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The effect of isotretinoin therapy on the circulatory system

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ABSTRACT

Isotretinoin is a drug belonging to the group of retinoids, which is mainly used in dermatology. Through its mechanism of action, it leads to a reduction in sebum production, which effectively inhibits the formation of acne. Unfortunately, this drug exhibits numerous side effects. This study aimed to review the literature in terms of clinical cases and articles on the side effects of isotretinoin in the context of the cardiovascular system. It has been proven that isotretinoin can harm the circulatory system, causing changes in the structure of the heart walls, thromboembolic episodes, coronary events and lipid metabolism disorders. Further clinical trials are needed to better understand these side effects.

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Keywords: isotretinoin, 13-cis-retinoic acid, retinoids, acne

INTRODUCTION

13-cis-retinoic acid, or isotretinoin, belongs to retinoids, so it has the activity of vitamin A. It was first approved for the treatment of acne in 1982 by the American Food and Drug Administration (FDA), which was a breakthrough in the treatment of severe forms of acne [1, 2]. Through the mechanism of its action, it affects the life cycle of sebocytes, keratinization and sebum secretion. In this way, it inhibits the formation of blackheads and limits the development of *Cutibacterium acnes* [2, 3]. Retinoids have been divided into four generations (Tab. 1) [4]. Isotretinoin belongs to the first generation of retinoids. Individual groups differ in chemical structure, bioavailability and lipophilicity [4]. These drugs are widely used in dermatological diseases. However, they are characterized by numerous side effects such as dry skin and mucous membranes, teratogenicity, neurological disorders, nephrotoxicity and visual impairment [5, 6]. Further exploration of adverse effects of therapy, including cardiovascular effects and cardiotoxicity, with the use of isotretinoin is still the subject of much scientific research.

MECHANISM OF ACTION

Isotretinoin is a lipophilic compound, therefore carrier proteins found in plasma (RBP, retinoid binding proteins) and cytoplasm (CRBP, cellular retinoid binding proteins) are necessary for its transport. After crossing the cell membrane, it is isomerized to ATRA (all-trans-retinoic acid). This compound is then transported to the cell nucleus with the participation of CRABP-2 (cellular retinoic acid-binding protein 2) and after reaching the cell nucleus, ATRA is bound to RAR (retinoic acid receptor). This process leads to the expression of TP53 and ARF. As a result, p14 and p53 are produced. These proteins, in a cascade of successive reactions, lead to apoptosis of the sebaceous cell. In addition, p53 inhibits the action of insulin growth factor 1 (IGF-1), which is one of the main factors leading to sebaceous cell overgrowth and leads to increased sebum secretion [7].

Table 1. Classes of retinoids [4]

1st generation	2nd generation	3rd generation	4th generation
Tretinoin (all-trans-retinoic acid)	There are no second-generation topical retinoid formulations available	Tazarotene Bexarotene Adapalene	Trifarotene

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USE

Isotretinoin is most often used in the treatment of acne because it has a documented effect here and has a very good therapeutic effect. It is used in selected cases, such as:

— severe and very severe forms of acne such as acne phlegmonosa, acne conglobata, acne nodulo-cistica and acne inversa;
— if conventional treatment for severe or moderate disease has not produced the desired results within 18 months, or if the disease has relapsed despite treatment;
— in case of no improvement exceeding 50% of the initial condition after 2–3 cycles of recommended antibiotic therapy lasting 3 months each in papuloprick acne;
— cases of moderate severity with a tendency to scarring;
— fulminant acne [2].

In addition, due to its anti-inflammatory and immunomodulatory properties, isotretinoin can be used in the treatment of such diseases as genodermatosis, inflammatory diseases, skin cancers (basal cell carcinoma or squamous cell carcinoma), psoriasis and genital warts. Therapies for the above-mentioned conditions, however, require further clinical research [8, 9].

Topical retinoids work by binding to retinoic acid receptors and directly activating them with the help of ligand-receptor formation, causing retinoic acid-responsive genes to be transcribed [4]. RXR retinoid X receptors form heterodimers with various ligands important for cell function and physiology, enabling the cell to function properly [4]. Retinoids normalize abnormal exfoliation in acne by increasing hair follicle epithelial replacement and accelerating corneocyte exfoliation, leading to the removal of mature blackheads and inhibition of the formation of microcomedones [4]. In psoriasis, only topical retinoid tazarotene is indicated. Tazarotene is hydrolysed in tissues to tazarotenoic acid, which then binds to retinoic acid receptors [4]. This combination leads to the regulation of genes responsible for cell proliferation and inflammation, which is a hallmark of psoriasis, a condition characterized by increased epidermal proliferation and inflammation [4]. Tretinoin is the only retinoid with an official indication for use in photoaging and rhytides. The mechanism by which this occurs is molecular in nature and occurs in two different ways, albeit synergistically [4]. The first mechanism of action occurs as a result of blocking the activator protein 1 (AP-1), responsible for the activation of matrix metalloproteinases (MMP) that break down collagen, thus inhibiting the breakdown of collagen [4]. Topical application of all-trans retinoic acid induces collagen synthesis by increasing the expression of type 1 procollagen. Bexarotene is indicated for the treatment of retinoid X receptor-selective retinoid (RXR) cutaneous T-cell lymphoma [4]. Bexarotene binds to RXR nuclear receptors, activating them, leading to inhibition of the G1, G2 and M phases of the cell cycle, reducing proliferation and increasing apoptosis of cancer cells [4]. Adapalene modulates cellular keratinization and inflammatory process [4]. This anti-inflammatory effect is due to the inhibition of the lipooxygenase activity and also to the oxidative metabolism of arachidonic acid [4]. Trifarotene is a new fourth-generation retinoid with a selective action on RAR-γ [10]. Trifarotene, by means of RAR-γ, causes an increased expression of transglutaminase 1, promoting keratinocyte cohesion [10]. Trifarotene is an agonist of retinoic acid receptors (RAR), with particular activity at the gamma subtype of RAR [10]. Stimulation of RAR results in modulation of target genes which are associated with various processes, including cell differentiation and mediation of inflammation [10].

CLINICAL CASES

According to many scientific studies, the use of oral isotretinoin has beneficial effects in the treatment of acne vulgaris, but it is associated with many adverse health effects (Tab. 2) [11], which is why the FDA has approved its use in the case of severe, refractory nodular acne [12]. Isotretinoin, as a derivative of retinoic acid, directly inhibits the activity of sebaceous glands, resulting in a decrease in sebum production and a reduction in blackheads. Reduced sebum production leads to a reduction in the growth of *Cutibacterium acnes bacteria*, which in turn leads to a decrease in the release of inflammatory mediators and reduces inflammation of the epidermis [12]. The recommended starting dose of isotretinoin for the treatment of moderate acne is 0.25–0.4 mg/kg/d and 0.5 mg/kg for severe acne, gradually increasing to 1 mg/kg/d. Pharmacotherapy with isotretinoin should be administered until the maximum dose of 120–150 mg/kg/day is reached in order to reduce the risk of relapse [12]. A study was conducted to check whether isotretinoin affects the functioning of the heart muscle [13]. For this purpose, 20 men suffering from acne vulgaris were included in the study. Patients were treated with isotretinoin at a dose of 0.5 mg/kg/d. The study lasted 10 weeks. Doppler echocardiography was performed before and at the end of the study. During treatment, patients showed a reduction in the vertical diameter of the right atrium, the longitudinal diameter of the left atrium, the volume of the left atrium, and the diastolic diameter of the left ventricle. A significant increase in diastolic septal thickness, posterior diastolic wall thickness, relative wall thickness and left ventricle (LV) mass was observed. The LV mass index showed an increase in ventricular mass and a decrease in cavity size. When examining the systolic activity of LV, a decrease in the cardiac index was observed [13]. The study proved that isotretinoin therapy at a dose of 0.5 mg/kg/d

Table 2. Characteristics of isotretinoin. Author's own elaboration based on literature [11]

Category	Details
Indicate	Treatment of severe forms of acne (e.g. nodular, conglobation) resistant to standard therapies using systemic antibiotics and topical therapy
Dosage	• Dosage: 0.5 mg/kg body weight/day taking into account individual characteristics • Method of administration: oral • Length of treatment: usually 15–20 weeks
Treatment monitoring	• Before starting therapy: pregnancy test, laboratory tests: complete blood count, lipidogram, liver enzymes (AST, ALT) • Follow-up blood tests every 1–3 months
Interactions	• In combination with vitamin A, it increases the risk of hypervitaminosis • Do not combine with tetracyclines due to the risk of developing intracranial hypertension • Isotretinoin cyproterone acetate with ethinylestradiol, increases the risk of cardiovascular events • Drospirenone + ethinylestradiol increase the risk of thromboembolism
Side effects	• Dryness of the skin and mucous membranes • Worsening of acne at the beginning of treatment • Visual disturbances, dry eyes • Muscle and joint pain • Elevated liver enzymes • Lipid disorders • Potential risk of enterocolitis
Contraindications	• Pregnancy, breastfeeding • Hypersensitivity to isotretinoin • Hepatic • Hypervitaminosis A • Tetracycline therapy
Comments	• Due to its teratogenic nature, isotretinoin therapy requires the use of effective contraception. Contraception contributes to an increased risk of thromboembolic events • Therapy poses a risk of mental disorders, including depression and suicidal thoughts • May affect the ability to drive and use machines, due to the risk of visual impairment and dizziness

ALT — alanine aminotransferase; AST — aspartate aminotransferase

promotes concentric cardiac remodelling due to the occurrence of two related cardiovascular events during treatment: cardiac hypertrophy and hypovolemia in the studied patients [13]. These lesions were not accompanied by clinical symptoms [13]. A comprehensive research acquisition strategy was conducted using Ovid/MEDLINE, EMBASE, and grey literature (1960–1 August 2013) to identify all relevant results on the use of isotretinoin in the treatment of acne vulgaris [14]. The inclusion criteria for the study were: clinical trials with oral isotretinoin at doses of 40 mg/d or greater of at least 4 weeks, patients aged 9 to 35 years with acne vulgaris, and a minimum number of 10 or more participants. Studies from all countries published in any language are included. The exclusion criteria were: the use of modified isotretinoin products, isotretinoin therapy for the treatment of conditions other than acne vulgaris, and concomitant treatment of acne. The initial search yielded 342 records, of which 116 were subjected to full-text examination [14]. Laboratory evaluation of lipid levels, liver function and total blood cell count was performed in the study. A total of 26 studies (1574 patients) were included in the meta-analysis. Mean (99% CI) triglyceride values during treatment (beyond baseline) were 119.98 mg/dL (98.58–141.39 mg/dL); for total cholesterol 184.74 mg/dL (178.17–191.31 mg/dL); for low-density lipoprotein cholesterol 109.23 mg/dL (103.68–114.79 mg/dL); for high-density lipoprotein cholesterol 42.80 mg/dL (39.84–45.76 mg/dL); for aspartate aminotransferase: 22.67 U/L (19.94–25.41 U/L); for alanine aminotransferase 21.77 U/L (18.96–24.59 U/L); for alkaline phosphatase 88.35 U/L (58.94–117.76 U/L); and white blood cell counts were 6890/µL (5700/µL–8030/µL) (Tab. 3) [14–16]. This meta-analysis showed that (1) isotretinoin is associated with a statistically significant change in mean laboratory parameters from several studies (it affects white blood cell counts and hepatic and lipid panels), but (2) mean changes across the patient group did not meet the high-risk criteria, and (3) the proportion of patients with laboratory abnormalities was low.

In August 2021, an 18-year-old man was admitted to the emergency department (ED) with a history of acne vulgaris due to left hip fossa pain and exertional dyspnoea [17]. Computed tomography (CT) scans revealed left renal infarction and echocardiography showed global left ventricular dilatation with a significantly reduced left ventricular ejection fraction (LVEF) (Fig. 1). Coronary artery disease, autoimmune, infectious or hereditary causes of dilated cardiomyopathy (DCM) have been excluded [17]. Cardiac magnetic resonance imaging revealed late gadolinium enhancement

Table 3. Laboratory parameters of patients aged 9–35 years with acne vulgaris taking isotretinoin at a dose of 40 mg/d for at least 4 weeks [14–16]; however, there are also reports indicating the emergence of a high cardiovascular risk associated with the use of isotretinoin in young patients [17–22]

Laboratory parameters	1574 patients (average value)	Normal value (European Society of Cardiology standards)
TG	119.98 mg/dL	< 150 mg/dL
TC	184.74 mg/dL	< 190 mg/dL
LDL	109.23 mg/dL	< 115 mg/dL
HDL	42.80 mg/dL	Women > 46 mg/dL Men > 40 mg/dL
AST	22.67 U/L	< 40 IU/L
ALT	21.77 U/L	< 40 IU/L
ALP	88.35 U/L	< 270 U/L
WBC	6890/μL	4000–10,000/μL

ALP — alkaline phosphatase; ALT — alanine transaminase; AST — aspartate aminotransferase; HDL — high-density lipoprotein; LDL — low-density lipoprotein; TC — total cholesterol; TG — triglycerides; WBC — white blood cells

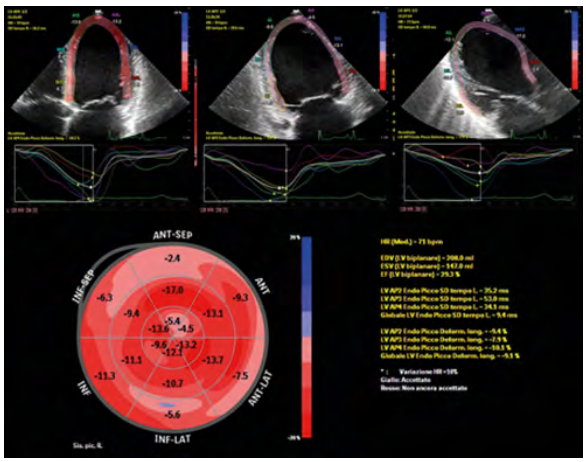

Figure 1. Echocardiography of an 18-year-old patient treated with isotretinoin admitted to the ED due to sudden pain in the left iliac fossa and exertional dyspnoea [17]

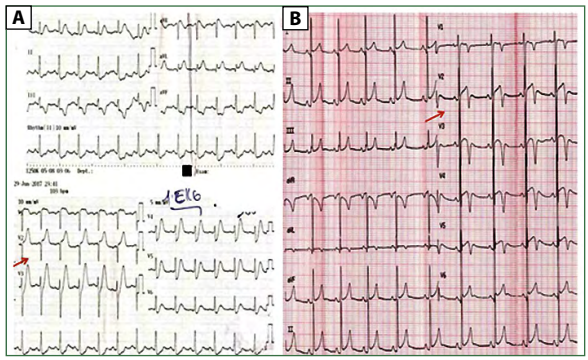

Figure 2. (**A**) Imaging of first-contact electrocardiography with sudden onset of chest pain (arrow indicates peak T-waves in the V1–V5 wires); (**B**) Imaging of follow-up electrocardiography after tirofiban infusion (arrow indicates biphasic T-waves in leads V1–V5) [17]

in the medial wall of the left ventricle, and ECG monitoring revealed several unfixed episodes of ventricular tachycardia (Fig. 1). Accordingly, bisoprolol, sacubitril/valsartan, and eplerenone were initiated and subsequently increased to the maximum tolerated doses, with only a weak improvement in LVEF [17]. This is the first reported case of renal disease thromboembolism and DCM requiring implantation of a subcutaneous implantable cardioverter defibrillator (S-ICD) and heart transplantation, occurring during isotretinoin treatment [17].

Another case report of the patient indicates a correlation between isotretinoin treatment and the occurrence of Kounis syndrome [18]. The diagnosis of Kounis syndrome is based on the clinical picture, observed signs and symptoms, especially after an allergic episode that is the result of a hypersensitivity reaction [18]. This is a multifactorial pathophysiological mechanism that is still unclear. A 25-year-old patient was admitted to the emergency department complaining of acute chest pain lasting for 1 hour [18]. Physical examination showed a systolic blood pressure of 120 mmHg, a diastolic blood pressure of 80 mmHg, and a heart rate of 100 beats per minute [18]. Auscultation of the heart did not reveal any abnormalities. Acute changes in the T-wave and dynamic ST segment were detected in V1–V5 electrocardiography derivatives (Fig. 2) [18]. Laboratory analysis revealed a high cardiac troponin I level of 4.1 ng/mL (normal range: 0.0–0.1 ng/mL) and a cardiac creatine kinase fraction concentration in the patient's blood of 8.2 ng/mL (normal range: 0.0–3.2 ng/mL) [18]. No risk factor for coronary artery disease was detected in the hospitalized patient, with the exception of smoking. There was no family history of coronary artery disease, no allergy or allergic reaction, and no substance abuse. The patient stated that he had been treated with isotretinoin (20 mg/day) for 1 week due to an acne diagnosis and that he had received the last dose 1 hour before the onset of chest pain [18]. Coronary angiography revealed

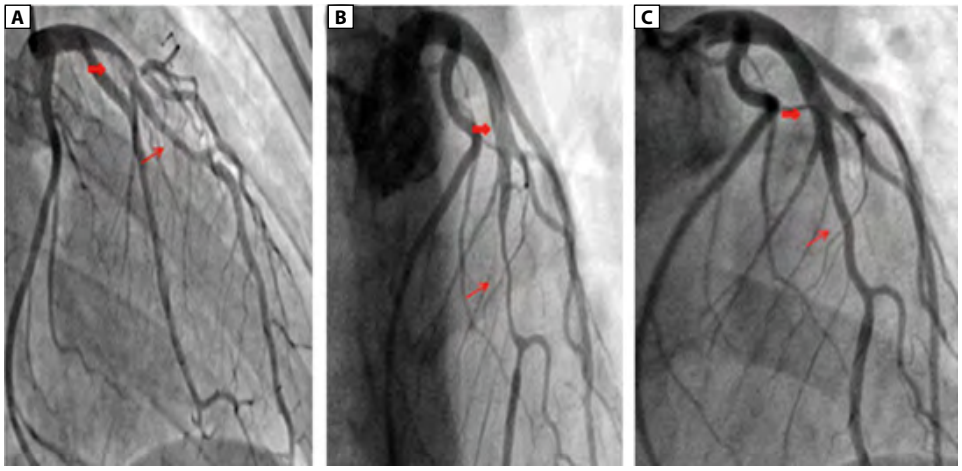

Figure 3. (**A**) Angiographic imaging of the left anterior descending (LAD) thrombotic lesion (thin arrow indicates the bridge of the myocardium, thick arrow indicates thrombus); (**B**) imaging of reduced LAD arterial thrombus after tirofiban infusion (thin arrow indicates myocardial ridge, thick arrow indicates thrombus); (**C**) imaging of dissolved LAD thrombus at 1 week (thin arrow indicates the area of the myocardial sternum, thick arrow indicates the area of dissolved thrombus [18]

thrombus and distal flow in the proximal left anterior descending coronary artery with a muscle bridge resulting in stenosis from 70% to 80% (Fig. 3) [18]. An infusion of tirofiban at a dose of 0.15 µg/kg/minute was administered over 18 hours. Chest pain has been completely eliminated. The assessment of thrombophilia, including mutations of the Leiden factor V gene and prothrombin, proteins C and S, antithrombin III, homocysteine levels, and resistance to active protein C, was completely negative [18]. Blood lipid and lipoprotein levels were within normal limits. Anti-nuclear, anti-dsDNA, and anticardiolipin antibodies were also within normal limits, ruling out the possibility of vasculitis and connective tissue diseases [18]. Subsequent follow-up coronary angiography showed that the thrombus had shrunk (Fig. 3). Biphasic negative T waves in V1–V5 derivatives were observed on electrocardiography (Fig. 2). Echocardiography showed mild hypokinesia of the anterior myocardial wall with no valvular abnormalities, intracardiac mass, or thrombus. Antiplatelet and anticoagulant therapy was continued, and 1 week later additional follow-up angiography showed that the thrombus had resolved (Fig. 3). The patient was discharged home without symptoms after administration of 200 mg of metoprolol, ticagrelor acetylsalicylic acid and atorvastatin. Isotretinoin treatment was not discontinued. A month later, there were no signs of ischaemia in the imaging of myocardial perfusion scintigraphy in the function performed in the described patient [18].

According to the literature to date, systemic isotretinoin treatment may cause some cardiac adverse reactions, such as atrial tachycardia, congenital heart defects and cardiac remodelling, as mentioned in the case reports [19]. A 26-year-old woman came to the emergency department as a result of sudden fainting after a prolonged episode of palpitations [19]. Physical examination showed no abnormalities, except for the presence of tachycardia. The woman was treated with isotretinoin at a dose of 0.5 mg/kg/day for 4 months due to nodular acne and did not take any other medications [19]. On ECG, the patient had atrial tachycardia in a 12-lead electrocardiogram and a heart rate of 149 beats/min. After an intravenous bolus injection of 25 mg of diltiazem hydrochloride, atrial tachycardia resolved and normal sinus rhythm was maintained [19]. Laboratory tests and chest X-rays were normal. Echocardiography revealed normal left ventricular function and pericardial effusion of 0.8 cm in the posterior part, 0.9 cm in the right atrium and 1.3 cm in the right ventricle [19]. Holter ECG revealed several episodes of atrial tachycardia. In the longest episode of atrial tachycardia, the heart rate was 149 beats/min [19]. After consultation with a dermatologist, isotretinoin was discontinued. Holter analysis showed a circadian sinus rhythm below 149 beats per minute only 2 months after discontinuation of drug therapy. Echocardiography revealed a gradual regression of pericardial effusion [19].

The subject of another case is a 16-year-old boy who, after three months of treatment with isotretinoin, began to experience episodes of palpitations both during physical exertion and at rest [20]. He started isotretinoin therapy due to cystic acne lesions on the face, initially receiving a dose of 30 mg/day for a month, and then 70 mg/day (1 mg/kg/day). The patient had a negative cardiac history and also denied taking cardiac drugs and dietary supplements. An ECG revealed a sinus rhythm with an incomplete right bundle branch block (iRBBB) [20]. Holter ECG showed a high incidence of isolated premature atrial excitations and

episodes of vestibular tachycardia that occurred ≥ 106 times daily, with the shortest lasting 3 beats and the longest 11 beats. The symptoms almost completely disappeared within a week of stopping the isotretinoin treatment. Follow-up ECG-Holter examinations performed 4 and 6 weeks after discontinuation of the drug showed sinus rhythm with an average heart rate of 62 and 58 beats per minute, respectively, and sporadic premature vestibular excitation in the number of 2 per day and none, respectively [20]. The results of the study clearly indicate a temporal relationship between isotretinoin treatment and the patient's symptoms in the presence of documented arrhythmias, suggesting a drug-related cause [20].

Another study shows a link between isotretinoin intake and a change in the lipid profile fraction in treated patients [21]. Sixty patients (32 men and 28 women) aged 18 to 50 years with an average age of 27 years were enrolled in the study. Patients were administered from January 2015 to December 2015. orally 20 mg of isotretinoin (according to a low-dose schedule) [21]. A thorough medical history and a thorough clinical examination were conducted. A medical history of concomitant medications that may interact with retinoids was collected. Laboratory tests such as a complete haemogram, liver function tests and a lipidogram were performed [21]. In the study population, hyperlipidaemia occurred in 25% (15 out of 60) of patients. Among hyperlipidaemias, hypertriglyceridemia was the most common (16.67%, 10 out of 60 patients), with increased levels of very low-density lipoprotein (VLDL) (11.67%, 7 out of sixty patients), increased low-density lipoprotein (LDL) (10%, 6 out of 60) and hypercholesterolaemia (5%, 3 out of 60). A combination of hyperlipidaemia occurred in 11.67% (7 out of 60) of patients. No changes in high-density lipoprotein (HDL) levels were observed. Among men, hyperlipidaemia after 3 months of isotretinoin treatment was 28.12% (9 out of 32), while in women the incidence of hyperlipidaemia was 21.43% (6 out of 28) [21]. Among women with hyperlipidaemia, hypertriglyceridemia occurred in 83.3% (5 out of 6) patients, while in men 55.5% (5 out of 9 patients). There was no statistical significance between hyperlipidaemia occurring in men and women with hyperlipidaemia ($p = 0.6869$) [21]. A 34-year-old female patient with no known cardiovascular disease, a non-smoker, and no diagnosed lipid disorders was admitted to the ward [22]. The patient was transported to the Cardiology Clinic on 6 October 2012 in a very serious condition due to sudden out-of-hospital cardiac arrest [brought by the ambulance after successful defibrillation (ventricular fibrillation) and cardiopulmonary resuscitation previously performed by her husband] [22]. It was determined that the patient did not smoke or drink alcohol. In biochemical tests, the concentration of total cholesterol was normal, and LDL cholesterol was 61 mg/dL. From the age of 18, the patient was treated for severe acne — she started the therapy by first taking isotretinoin for 5 months and cyproterone acetate and ethinylestradiol as an adjunct. After the acne lesions disappeared, she started taking the contraceptive drospirenone and ethinylestradiol, but due to the increase in acne symptoms, she returned to cyproterone acetate and ethinylestradiol about 2 years before her heart attack, taking it for 10 months. In addition, in 2010 she was given another one-year treatment with isotretinoin, which was discontinued due to pregnancy, after which the patient returned to taking cyproterone acetate and ethinylestradiol [22]. The patient underwent coronary angiography, which revealed amputation of the anterior descending branch, just behind its departure from the left coronary artery [22]. Aspiration thrombectomy (evacuation of a large thrombus) and left anterior descending (LAD) primary anterior descending coronary artery disease (LAD) with implantation of 2 amfillimus CRE 3 × 25 mm, 3.0 × 16 mm stents and administration of abciximab were performed simultaneously, achieving full vessel opening and TIMI 3 peripheral inflow. To sum up, the long-term anti-acne therapy that was applied to the patient may have contributed to the occurrence of sudden thromboembolic changes. Drugs such as isotretinoin and cyproterone acetate together with ethinyl oestradiol, as well as their side effects, may have significantly contributed to the development of thrombosis and myocardial infarction complicated by sudden cardiac arrest in a hospitalized woman [22]. According to previous studies, the contraceptive therapy used in the patient drospirenone and ethinylestradiol could also affect thromboembolic disorders [23–25].

Although cases such as those described in the following article (Tab. 4) and other articles (Tab. 5) may indicate a potential cardiovascular risk, an overall correlation between isotretinoin and cardiovascular disorders has not been proven in large population-based studies [26]. This is important in the context of assessing the risks and benefits of using isotretinoin to treat acne.

SUMMARY

Isotretinoin is definitely effective in dermatological treatment, but unfortunately, it has numerous side effects, including those related to the cardiovascular system. Studies have shown that it affects lipid metabolism, especially the concentration of triglycerides in the blood. However, it is worth noting that these values do not exceed the ceiling considered a high cardiovascular risk. Isotretinoin also directly affects the heart, causing it to remodel and resulting in a decrease in the cardiac index. Particular attention should be paid to young patients with thromboembolic events,

Table 4. Summary of cited clinical cases

Reference	Cardiac abnormalities	Patient	Indications for isotretinoin	Treatment data	Evidence suggesting isotretinoin as a cause of cardiovascular disorders
Pepe et al. [17]	Global left ventricular dilatation with a significantly reduced left ventricular ejection fraction	18-year-old man	Acne vulgaris	5 months	The patient was healthy before starting isotretinoin therapy, which he took for five months. Investigations, including cardiac MRI, ruled out ischaemic, autoimmune, infectious and hereditary dilated cardiomyopathy causes
Akçay et al. [18]	Kounis syndrome	25-year-old man	Acne	1 week	There was no family history of coronary artery disease and no risk factor, except smoking. Symptoms of Kounis syndrome appeared after 1 week of starting isotretinoin treatment
Güler et al. [19]	Pericardial effusion with atrial tachycardia	26-year-old woman	Nodular acne	4 months	Symptoms of pericardial effusion with atrial tachycardia appeared during treatment with isotretinoin. The woman was not taking any other medications, laboratory tests and a chest X-ray were normal
Hasdemir et al. [20]	Episodes of palpitations both during physical exertion and at rest	16-year-old boy	Cystic acne lesions on the face	3 months	The patient had no previous episodes of palpitations. His symptoms almost completely disappeared within a week after stopping treatment and has remained asymptomatic since discontinuing the drug
Sarkar et al. [21]	Change in the lipid profile fraction in treated patients	Sixty patients (32 men and 28 women) aged 18 to 50 years (an average age of 27 years)	Various skin diseases	January 2015 to December 2015	Regular observation of changes in the lipid profile during isotretinoin treatment indicates a direct link between the therapy and lipid disorders
Figiel et al. [22]	Cardiac arrest	34-year-old female	Severe acne	One-year	Patient without diagnosed cardiovascular disease, non-smoker and without diagnosed lipid disorders was transported to the Cardiology Clinic after long-term anti-acne therapy

Table 5. Some of the isotretinoin-associated cardiovascular side effects reported in the literature

Age and gender	Drug use time	Symptoms	Risk factors	Diagnosis	Therapy	Imaging	Physiopathology
35-year-old female [27]	One month	Palpitation	No	Premature ventricular contractions	Drug cessation	No	Unknown
18-year-old male [28]	Three months	Palpitation	No	Sinus tachycardia and right bundle branch block	Drug cessation	No	Unknown
28-year-old female [29]	One year	Chest pain	Cigarettes, oral contraceptives, high glycaemia and cholesterol levels	Inferior-STEMI	Thrombus aspiration and stent implantation	Optical coherence tomography	Complicated atherosclerotic plaque

Inferior-STEMI — inferior ST-elevation myocardial infarction; non-STEMI — non-ST-elevation myocardial infarction

coronary events and cardiac arrhythmias. It should be noted that the cases of cardiotoxicity that occur are singular in relation to the number of people who are successfully treated with isotretinoin without cardiovascular effects. Therefore, isotretinoin should be considered a relatively safe drug.

Despite the positive effects of isotretinoin, it is still necessary to monitor its effects through subsequent clinical trials so that the effectiveness of the therapy is fully evaluated and its use is safe.

Article information and declarations

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The contribution of each author in the creation of the review article was equal, accounting for 25% per author. The tasks performed by the authors included selecting the topic, conducting a literature review, performing an in-depth analysis of the subject, and writing the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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