, but their exact roles in clinical cancer management require more investigation.

In their 2022 study on metastatic castration-resistant prostate cancer, ***Wilson et al.*** **[78]** found that metformin, particularly in combination with abiraterone acetate plus prednisone/prednisolone (AAP), was associated with improved prostate-specific antigen response rate (PSA-RR) and overall survival (OS). Statin use, especially alongside AAP, also correlated with extended OS. These findings suggest potential benefits of metformin and statins as adjuncts in treating this form of prostate cancer.

In a 2023 study by ***Antonio et al.*** **[79]**, metformin and simvastatin exhibited powerful anti-tumor effects in glioblastoma cells. When used together, they enhanced these effects, inhibiting cell functions like proliferation and migration. They influenced key oncogenic pathways and induced apoptosis and senescence in cells. This combination also showed promise in reducing tumor progression in mice and extending overall survival in human subjects, indicating a potential therapeutic approach for glioblastoma treatment.

In a 2023 study by ***Teper et al.*** **[80]**, combining low doses of metformin and simvastatin showed promise in preventing pancreatic cancer in mice predisposed to the disease. Individually, these drugs didn't significantly affect cancer development, but together, they reduced weight gain, limited the progression of precursor lesions, and inhibited pancreatic cancer cell growth. This combination might hold potential as a preventive strategy for pancreatic cancer, suggesting a need for clinical trials to explore its effectiveness further.

In 2023, ***Liu et al.*** **[81]** found that combining metformin and simvastatin had powerful anti-cancer effects in breast cancer models. This combination reduced tumor growth by targeting angiogenesis and the hypoxic tumor environment more effectively than using either drug alone. The treatment decreased a key regulator of these processes, endothelin 1 (ET-1), leading to reduced cell growth and improved normalization of blood vessels within tumors. This combined therapy demonstrated stronger anticancer effects compared to a known ET-1 receptor antagonist, suggesting its potential in fighting cancer by addressing these critical tumor environments.

Other clinical advantages

In 2010 ***Chandrashekhar et al*** **[82]** conducted the study that how gliclazide (a diabetes medicine) behaves when given with pravastatin and gemfibrozil (drugs for high cholesterol) in rats. Gliclazide alone lowered blood sugar levels in both normal and diabetic rats, peaking at 2 and 8 hours after taking it. When combined with pravastatin and gemfibrozil, the effect of gliclazide became stronger in rats. This happened because these combinations blocked enzymes responsible for breaking down gliclazide, making it stay in the body longer. The study suggested caution or avoiding using gliclazide with pravastatin and gemfibrozil in diabetes patients at risk of atherosclerosis.

In 2011, ***Kandhwal et al.*** **[83]** compared a fixed-dose combination (FDC) tablet of atorvastatin and metformin to taking separate tablets of each drug together. The study involved 40 male subjects and found that the FDC tablet had similar levels of atorvastatin and metformin in the blood as taking the separate tablets together. Both treatments were well tolerated without significant side effects. This suggests that the FDC tablet is as effective and safe as taking the individual tablets together, potentially

offering a simpler treatment regimen for patients with type 2 diabetes and/or high cholesterol.

In 2011, ***Metafome et al.*** **[84]** investigated liver issues in type 2 diabetes with high cholesterol levels using Goto-Kakizaki rats. They found that separately, atorvastatin and metformin improved blood sugar, insulin resistance, and fatty acid levels. However, when combined, these medications had a more significant impact, notably reducing liver inflammation markers and oxidative stress. This suggests that using atorvastatin and metformin together could offer enhanced benefits for liver health in this specific type of diabetes with high cholesterol.

In 2014, ***Lee et al.*** **[85]** studied the interaction between rosuvastatin (for cholesterol) and metformin (for type 2 diabetes) in healthy male volunteers. When taken together, rosuvastatin's blood levels showed a slight increase, but this change wasn't considered clinically significant. The overall impact on the drugs' behaviour or safety wasn't substantial, suggesting that combining them doesn't notably affect their effectiveness or safety.

In 2016, ***Kashi et al.*** **[86]** studied newly diagnosed type 2 diabetes patients taking metformin, dividing them into responders (≥1% reduction in HbA1c) and non-responders (<1% reduction). Among those responding well to metformin and taking atorvastatin, there were significant improvements in HbA1c, glucose, and lipid markers like LDL-C/HDL-C ratio, total cholesterol/HDL-C ratio, and atherogenic index. These improvements weren't as pronounced in nonresponders, especially regarding HDL-C levels. Metformin response also correlated with changes in triglycerides, total cholesterol, HDL-C, and LDL-C levels, indicating its influence on lipid profiles in these patients. Additionally, responders experienced more significant BMI changes from metformin compared to nonresponders. This suggests tailoring therapeutic strategies for nonresponders to metformin regarding lipid-related risks.

In 2016, ***Krysiak et al.*** [87] studied women with non-classic congenital adrenal hyperplasia (NC-CAH) and glucose metabolism issues, comparing them to a control group with similar glucose problems but normal adrenal function. All received metformin for at least 6 months, followed by 12 weeks of simvastatin (20 mg daily). Metformin alone in NC-CAH women increased plasma hormones linked to hyperandrogenism. However, simvastatin reduced cholesterol levels in both groups. The

combination of metformin and statin therapy in NC-CAH women decreased levels of testosterone, free testosterone, and other hormones linked to hyperandrogenism, suggesting a potential benefit in managing NC-CAH symptoms.

In 2018, ***Stopher et al.*** **[88]** examined a combination of drugs—digoxin, furosemide, metformin, and rosuvastatin—to understand their interactions. They found that the combination had minimal effects on most drugs except for rosuvastatin, which showed increased levels in the body. They tested varying doses of metformin and furosemide with rosuvastatin and noted that high doses of metformin significantly increased rosuvastatin levels, while furosemide had a minor effect, mostly at higher doses. Lowering metformin and furosemide doses could potentially reduce the interaction between these drugs.

In 2019, ***Jong et al.*** **[89]** studied atorvastatin and metformin individually and in a combined tablet to understand their interactions and the impact of food on their absorption. When taken together, atorvastatin and metformin didn't significantly alter each other's levels. However, the combined tablet's absorption was affected by food: it delayed atorvastatin absorption, reducing its concentration by 32%, while increasing metformin absorption by 56%, reflecting similar effects seen when these drugs were taken separately with food.

In 2020, ***Al Mozie et al.*** **[90]** conducted a study on male rats, administering simvastatin, metformin, and their combination orally over 40 days. The treated groups showed elevated blood parameters, including HDL cholesterol and blood glucose, along with increased sperm abnormalities. Testicular histopathology revealed germinal epithelium degeneration, while liver and kidney tissues exhibited various abnormalities such as hepatocyte and renal tubule vacuolation. Simvastatin showed more pronounced effects on lipid profile and testicular function compared to metformin, suggesting potential implications for male reproductive health.

In 2021, ***Jakab et al.*** **[91]** investigated the impact of metformin (MET) and simvastatin (SIM) on fat cell formation (adipogenesis). Using 3T3-L1 preadipocytes, the combination treatment of MET and SIM led to reduced fat cell accumulation, indicated by decreased Oil Red O staining intensity. This combined treatment also lowered the expression levels of important adipogenic transcription factors like PPARγ, C/EBPα, and SREBP-1C, suggesting an inhibitory effect on adipocyte differentiation.

In 2021, ***Buist et al.*** **[92]** studied the impact of metformin and simvastatin on gene expression in a human brain cell line. Metformin induced the expression of brain-derived neurotrophic factor (BDNF) and a specific MECP2 isoform (E1) while inhibiting another isoform (E2). Simvastatin, on the other hand, notably suppressed BDNF transcription without a significant effect on MECP2E2 transcripts. The study highlighted distinct transcriptional effects of these drugs on specific genetic variants, suggesting their potential in related disorders.

In a 2022 study by ***Douglas et al.*** **[93]**, the effects of metformin and statins, both under investigation for age-related health decline, were explored in older adults undergoing resistance training. The study, a secondary analysis of the MASTERS trial, found that combining metformin and statins seemed to counteract metformin-induced impaired muscle growth during resistance training, potentially linked to increased M2-like macrophages. This interaction might have implications for mitigating age-related muscle loss, offering insights into preserving muscle benefits despite metformin use in older individuals.

In a 2022 study by ***Long et al.*** **[94]**, metformin was found to reduce muscle growth response to exercise in older adults. However, when combined with statins, the negative effect of metformin on muscle growth was reversed. Although the combination didn't notably affect strength, it appeared to boost muscle fiber growth, possibly due to an increase in specific types of immune cells. This interaction between metformin and statins might help offset metformin's negative impact on the benefits of resistance training in preventing age-related muscle decline.

In a 2023 study by ***Bak et al.*** **[95]**, analysing Korean health data, adding metformin to statin therapy in dyslipidemia patients was linked to a reduced risk of myopathy compared to using statins alone. The study suggests that combining metformin with statins might offer protective effects against muscle issues induced by statin therapy.

In a 2023 study by ***Krysiak et al.*** **[96]**, postmenopausal women with prediabetes were given metformin alongside rosuvastatin or without statin therapy. The research suggested that metformin reduced certain hormone levels, FSH and LH, more significantly in women on rosuvastatin compared to those not on statins. This indicates that statin therapy might enhance metformin's effects on hormone levels in this group of women.

In a 2023 study by ***Lundin et al.*** **[97]**, hypertensive patients with mild cognitive impairment (MCI) using antihypertensive medications (AHMs) showed a reduced risk of progressing to Alzheimer's disease and related dementias (ADRD). All five AHM classes studied independently reduced ADRD risk. Combining diuretics or calcium channel blockers with Metformin, or any AHM with statins, displayed a stronger protective effect against ADRD progression compared to individual AHM use, suggesting potential benefits from these drug combinations in slowing cognitive decline.

It's important to note that the specific outcomes may vary depending on the individual patient, the combination of drugs used, and other factors like diet, exercise, and lifestyle. The choice of antidiabetic and antilipidemic medications should be tailored to the patient's unique needs and medical history, and the treatment plan should be closely monitored and adjusted as necessary to achieve optimal results.

Patients on this combination therapy should work closely with their healthcare providers to assess their progress, manage potential side effects, and make necessary lifestyle changes to support their overall health and well-being. Additionally, the benefits and risks of combination therapy should be discussed thoroughly with the healthcare team to ensure the most appropriate treatment approach.

REFERENCES:

1. "Diabetes Mellitus (DM) - Hormonal and Metabolic Disorders". MSD Manual Consumer Version. Retrieved 1 October 2022.
2. Shoback DG, Gardner D, eds. (2011). "Chapter 17". Greenspan's basic & clinical endocrinology (9th ed.). New York: McGraw-Hill Medical. ISBN 978-0-07-162243-1.
3. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN (July 2009). "Hyperglycemic crises in adult patients with diabetes". Diabetes Care. 32 (7): 1335–1343. doi:10.2337/dc09-9032. PMC 2699725.
4. Facts & figures". International Diabetes Federation. Retrieved 2023-08-10.
5. De Silva AP, De Silva SH, Haniffa R, Liyanage IK, Jayasinghe S, Katulanda P, et al. (April 2018). "Inequalities in the prevalence of diabetes mellitus and its risk factors in Sri Lanka: a lower middle income country". International Journal for Equity in Health. 17 (1): 45. doi:10.1186/s12939-018-0759-3. PMC 5905173. PMID 29665834.
6. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. (December 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010". Lancet. 380 (9859): 2163–2196. doi:10.1016/S0140-6736(12)61729-2. PMC 6350784. PMID 23245607.
7. Wing, Edward J; Schiffman, Fred (2022). Cecil Essentials of Medicine (10th ed.). Pennsylvania: Elsevier. pp. 282–297, 662–677. ISBN 978-0-323-72271-1
8. Rother KI (April 2007). "Diabetes treatment--bridging the divide". The New England Journal of Medicine. 356 (15): 1499–1501. doi:10.1056/NEJMp078030. PMC 4152979. PMID 17429082.
9. Petzold A, Solimena M, Knoch KP (October 2015). "Mechanisms of Beta Cell Dysfunction Associated With Viral Infection". Current Diabetes Reports (Review). 15 (10): 73. doi:10.1007/s11892-015-0654-x. PMC 4539350. PMID 26280364. So far, none of the hypotheses accounting for virus-induced beta cell autoimmunity has been supported by stringent evidence in humans, and the involvement of several mechanisms rather than just one is also plausible.
10. Laugesen E, Østergaard JA, Leslie RD (July 2015). "Latent autoimmune diabetes of the adult: current knowledge and uncertainty". Diabetic Medicine. 32 (7): 843–852. doi:10.1111/dme.12700. PMC 4676295. PMID 25601320.
11. Shoback DG, Gardner D, eds. (2011). "Chapter 17". Greenspan's basic & clinical endocrinology (9th ed.). New York: McGraw-Hill Medical. ISBN 978-0-07-162243-1.
12. "Diabetes". www.who.int. Retrieved 1 October 2022.
13. Carris NW, Magness RR, Labovitz AJ (February 2019). "Prevention of Diabetes Mellitus in Patients With Prediabetes". The American Journal of Cardiology. 123 (3): 507–512. doi:10.1016/j.amjcard.2018.10.032. PMC 6350898. PMID 30528418.
14. Williams textbook of endocrinology (12th ed.). Elsevier/Saunders. 2011. pp. 1371–1435. ISBN 978-1-4377-0324-5.

15. https://www.drugs.com/drug-class/antihyperlipidemic-agents.html
16. AMDA – The Society for Post-Acute and Long-Term Care Medicine (February 2014), "Ten Things Physicians and Patients Should Question", Choosing Wisely: an initiative of the ABIM Foundation, AMDA – The Society for Post-Acute and Long-Term Care Medicine, retrieved 20 April 2015.
17. Jun M, Foote C, Lv J, et al. (2010). "Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis". Lancet. 375 (9729): 1875–1884. doi:10.1016/S0140-6736(10)60656-3. PMID 20462635. S2CID 15570639.
18. Which Medicines Lower 'Bad' (LDL) Cholesterol?
19. ^ FDA Heart Health Online – Bile Acid Sequestrants
20. "Ezetimibe Monograph for Professionals". Drugs.com. American Society of Health-System Pharmacists. Archived from the original on 17 June 2019. Retrieved 13 April 2019.
21. Zhang L, Song K, Zhu M, Shi J, Zhang H, Xu L, Chen Y (August 2016). "Proprotein convertase subtilisin/kexin type 9 (PCSK9) in lipid metabolism, atherosclerosis and ischemic stroke". International Journal of Neuroscience. 126 (8): 675–680. doi:10.3109/00207454.2015.1057636. PMID 26040332. S2CID 40377207.
22. Chapter P-6. Applications to Specific Classes of Compounds". Nomenclature of Organic Chemistry : IUPAC Recommendations and Preferred Names 2013 (Blue Book). Cambridge: Royal Society of Chemistry. 2014. pp. 648–1047. doi:10.1039/9781849733069-00648. ISBN 978-0-85404-182-4.
23. "Omega−3 Fatty Acids". Office of Dietary Supplements, US National Institutes of Health. 26 March 2021. Retrieved 10 June 2021.
24. Nicole Fusco, Brian Sils, Jennifer S Graff, Kristin Kistler, Kimberly Ruiz. (2023) Cost-sharing and adherence, clinical outcomes, health care utilization, and costs: A systematic literature review. Journal of Managed Care & Specialty Pharmacy 29:1, 4-16.
25. Houy M. Value-based benefit design: a purchaser guide. NationalBusiness Coalition on Health. January 2009. Available at: http://www.nbch.org/NBCH/files/ccLibraryFiles/Filename/000000000222/VBBD%20Purchaser%20Guide.pdf. Accessed July 22, 2013
26. Anjana RM, Ali MK, Pradeepa R, et al The need for obtaining accurate nationwide estimates of diabetes prevalence in India: rationale for a national study on diabetes. Indian J Med Res 2011;1133:369–80.
27. Ahmad, Z., Banerjee, P., Hamon, S., Chan, K. C., Bouzelmat, A., Sasiela, W. J., et al. (2019). Inhibition of Angiopoietin-like Protein 3 with a Monoclonal Antibody Reduces Triglycerides in Hypertriglyceridemia. Circulation 140 (6), 470–486. doi:10.1161/CIRCULATIONAHA.118.039107
28. Hibiscus sabdariffa in Diabetes Prevention and Treatment-Does It Work? An Evidence-Based Review. Jamrozik D, Borymska W, Kaczmarczyk-Żebrowska Foods. 2022 Jul 19;11(14):2134. doi: 10.3390/foods11142134.
29. Gupta A, Gupta R, Sharma KK, et alPrevalence of diabetes and cardiovascular risk factors in middle-class urban participants in IndiaBMJ Open Diabetes Research and Care 2014;2:e000048. doi: 10.1136/bmjdrc-2014-000048

30. Bulcao, Caroline, Fernando Flexa Ribeiro-Filho, Adriana Sanudo, and Sandra G. Roberta Ferreira. "Effects of simvastatin and metformin on inflammation and insulin resistance in individuals with mild metabolic syndrome." American journal of cardiovascular drugs 7 (2007): 219-224.
31. Balasubramanian, R., et al. "Assessment of the efficacy and tolerability of a fixed dose combination of atorvastatin 10 mg+ metformin SR 500 mg in diabetic dyslipidaemia in adult Indian patients." Journal of the Indian Medical Association 106.7 (2008): 464-467.
32. Tousoulis, Dimitris, et al. "Impact of 6 weeks of treatment with low-dose metformin and atorvastatin on glucose-induced changes of endothelial function in adults with newly diagnosed type 2 diabetes mellitus: A single-blind study." Clinical therapeutics 32.10 (2010): 1720-1728.
33. Kandhwal, Kirti, et al. "Pharmacokinetics of a fixed-dose combination of atorvastatin and metformin extended release versus concurrent administration of individual formulations: a randomized, open-label, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study." Clinical drug investigation 31 (2011): 853-863.
34. Tousoulis, Dimitris, et al. "Combined effects of atorvastatin and metformin on glucose-induced variations of inflammatory process in patients with diabetes mellitus." International journal of cardiology 149.1 (2011): 46-49.
35. Tousoulis, Dimitris, et al. "Combined effects of atorvastatin and metformin on glucose-induced variations of inflammatory process in patients with diabetes mellitus." International journal of cardiology 149.1 (2011): 46-49.
36. Islam, M. S., Alam, A. H. M. K., Rahman, M. A. A., Ali, Y., Mamun, A., Rahman, M., & Rashid, M. (2012). Effects of Combination of Antidiabetic Agent and Statin on Alloxan-induced Diabetes with Cardiovascular Diseases in Rats. Journal of Scientific Research, 4(3).
37. Krysiak, Robert, and Boguslaw Okopien. "Haemostatic Effects of Metformin in Simvastatin-Treated Volunteers with Impaired Fasting Glucose." Basic & clinical pharmacology & toxicology 111, no. 6 (2012): 380-384.
38. Krysiak, Robert, and Boguslaw Okopien. "Lymphocyte-suppressing and systemic anti-inflammatory effects of high-dose metformin in simvastatin-treated patients with impaired fasting glucose." Atherosclerosis 225.2 (2012): 403-407.
39. Krysiak, Robert, and Bogusław Okopien. "The effect of metformin on monocyte secretory function in simvastatin-treated patients with impaired fasting glucose." Metabolism 62, no. 1 (2013): 39-43.
40. Singh, B. K., A. Singh, and V. Kumar. "Ameliorative effect of adjunct therapy of metformin with atorvastatin on streptozotocin-induced diabetes mellitus in rats." Drug Research (2015): 28-32
41. Ramadan, W. H., & Kabbara, W. K. (2015). Sitagliptin/Simvastatin: a first combination tablet to treat type 2 diabetes and hypercholesterolemia–a review of its characteristics. Vascular health and risk management, 125-132.

42. Oh, Ju-Hee, et al. "Designing of the fixed-dose gastroretentive bilayer tablet for sustained release of metformin and immediate release of atorvastatin." Drug development and industrial pharmacy 42.2 (2016): 340-349.
43. Hao, Z., et al. "Atorvastatin plus metformin confer additive benefits on subjects with dyslipidemia and overweight/obese via reducing ROCK2 concentration." Experimental and Clinical Endocrinology & Diabetes 124.04 (2016): 246-250.
44. Luo, Fei, Yuan Guo, Gui-yun Ruan, Jun-ke Long, Xi-long Zheng, Qin Xia, Shui-ping Zhao, Dao-quan Peng, Zhen-fei Fang, and Xiang-ping Li. "Combined use of metformin and atorvastatin attenuates atherosclerosis in rabbits fed a high-cholesterol diet." Scientific reports 7, no. 1 (2017): 2169.o
45. Van Stee, Mariël F., Albert A. de Graaf, and Albert K. Groen. "Actions of metformin and statins on lipid and glucose metabolism and possible benefit of combination therapy." Cardiovascular diabetology 17 (2018): 1-22.
46. Jia, W., Bai, T., Zeng, J., Niu, Z., Fan, D., Xu, X., ... & Dai, X. (2021). Combined administration of metformin and atorvastatin attenuates diabetic cardiomyopathy by inhibiting inflammation, apoptosis, and oxidative stress in type 2 diabetic mice. Frontiers in Cell and Developmental Biology, 9, 634900.
47. HASYMI, ABDURRAHMAN, et al. "Combination Use of Simvastatin and Metformin in Male Wistar Rats Following the Atherogenic Diet." International Journal of Pharmaceutical Research 13.2 (2021).
48. Banaszewska, Beata, et al. "Comparison of simvastatin and metformin in treatment of polycystic ovary syndrome: prospective randomized trial." The Journal of Clinical Endocrinology & Metabolism 94.12 (2009): 4938-4945.
49. Kazerooni, Talieh, Azam Shojaei-Baghini, Sedigheh Dehbashi, Nasrin Asadi, Fariborz Ghaffarpasand, and Yasaman Kazerooni. "Effects of metformin plus simvastatin on polycystic ovary syndrome: a prospective, randomized, double-blind, placebo-controlled study." Fertility and sterility 94, no. 6 (2010): 2208-2213.
50. Banaszewska, Beata, et al. "Effects of simvastatin and metformin on polycystic ovary syndrome after six months of treatment." The Journal of Clinical Endocrinology & Metabolism 96.11 (2011): 3493-3501
51. Celik, O., and O. Acbay. "Effects of metformin plus rosuvastatin on hyperandrogenism in polycystic ovary syndrome patients with hyperlipidemia and impaired glucose tolerance." Journal of endocrinological investigation 35 (2012): 905-910.
52. Hamdy, I., and N. Shiry. "Comparison between Metformin and Simvastatin in Treatment of Polycystic Ovary Syndrome." Population Sciences 37 (2012): 1-9.
53. Karakas, Sidika E., et al. "Free fatty acid binding protein-4 and retinol binding protein-4 in polycystic ovary syndrome: response to simvastatin and metformin therapies." Gynecological Endocrinology 29.5 (2013): 483-487.
54. Sun, Jie, Yang Yuan, Rongrong Cai, Haixia Sun, Yi Zhou, Pin Wang, Rong Huang, Wenqing Xia, and Shaohua Wang. "An investigation into the therapeutic effects of statins with metformin on polycystic ovary syndrome: a meta-analysis of randomised controlled trials." BMJ open 5, no. 3 (2015): e007280.
55. Pourmatroud, E., Mohammadjafari, R., & Roozitalab, M. (2015). Comparison of metformin and simvastatin administration in women with polycystic ovary syndrome

before intra-cytoplasmic sperm injection cycle: a prospective, randomized, clinical trial study. Iranian Red Crescent Medical Journal, 17(12).

56. Seyam, Emaduldin, and Enas Hefzy. "Long-term effects of combined simvastatin and metformin treatment on the clinical abnormalities and ovulation dysfunction in single young women with polycystic ovary syndrome." Gynecological Endocrinology 34, no. 12 (2018): 1073-1080.
57. Malik, M., Tasnim, N., & Mahmud, G. (2018). Effect of metformin alone compared with metformin plus simvastatin on polycystic ovarian syndrome in Pakistani women. Journal of the College of Physicians and Surgeons Pakistan, 28(3), 184-188.
58. Shah, Mohsin, Asif Ali, Muhammad Omar Malik, Farhat Rehman, Haroon Badshah, Ehtesham Ehtesham, and Salvatore Giovanni Vitale. "Treatment with metformin and combination of metformin plus pioglitazone on serum levels of IL-6 and IL-8 in polycystic ovary syndrome: a randomized clinical trial." Hormone and Metabolic Research 51, no. 11 (2019): 714-722
59. Almalki, Hussain H., Turki M. Alshibani, Abdullah A. Alhifany, and Omar A. Almohammed. "Comparative efficacy of statins, metformin, spironolactone and combined oral contraceptives in reducing testosterone levels in women with polycystic ovary syndrome: a network meta-analysis of randomized clinical trials." BMC women's health 20 (2020): 1-6.
60. Liu, Yanbo, Yupei Shao, Jiping Xie, Linlin Chen, and Guang Zhu. "The efficacy and safety of metformin combined with simvastatin in the treatment of polycystic ovary syndrome: A meta-analysis and systematic review." Medicine 100, no. 31 (2021).
61. Meng, Jie, and Yingjun Zhu. "Efficacy of simvastatin plus metformin for polycystic ovary syndrome: A meta-analysis of randomized controlled trials." European Journal of Obstetrics & Gynecology and Reproductive Biology 257 (2021): 19-24.
62. Nakai, Y., Isayama, H., Sasaki, T., Mizuno, S., Sasahira, N., Kogure, H., ... & Koike, K. (2013). Clinical outcomes of chemotherapy for diabetic and nondiabetic patients with pancreatic cancer: better prognosis with statin use in diabetic patients. *Pancreas*, *42*(2), 202-208.
63. Babcook, M. A., R. M. Sramkoski, H. Fujioka, F. Daneshgari, A. Almasan, S. Shukla, R. R. Nanavaty, and S. Gupta. "Combination simvastatin and metformin induces G1-phase cell cycle arrest and Ripk1-and Ripk3-dependent necrosis in C4-2B osseous metastatic castration-resistant prostate cancer cells." Cell death & disease 5, no. 11 (2014): e1536-e1536.
64. Babcook, Melissa A., et al. "Synergistic simvastatin and metformin combination chemotherapy for osseous metastatic castration-resistant prostate cancer." Molecular cancer therapeutics 13.10 (2014): 2288-2302.
65. Chen, Hsin-Hung, Ming-Chia Lin, Chih-Hsin Muo, Su-Yin Yeh, Fung-Chang Sung, and Chia-Hung Kao. "Combination therapy of metformin and statin may decrease hepatocellular carcinoma among diabetic patients in Asia." Medicine 94, no. 24 (2015).
66. Danzig, M. R., S. Kotamarti, R. A. Ghandour, M. B. Rothberg, B. P. Dubow, M. C. Benson, K. K. Badani, and J. M. McKiernan. "Synergism between metformin and

statins in modifying the risk of biochemical recurrence following radical prostatectomy in men with diabetes." Prostate cancer and prostatic diseases 18, no. 1 (2015): 63-68.
67. Chen, Chang-I., et al. "Cancer risk in HBV patients with statin and metformin use: a population-based cohort study." Medicine 94.6 (2015).
68. Pennanen, Pasi, et al. "The effects of metformin and simvastatin on the growth of LNCaP and RWPE-1 prostate epithelial cell lines." European Journal of Pharmacology 788 (2016): 160-167.
69. Kozak, Margaret M., et al. "Statin and metformin use prolongs survival in patients with resectable pancreatic cancer." Pancreas 45.1 (2016): 64-70.
70. Wang, Zhen-Shi, Hua-Rong Huang, Lan-Yue Zhang, Seungkee Kim, Yan He, Dong-Li Li, Chelsea Farischon et al. "Mechanistic study of inhibitory effects of metformin and atorvastatin in combination on prostate cancer cells in vitro and in vivo." Biological and Pharmaceutical Bulletin 40, no. 8 (2017): 1247-1254.
71. Nimako, G. K., Wintrob, Z. A., Sulik, D. A., Donato, J. L., & Ceacareanu, A. C. (2017). Synergistic benefit of statin and metformin in gastrointestinal malignancies. Journal of pharmacy practice, 30(2), 185-194.
72. Del Campo, José A., Marta García-Valdecasas, Antonio Gil-Gómez, Ángela Rojas, Paloma Gallego, Javier Ampuero, Rocío Gallego-Durán et al. "Simvastatin and metformin inhibit cell growth in hepatitis C virus infected cells via mTOR increasing PTEN and autophagy." PloS one 13, no. 1 (2018): e0191805.
73. Kim, Josephine S., Jane Turbov, Rebecca Rosales, Larry G. Thaete, and Gustavo C. Rodriguez. "Combination simvastatin and metformin synergistically inhibits endometrial cancer cell growth." Gynecologic oncology 154, no. 2 (2019): 432-440.
74. Liu, Shi-He, Juehua Yu, Justin F. Creeden, Jeffrey M. Sutton, Stephen Markowiak, Robbi Sanchez, John Nemunaitis et al. "Repurposing metformin, simvastatin and digoxin as a combination for targeted therapy for pancreatic ductal adenocarcinoma." Cancer letters 491 (2020): 97-107.
75. Tan, Xiang-Lin, et al. "Individual and joint effects of metformin and statins on mortality among patients with high-risk prostate cancer." Cancer Medicine 9.7 (2020): 2379-2389.
76. Liu, Shi-He, et al. "Repurposing metformin, simvastatin and digoxin as a combination for targeted therapy for pancreatic ductal adenocarcinoma." Cancer letters 491 (2020): 97-107.
77. Leon-Gonzalez, Antonio J., Juan M. Jimenez-Vacas, Antonio C. Fuentes-Fayos, Andre Sarmento-Cabral, Aura D. Herrera-Martinez, Manuel D. Gahete, and Raul M. Luque. "Role of metformin and other metabolic drugs in the prevention and therapy of endocrine-related cancers." Current Opinion in Pharmacology 60 (2021): 17-26.
78. Wilson, Brooke E., et al. "Effects of metformin and statins on outcomes in men with castration-resistant metastatic prostate cancer: Secondary analysis of COU-AA-301 and COU-AA-302." European Journal of Cancer 170 (2022): 296-304.
79. Fuentes-Fayos, Antonio C., Miguel E. G-García, Jesús M. Pérez-Gómez, Antonio J. Montero-Hidalgo, Julia Martín-Colom, Carlos Doval-Rosa, Cristóbal Blanco-Acevedo

et al. "Metformin and simvastatin exert additive antitumour effects in glioblastoma via senescence-state: clinical and translational evidence." EBioMedicine 90 (2023).
80. Teper, Yaroslav, et al. "Low dosage combination treatment with metformin and simvastatin inhibits obesity-promoted pancreatic cancer development in male KrasG12D mice." Scientific Reports 13.1 (2023): 16144.
81. Liu, Jie, et al. "Metformin and simvastatin synergistically suppress endothelin 1-induced hypoxia and angiogenesis in multiple cancer types." Cancer Science 114.2 (2023): 640.
82. Sultanpur, Chandrashekhar M., N. S. Reddy, S. Kumar, S. Satyanarayana, and K. E. Kumar. "Drug-drug interaction between pravastatin and gemfibrozil (antihyperlipidemic) with gliclazide (antidiabetic) in rats." Journal of Young Pharmacists 2, no. 2 (2010): 152-155.
83. Kandhwal, K., Dey, S., Nazarudheen, S., Arora, R., Reyar, S., Thudi, N. R., ... & Rao, S. (2011). Pharmacokinetics of a fixed-dose combination of atorvastatin and metformin extended release versus concurrent administration of individual formulations: a randomized, open-label, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study. Clinical drug investigation, 31, 853-863.
84. Matafome, P., Louro, T., Rodrigues, L., Crisóstomo, J., Nunes, E., Amaral, C., Monteiro, P., Cipriano, A. and Seiça, R. (2011), Metformin and atorvastatin combination further protect the liver in type 2 diabetes with hyperlipidaemia. Diabetes Metab. Res. Rev., 27: 54-62.
85. Lee, D., Roh, H., Son, H., Jang, S. B., Lee, S., Nam, S. Y., & Park, K. (2014). Pharmacokinetic interaction between rosuvastatin and metformin in healthy Korean male volunteers: a randomized, open-label, 3-period, crossover, multiple-dose study. Clinical Therapeutics, 36(8), 1171-1181.
86. Kashi, Z., Mahrooz, A., Kianmehr, A., & Alizadeh, A. (2016). The role of metformin response in lipid metabolism in patients with recent-onset type 2 diabetes: HbA1c level as a criterion for designating patients as responders or nonresponders to metformin. PloS one, 11(3), e0151543.
87. Krysiak, R., et al. "The effect of simvastatin on plasma steroid hormone levels in metformin-treated women with non-classic congenital adrenal hyperplasia." Experimental and Clinical Endocrinology & Diabetes (2016): 215-219.
88. Stopfer, Peter, et al. "Effects of metformin and furosemide on rosuvastatin pharmacokinetics in healthy volunteers: implications for their use as probe drugs in a transporter cocktail." European journal of drug metabolism and pharmacokinetics 43 (2018): 69-80.
89. Jong-Lyul Ghim, Nguyen Thi Thu Phuong, Min Jung Kim, Eun-Ji Kim, Geun Seog Song, Sangzin Ahn, Jae-Gook Shin & Eun-Young Kim (2019) Pharmacokinetics of fixed-dose combination of atorvastatin and metformin compared with individual tablets, Drug Design, Development and Therapy, 13:, 1623-1632, DOI: 10.2147/DDDT.S193254
90. Al_Mozie, Muhsin SG, Abbas A. Khudhair, and Noora S. Ghalib. "Effects of Simvastatin and/or Metformin Administration on Lipid Profile and Reproductive Function in Adults Male Rats." Medico-legal Update 20.3 (2020): 507.

91. Jakab, Jelena, et al. "Effect of Metformin and Simvastatin in Inhibiting Proadipogenic Transcription Factors." Current Issues in Molecular Biology 43.3 (2021): 2082-2097.
92. Buist, Marjorie, David Fuss, and Mojgan Rastegar. "Transcriptional regulation of MECP2E1-E2 isoforms and BDNF by metformin and simvastatin through analyzing nascent RNA synthesis in a human brain cell line." Biomolecules 11.8 (2021): 1253.
93. Long, Douglas E., Kate Kosmac, Cory M. Dungan, Marcas M. Bamman, Charlotte A. Peterson, and Philip A. Kern. "Potential benefits of combined statin and metformin therapy on resistance training response in older individuals." Frontiers in Physiology 13 (2022): 872745.
94. Long, D. E., Kosmac, K., Dungan, C. M., Bamman, M. M., Peterson, C. A., & Kern, P. A. (2022). Potential benefits of combined statin and metformin therapy on resistance training response in older individuals. Frontiers in Physiology, 13, 872745.
95. Bak, Keunhyeong, et al. "Impact of metformin on statin-associated myopathy risks in dyslipidemia patients." Pharmacology Research & Perspectives 11.4 (2023): e01114.
96. Krysiak, Robert, Karolina Kowalcze, and Bogusław Okopień. "Rosuvastatin potentiates gonadotropin-lowering effects of metformin in postmenopausal women: A pilot study." Pharmacology 108.3 (2023): 245-254.
97. Lundin, Sori K., et al. "Associations of Antihypertensive Medication Consumption and Drug-Drug Interaction with Statin and Metformin with Reduced Alzheimer's Disease and Related Dementias Risk among Hypertensive Patients with Mild Cognitive Impairment using High Volume Claims Data." Research Square (2023).