Preventive Medicine Reports 39 (2024) 102643

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Review article

# Prognostic factors of MINOCA and their possible mechanisms

Mowei Kong [a], Zhenying Pei [a,*], Yuyu Xie [b], Yu Gao [c], Jun Li [a], Guoxiang He [a,*]

[a] Department of Cardiology, Guiqian International General Hospital, Guiyang, Guizhou 550018, PR China
[b] Department of Dermatology, Chengdu Fifth People's Hospital, Chengdu, Sichuan 610000, PR China
[c] Department of Endocrinology, Affiliated Hospital of Chengde Medical University, Chengde, Hebei 067000, PR China

ARTICLE INFO

*Keywords:*
Myocardial infarction with non-obstructive coronary arteries
Cardiovascular outcomes
Metabolic disorders
Risk factors
Biological landmark

ABSTRACT

*Objective:* Despite not showing substantial stenosis of coronary arteries, Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) presents with myocardial ischemia injury, thus having a grave prognosis and a high risk of long-term complications. This necessitates increased clinical attention and exploration of its root causes to prevent a similar crisis.

*Methods:* Research on MINOCA is limited, especially in terms of its clinical attributes, long-term outlook, risk stratification, and prognosis-linked cardiometabolic risk factors. This review aims to fill these gaps, providing an extensive overview of clinical trials and studies on MINOCA to separate the issue from the presence of non-obstructive coronary arteries in cardiac patients.

*Results:* It has been found that MINOCA patients still face a high risk of long-term adverse events. Due to social and physiological factors, the hospital mortality rate is higher among women, and they are also more susceptible to MINOCA. Cardiac metabolic risk factors, including disorder of glucose and lipid metabolism, as well as changes in serum CysC levels, have significant impacts on the occurrence and prognosis of MINOCA.

*Conclusions:* Further research is still needed to fully understand the complex biological mechanisms underlying the prognostic factors of MINOCA. A profound understanding of these factors could reveal potential targets for improving prognosis, thereby indicating new strategies for managing this cardiovascular condition.

## 1. Introduction

Coronary artery disease (CAD), the most common global cardiovascular disease, often leads to acute myocardial infarction (AMI)—a lethal cardiovascular disease (Barbara et al., 2019). AMI's pathophysiology primarily involves the progression of coronary atherosclerotic plaques which induce coronary thrombosis, luminal obstruction, and myocardial ischemic necrosis (Desiderio et al., 2003; Nakamura et al., 2001). Despite most AMI patients having obstructive myocardial infarction (MI) during coronary angiography (CAG), 5–10 % are without coronary artery obstruction, a condition known as MI with non-obstructive coronary arteries (MINOCA) (Giancarla et al., 2019). MINOCA causes, categorized into epicardial and microvascular causes, diverse patient prognosis (Giancarla et al., 2019). The diagnosis of MINOCA requires AMI diagnostic criteria, absence of obstructive CAD, and exclusion of other diseases triggering elevated troponin or non-ischemic myocardial injury (Agewall et al., 2017; Tamis-Holland Jacqueline et al., 2019). Diagnostic cardiac imaging plays an emerging and crucial role in evaluating suspected or diagnosed MINOCA patients, aiming to accurately identify and treat the specific causes of MINOCA, thus improving the prognosis and quality of life for these patients (Montone Rocco et al., 2021). While considering MINOCA's prognosis more optimal than MI-CAD, recent studies indicate poor prognosis and high long-term adverse event risk, drawing attention in clinical practice (Evbayekha Endurance et al., 2022; Mehmet et al., 2022). The present review systemically analyzes baseline characteristics and cardiometabolic risk factors of MINOCA, aiding future clinical management and scientific research.

## 2. The overall prognosis of MINOCA

Beltrame *et al* (Beltrame, 2013) first proposed the concept of MINOCA in 2013. MINOCA is considered to be a heterogeneous group of disorders caused by a number of etiologies, of which atherosclerotic plaque rupture is the most common (Evbayekha Endurance et al., 2022). Other coronary lesions, such as coronary spasm, spontaneous dissection, embolism and microvascular dysfunction can also cause MINOCA, but these are less common. It is worth noting that the use of acetylcholine or

* Corresponding authors.
*E-mail addresses:* 786889175@qq.com (Z. Pei), heguoxiangsw@aliyun.com (G. He).

https://doi.org/10.1016/j.pmedr.2024.102643
Received 29 November 2023; Received in revised form 24 January 2024; Accepted 2 February 2024
Available online 4 February 2024

**Table 1**
Related information from studies with different conclusions regarding the prognosis of myocardial infarction with non-obstructive coronary arteries.

| First author, year | Conclusion | Type of research | Number of cases | Intervention measures | Follow-up time, months | (Refs.) |
|---|---|---|---|---|---|---|
| Nordenskjöld *et al*, 2019 | Positive | Retrospective cohort study | 9,092 | – | - | (Montone Rocco, 2021) |
| He *et al*, 2020 | Positive | Prospective cohort study | 524 | Exercise training program | 36 | (Nordenskjöld Anna et al., 2019) |
| Bainey *et al*, 2018 | Positive | Prospective cohort study | 35,928 | Secondary prevention medication for myocardial infarction | 72 | (Chao-Jie et al., 2020) |
| Abdu *et al*, 2019 | Positive | Prospective cohort study | 2,029 | – | 12 | (Bainey et al., 2018) |
| Dreyer *et al*, 2020 | Positive | Retrospective cohort study | 276,522 | Coronary angiography | - | (Abdu Fuad et al., 2019) |
| Yeh *et al*, 2010 | Negative | Prospective cohort study | 46,086 | – | 96 | (Dreyer Rachel et al., 2020) |
| Safdar *et al*, 2018 | Negative | Prospective cohort study | 2,690 | – | 12 | (Yeh et al., 2010) |
| Zhang *et al*, 2022 | Negative | Retrospective cohort study | 165 | – | - | (Safdar et al., 2018) |
| Andersson *et al*, 2018 | Negative | Prospective cohort study | 4,793 | Coronary angiography | 30 | (Zhang et al., 2022) |
| Planer *et al*, 2014 | Negative | Prospective cohort study | 6,921 | Coronary angiography | - | (Ciliberti et al., 2020) |

coronary artery provocation tests has been effective in diagnosing MINOCA caused by coronary artery spasm, which has certain value in evaluating patient prognosis (Montone Rocco, 2021). Depending on the underlying cause, MINOCA lacks specific treatment and most patients are still treated with secondary prophylaxis for MI-CAD (Mehmet et al., 2022). In recent years, more studies have explored the clinical features and prognosis of MINOCA compared with MI-CAD, but there remains few studies concerning risk stratification and survival analysis of MINOCA. Recent studies have shown that patients with MINOCA have a younger age of onset, recent studies have shown that patients with MINOCA have a younger age (average 5–8 years) of onset than traditional cardiovascular diseases (Mehmet et al., 2022; Nordenskjöld Anna et al., 2019). It has previously been suggested that patients with MINOCA do not have significant coronary stenosis and that their prognosis is more optimal than that of patients with MI-CAD (Giancarla et al., 2019; Chao-Jie et al., 2020). A study found that the rates of in-hospital mortality or MI within 1 year in patients with MINOCA were lower than those in patients with MI-CAD (Bainey et al., 2018), which was consistent with the conclusion of another study in China (Abdu Fuad et al., 2019). A large-scale study also demonstrated that the rates of patients with MINOCA (18.7 vs. 27.6 %), mortality (12.3 vs. 16.7 %), hospitalization (1.3 vs. 6.1 %) and hospitalization for heart failure episode (5.9 vs. 9.3 %) were lower than that for patients with MI-CAD (all $P < 0.001$) (Dreyer Rachel et al., 2020).

However, a number of studies have shown that the risk of major adverse cardiovascular events (MACEs) in patients with MINOCA remains high and that their prognosis is not optimistic. According to a Swedish study, up to 23.9 % of patients with MINOCA developed a MACE within an average follow-up time of 4.1 years (Yeh et al., 2010). Safdar *et al* (Safdar et al., 2018) compared 2,690 patients in 103 hospitals and found that the 1-year all-cause mortality of patients with MINOCA was similar to that of patients with MI-CAD. This conclusion was contrary to the results of previous studies and has attracted attention. Coincidentally, a more recent study also cautions that MINOCA is not a benign condition and stated that its 3-year mortality rate reaches as high as 16 % (Zhang et al., 2022). Further research has found that some MINOCA patients, specifically those with spontaneous coronary artery dissection (Ciliberti et al., 2020), are at risk of sudden cardiac death. Andersson *et al* (Andersson et al., 2018) and Planer *et al* (Planer et al., 2014) confirmed in ST-elevation MI (STEMI) and non-ST elevation-acute coronary syndrome (NSTE-ACS) populations that the long-term mortality risk of patients with MINOCA or MI-CAD was not statistically different.

Notably, the conclusions of the aforementioned studies on the prognosis of MINOCA are not entirely consistent, which may be related to the different populations included in each study, the number of cases, the proportion of potential causes, the drug treatment and the follow-up time (Table 1). For example, among the studies that support the more optimal prognosis of MINOCA, the study by Bainey *et al* study (Nordenskjöld Anna et al., 2019) included individuals aged 59–63 years old. By contrast, a study that suggested that the prognosis of MINOCA was poor, included subjects aged 18–55 years old, which was younger than the former study (Yeh et al., 2010). According to previous study, an age of $>$ 60 years old is a risk factor for MINOCA (Beltrame, 2013), which may explain the inconsistent conclusions of the aforementioned studies. Additionally, mechanisms undrlying MINOCA are multiple and completely different among them and possible differences in prognosis may be related to different mechanisms (Del et al., 2021). Recent studies have also found that the "one-size-fits-all" approach used for MICAD treatment may not be suitable for all MINOCA patients (Antonio et al., 2022). Therefore, personalized etiology-targeted therapy should be implemented to improve the prognosis of MINOCA based on different pathogenic mechanisms.

## 3. Clinical features and prognosis of patients of different sexes with MINOCA

*Sex differences in the predictors and prognosis of MINOCA*. Epidemiological data indicate that the mortality rate of patients following AMI in the United States is increasing rapidly (increase 18.71 % from 2010) and sex differences are beginning to develop, as the in-hospital mortality rate following AMI in women is relatively higher than in men (Virani et al., 2020). Another study similarly demonstrated that women with AMI have a higher rate (11.1 % increase) of cardiovascular death per year than men (Bucholz et al., 2014). These studies indicate that the prognosis of patients of different sexes with AMI may be different. However, this topic is rarely reported and there is a lack of data from studies with long-term follow-up.

Recent study have shown that the mean age of MINOCA onset in women is significantly higher than that in men, revealing differences in patient characteristics between the sexes (Lisa et al., 2023). A multivariate regression analysis in another study also identified women and cancer as independent predictors of MINOCA. This appeared to identify the role of sex in the prognosis of MINOCA (Cobi et al., 2022). However, Mohammed *et al* (Abdul-Quddus et al., 2021) studied the differences in clinical features, predictors and outcomes in patients with MINOCA and

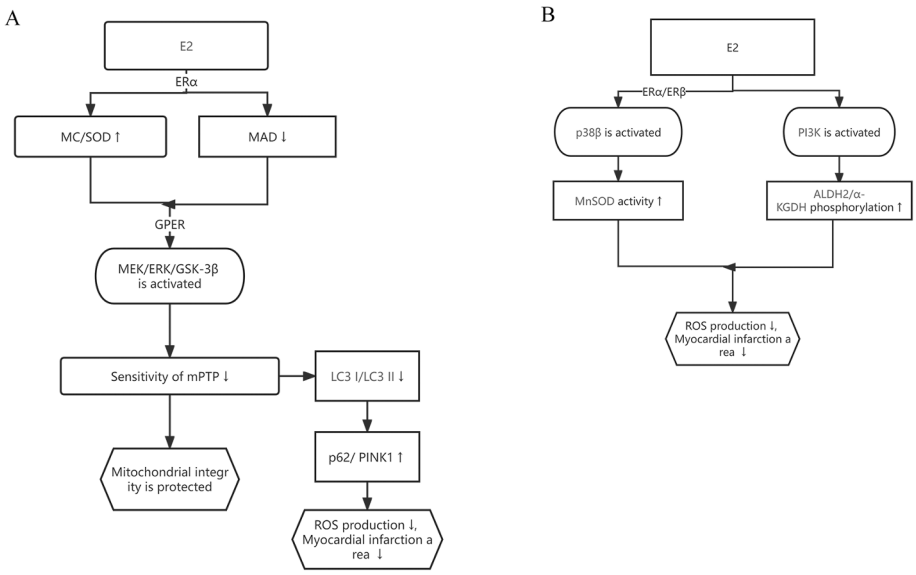


**Fig. 1.** (A) The acute therapeutic effect of the ER through I/R protects the heart from myocardial infarction with non-obstructive coronary arteries. (B) The preventive effect of the ER on I/R. α-KGDH, α-ketogluterate dehydrogenase; ALDH2, aldehyde dehydrogenase; E2, estradiol; ER, estrogen receptor; GPER, G protein-coupled estrogen receptor; I/R, ischemia reperfusion; MAD, malondialdehyde; mPTP, mitochondrial permeability transition pore; ROS, reactive oxygen species; (Mn)SOD, (mitochondrial) superoxide dismutase.

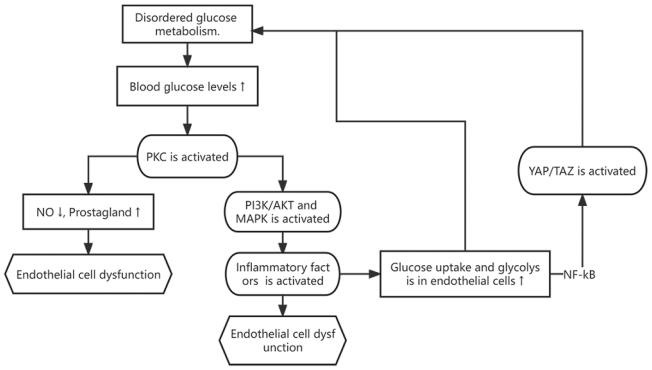


**Fig. 2.** Mechanism of endothelial dysfunction caused by disordered glucose metabolism in myocardial infarction with non-obstructive coronary arteries. NO, nitric oxide; PKC, protein kinase C; TAZ, transcriptional coactivator with PDZ-binding motif; YAP, Yes-associated protein.

found that, although the predicted risk factors for MACE were different in men and women [the multivariate predictors of MACE in the female group were age, hypertension and left ventricular ejection fraction (LVEF), while diabetes, smoking and LVEF were the multivariate predictors of MACE in the male group], the clinical outcomes were similar in both groups. In a *meta*-analysis involving 28,671 patients with MINOCA, MACE events were higher in women than in men, while there were no statistically significant differences in all-cause mortality, non-fatal MI and cardiovascular readmission rates between men and women (Rahul et al., 2022). The conclusions of the aforementioned studies are not entirely consistent, and this difference may be due to the different number of patients included in the studies and the different follow-up times.

*Social factors of sex differences in MINOCA*. As mentioned above, Females with MINOCA have a higher risk of developing MACE compared to males, but the overall mortality rate is similar for both genders (Andersson et al., 2018; Antonio et al., 2022). This is consistent with what researchers understand about AMI (Xu et al., 2015; Nauta et al., 2012), and this conclusion can be explained with similar reasons, there is a combined effect of both social and physiological factors. In terms of social factors, hospitalized female patients have more mental stress and depressive symptoms compared with men, which in turn leads to adverse health behaviors as well as poorer cardiovascular outcomes (Shively Carol et al., 2009). This may further result in a higher proportion of women with hypertension, diabetes and hyperlipidemia, a worse baseline clinical status in women and a significantly higher rate of Killip grade III in women compared with men (Hsue Priscilla et al., 2015). Moreover, compared with men, women have fewer clinical symptoms, and delayed or irregular treatment is more prominent (Orth-Gomér et al., 1998). In addition, women are less likely to receive standard secondary prophylaxis treatment (such as antiplatelet drugs, statins, β-blockers or angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers) in hospital than men, thus women are more likely to develop heart failure or cardiogenic shock after the onset of MINOCA, leading to a higher incidence of all-cause mortality and

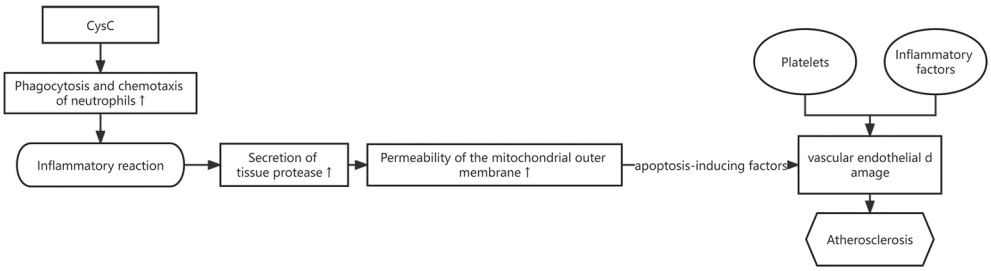


**Fig. 3.** Mechanism by which CysC promotes atherosclerosis development. CysC, cystatin C.

**Table 2**
Summary of factors and mechanisms affecting MINOCA prognosis.

| A, Sex factors | | | |
|---|---|---|---|
| Factors affecting prognosis | Related mechanisms | Impact on MINOCA prognosis | (Refs.) |
| Social | – | Female patients with MINOCA have more psychological stress and depressive symptoms than men, which in turn leads to poorer health behaviors and cardiovascular outcomes. | (Planer et al., 2014; Virani et al., 2020; Lisa et al., 2023; Cobi et al., 2022; Abdul-Quddus et al., 2021; Rahul et al., 2022; Xu et al., 2015; Nauta et al., 2012; Shively Carol et al., 2009) |
| Physiological | MEK/ERK/GSK-3β, PI3K/ALDH2/ α-KGDH and p38β/ MnSOD | Estrogen achieves acute therapeutic effects and preventive effects on I/R by activating the ER, thereby protecting the heart. | (Hsue Priscilla et al., 2015; Orth-Gomér et al., 1998; Hui-Xin et al., 2006; Planer et al., 2014; Aryan et al., 2020; Steagall et al., 2017; Feng et al., 2017) |
| B, Cardiometabolic factors | | | |
| Factors affecting prognosis | Related mechanisms | Impact on MINOCA prognosis | [Refs.] |
| Glucose metabolism disorder | PI3K/AKT, PKC/ MAPK and PKC/ YAP/TAZ | Disordered glucose metabolism promotes increased secretion of inflammatory factors, leading to endothelial dysfunction. Meanwhile, the increased levels of inflammatory factors further contribute to impaired glucose uptake and metabolism in blood vessels, forming a cycle of disordered glucose metabolism. | (van Helden et al., 2020; Songzan et al., 2023; O'Sullivan Jack et al., 2023; Abdu Fuad et al., 2023; Pasquale et al., 2021; Choo et al., 2019; Nordenskjöld et al., 2018; Luying et al., 2023; Marlene et al., 2022; Hiroaki, 2014; Bye Bailey et al., 2023; Paula et al., 2023; Driskill Jordan and Duojia, 2023; Tedy et al., 2022; Fangdi et al., 2022; Elias et al., 2023; Roshanzamir and Showkathali, 2013) |
| Lipid metabolism disorder | Lack of research temporarily. | The role of cholesterol in the pathogenesis of MINOCA is controversial; total cholesterol is a predictor of pathogenesis in patients with NSTE MINOCA; a high LDL-C level is an independent risk factor for MACE in STE MINOCA; reducing Lp[a] levels improves survival in patients with MINOCA. | (Abdu Fuad et al., 2023; Pasquale et al., 2021; Choo et al., 2019; Nordenskjöld et al., 2018; Luying et al., 2023; Marlene et al., 2022; Hiroaki, 2014; Bye Bailey et al., 2023; Paula et al., 2023; Driskill Jordan and Duojia, 2023; Tedy et al., 2022; Fangdi et al., 2022; Elias et al., 2023; Roshanzamir and Showkathali, 2013; Abhishek, 2017; Nadine et al., 2022; Poznyak Anastasia et al., 2022; Lin et al., 2023; Side et al., 2022; Andrea et al., 2023; Zhi et al., 2023; Nimrat and Onur, 2022; Agewall et al., 2017; Nelson et al., 2020; Larsen Alf et al., 2014; Smilowitz Nathaniel et al., 2017; Abdu Fuad et al., 2019; Xu et al., 2020; Baigent et al., 2010; Choo et al., 2019; Stefanescu et al., 2017; Nordenskjöld et al., 2019; Yaxin et al., 2023) |
| CysC metabolic disturbance | Promotion of inflammatory response, promotion of free radical generation, promotion of proliferation and migration of vascular smooth muscle cells, alteration of coagulation factor function, reduction in NO production and activation of CD40 ligand. | High levels of CysC are an independent risk factor for adverse events in patients with MINOCA. | (Azadeh et al., 2023; Lena et al., 2023; Ya-Wen et al., 2021; Brolin Elin et al., 2018; Cheng et al., 2009; Leung-Tack et al., 1990; Kavindi et al., 2023; Marycarmen et al., 2023; Yiwei et al., 2023; Ward Nathan, 2023) |

α-KGDH, α-ketogluterate dehydrogenase; ALDH2, aldehyde dehydrogenase; CysC, cystatin C; ER, estrogen receptor; I/R, ischemia reperfusion; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); MACE, major adverse cardiovascular event; MINOCA, myocardial infarction with non-obstructive coronary arteries; MnSOD, mitochondrial SOD; NO, nitric oxide; (N)STE, (non-)ST elevation; PKC, protein kinase C; TAZ, transcriptional coactivator with PDZ-binding motif; YAP, Yes-associated protein.

MACE than in men (Abdul-Quddus et al., 2021; Rahul et al., 2022; Xu et al., 2015; Nauta et al., 2012; Shively Carol et al., 2009; Hsue Priscilla et al., 2015; Orth-Gomér et al., 1998; Hui-Xin et al., 2006). These factors indicate why women have a higher risk of MACE than men.

*Physiological factors of sex differences in MINOCA*. Women live longer on average and have the cardioprotective effects of estrogen. Estrogen delays the progression of atherosclerosis, and the risk of pre-menopausal MINOCA is low (Planer et al., 2014). The biological effects of estrogen are realized through the estrogen receptors (ERs), including ERα, ERβ and G protein-coupled ER (GPER). These three types of ER are widely expressed in various tissues and organs throughout the body, including the heart and vascular walls (Nauta et al., 2012). After estrogen activates the related receptors, it can play a role via non-genomic pathways (Aryan et al., 2020). Estrogen at physiological concentration can act rapidly (in seconds or minutes) in non-genomic pathways, which is currently recognized as the main pathway type for estrogen to protect the cardiovascular system (Shively Carol et al., 2009). In this pathway, estrogen acts by changing the level of the classical secondary messenger (Cellular cytokine receptors ect) by activating the ER on the plasma membrane, leading to the rapid activation of various kinase pathways (Steagall et al., 2017; Feng et al., 2017).

Activation of the ER can protect the heart from MINOCA through two mechanisms: The acute therapeutic effect of ischemia reperfusion (I/R)

and the preventive effect on I/R. In examining the acute therapeutic effect of I/R, an animal study reported that myocardial catalase and superoxide dismutase (SOD) activity and the phosphorylation of AKT were enhanced after rats were injected with estradiol (E2) or selective ERα agonists with reduced malondialdehyde content (Hsue Priscilla et al., 2015). Changes in the levels of these factors activates the MEK/ERK/GSK-3β axis through the GPER to reduce the sensitivity of the mitochondrial permeability transition pore (mPTP) to $Ca^{2+}$ overload, resulting in a delayed opening of the mPTP (Orth-Gomér et al., 1998). This delayed opening protects the integrity of the structure of the mitochondria, while reducing LC3 I and LC3 II protein levels, and increasing the expression of p62 and PINK1. PINK1 inactivation of the Parkin pathway reduces mitophagy and ultimately results in reduced reactive oxygen species (ROS) production and MI area. This acute therapeutic effect against I/R can be antagonized by ER antagonists or nitric oxide synthase inhibitors (Planer et al., 2014). The mechanism of the acute therapeutic effect of the ER through I/R is outlined in Fig. 1A. As for the preventive effect on I/R, it was found that the left MI area of mice with coronary ischemia was reduced by E2 administration, accompanied by an increase in mitochondrial p38β and mitochondrial SOD (MnSOD) activity (Sivasinprasasn et al., 2019). E2 enhances MnSOD activity in cardiomyocytes via ERα and ERβ enhancing the activation of mitochondrial p38β, thereby inhibiting intracellular ROS production and reducing myocardial injury and infarct area during I/R (Luo et al., 2016). The mechanism of the preventative effect of the ER on I/R is outlined in Fig. 1B. Another study found that 4-week estrogen therapy administered to female rats 12 weeks after bilateral oophorectomy not only preserved the structural integrity of mitochondria, but also improved insulin resistance and dyslipidemia (Kilanowski-Doroh Isabella et al., 2023). A possible explanation for this is that long-term estrogen therapy activates PI3K and increases phosphorylation of the E2-binding subunits of aldehyde dehydrogenase 2 and α-ketoglutarate dehydrogenase, thereby reducing ROS production in mitochondria (Aryan et al., 2020). This suggests that estrogen prophylaxis may have a significant advantage in cardiac ischemia due to MINOCA.

## 4. Effect of cardiometabolic risk factors on the prognosis -+of patients with MINOCA

*Glucose metabolism disorder and MINOCA.* Glucose metabolism disorders mainly refer to glucose, fructose, galactose and metabolic hormones or enzymes with abnormal structure, function or concentration. Clinically important glucose metabolism disorders mainly result in too high or low blood glucose concentrations (van Helden et al., 2020). Previous studies have confirmed the association between diabetes and CAD prognosis (Songzan et al., 2023; O'Sullivan Jack et al., 2023), but the effect of diabetes on cardiovascular outcomes in patients with MINOCA is unclear.

Diabetes often coexists with cardiovascular risk factors, such as obesity, hypertension and abnormal lipid metabolism, and mediates extensive macrovascular and microangiopathy complications throughout the body, which is speculated to play a key role in the occurrence and development of MINOCA (Steagall et al., 2017). A recent study by Abdu *et al* (Abdu Fuad et al., 2023) provided some basis for this speculation. In the study, 410 patients with MINOCA were analyzed and it was found that stress hyperglycemia was independently associated with poor long-term prognosis in patients with MINOCA. Another study also demonstrated that stress hyperglycemia measured at hospital admission is a strong predictor of adverse short and long-term outcomes for MINOCA (Pasquale et al., 2021). Recent studies suggest that type 2 diabetes is less common in patients with MINOCA than in patients with MI-CAD, but it remains an independent predictor of all-cause mortality over time (Choo et al., 2019; Nordenskjöld et al., 2018).

The conclusions of the aforementioned studies are similar to what is known about MI-CAD. In patients with MI-CAD, the damage caused by diabetes mainly originates from promotion of the vascular inflammatory response, promotion of oxidative stress, mediation of vascular endothelial damage and smooth muscle cell proliferation (Luying et al., 2023). These factors can interact in a chain that ultimately leads to atherosclerotic plaque formation and progression, inducing plaque rupture and thrombosis and leading to myocardial damage and necrosis (Marlene et al., 2022). However, these mechanisms are somewhat different for MINOCA. In epicardial MINOCA, coronary artery spasm is the main cause of disease (O'Sullivan Jack et al., 2023; Abdu Fuad et al., 2023). There are two main factors that induce coronary artery spasm: Hyperresponsiveness of vascular smooth muscle cells (VSMCs) to local or multiple attacks and the transient stimulation of VSMCs by vasoconstrictors (Hiroaki, 2014). It is currently suggested that the increase of vascular endothelial inflammatory factors caused by glucose metabolism disorders is a notable factor in the hyperresponsiveness of VSMCs. Elevated blood glucose levels can activate the protein kinase C (PKC) pathway, leading to a decrease in endothelial nitric oxide production and an increase in prostaglandin synthesis, causing endothelial dysfunction (Pasquale et al., 2021). In addition, PKC can also regulate the activity of other protein kinases, such as PI3K/AKT and MAPK, damaging endothelial function and increasing vasoconstriction (Bye Bailey et al., 2023). When endothelial cells are stimulated by inflammation, pro-inflammatory factors increase glucose uptake and glycolysis. Lactate-induced NF-κB activation plays a major role in this process (Paula et al., 2023). Pro-inflammatory factors can also activate mechanotransducers, Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) (Driskill Jordan and Duojia, 2023). Similar to NF-κB, YAP/TAZ signaling also promotes endothelial cell glycolysis. Thus, inflammation and endothelial cell glucose metabolism appear to have a causal relationship, mutually promoting a cycle of disordered glucose metabolism (Fig. 2). However, the main trigger for stimulating VSMC hyperresponsiveness is increased Rho kinase activity (Tedy et al., 2022). Abnormal elevation of blood glucose can induce increased Rho kinase activity and further stimulate spasm in VSMCs. In clinical practice, active diabetes screening and early intervention can aid in the early prevention and prognosis of CAD.

Another mechanism of epicardial etiology in MINOCA is the presence of off-center plaques that develop centrifugally due to positive vascular remodeling (Fangdi et al., 2022). However, these lesions tend to have features of fragile plaques, such as large lipid pools and thin fibrous caps (Montone Rocco et al., 2021), which can induce plaque rupture, resulting in transient local thrombosis and spontaneous fibrinolysis, causing distal coronary thromboembolism and MINOCA. Although there have been no studies concerning glucose metabolism and plaque morphology, diabetes is a risk factor for intravascular plaque formation, which may also greatly increase the incidence of MINOCA (van Helden et al., 2020; Songzan et al., 2023). Moreover, abnormal blood sugar levels can directly damage the vascular endothelium to cause arterial spasm or atherosclerotic plaque formation, mediated by non-enzymatic glycosylation of low-density lipoprotein cholesterol (LDL-C), other apolipoproteins and blood clotting factors like Apolipoprotein B, Fibrinogen, Factor V and Factor VII (Elias et al., 2023).

The common causes of microvascular MINOCA include Takotsubo syndrome (TS), MI-like myocarditis, microvasospasm and coronary embolism (Paula et al., 2023). TS accounts for 1.2–2.2 % of coronary artery spasm incidences and its pathogenesis remains unknown (Roshanzamir and Showkathali, 2013). Patients with TS are characterized by the onset of recent physical or psychological pressure, and often exhibit visible ST segment elevation, T wave inversion (Abhishek, 2017). However, a recent study have found that glucose and lipid metabolism pathways are dysregulated in TS, and glycolysis and decreased levels of β oxidation metabolites are responsible for the above changes (Nadine et al., 2022). In microvasospasm pathogenesis, abnormally elevated blood glucose levels and abnormal glucose tolerance leads to the activation of PKC, the production of advanced glycation end products and ROS, upregulation of growth factors and inflammatory factors and a loss of insulin signaling, which contribute to microangiopathy (Poznyak

Anastasia et al., 2022).

*Lipid metabolism disorder and MINOCA*. Unlike conventional MI-CAD, dyslipidemia is less frequently observed in patients with MINOCA (Evbayekha Endurance et al., 2022). However, relevant studies have shown that dyslipidemia still plays an important role in the pathogenesis and prognosis of MINOCA (Elias et al., 2023; Roshanzamir and Showkathali, 2013; Abhishek, 2017). In a study of 196 individuals, independent predictors of risk of MACE in patients with MINOCA included high LDL-C levels (Lin et al., 2023). Another study found that elevated residual cholesterol is an independent risk factor for adverse prognosis in MINOCA (Side et al., 2022). A recent study have also demonstrated that lipoprotein (a) [Lp(a)] level is an independent predictor of MINOCA ischemic events or death (Andrea et al., 2023).

*Comparison of lipid metabolism abnormalities in the pathogenesis of MINOCA and MI-CAD*. Excess cholesterol accumulates in the blood vessel wall, leading to plaque formation, and lipid metabolism disorders and hyperlipidemia are the main risk factors for this. MINOCA and MI-CAD can both be caused by MI due to plaque problems. Plaque problems include plaque rupture, plaque erosion and calcified nodules, of which plaque rupture is the most common cause (Zhi et al., 2023). Plaque rupture is typically associated with thin-fiber cap atherosclerotic plaques, which can induce thrombosis and, in some cases, transient vascular occlusion due to spontaneous thrombolysis. In plaque rupture, CAG (Nimrat and Onur, 2022) typical reveals few thrombus fragments without significant vascular embolism. Plaque erosion refers to histologically visible vascular endothelial thromboses in unruptured coronary arteries, and it may be associated with apoptosis of endothelial cells and loss of endothelial-extracellular matrix connections (Evbayekha Endurance et al., 2022). Calcified nodules are a type of vulnerable plaque that mostly occur in the elderly. CAG examination displays granular nodules protruding from the lumen with a red thrombus attached to the surface (Poznyak Anastasia et al., 2022). The incidence of plaque rupture and plaque erosion in patients with MINOCA can be $>$ 40 % (Agewall et al., 2017).

The role of lipid metabolism in the pathogenesis of MINOCA and MI-CAD differs. The causal relationship between dyslipidemia, hypercholesterolemia, hypertriglyceridemia and coronary atherosclerosis is well established (O'Sullivan Jack et al., 2023). Dysregulated lipid metabolism is a major risk factor for coronary atherosclerosis, in which LDL-C is positively associated with cardiovascular disease onset. In a study by Wang *et al* (Nelson et al., 2020), it was demonstrated that, for every 1 mmol/l decrease in blood LDL-C levels, the risk of coronary heart disease was decreased by 55 %. However, for patients with MINOCA, the prevalence of hyperlipidemia was lower than that observed or not significantly different to the whole MI-CAD cohort (O'Sullivan Jack et al., 2023). Moreover, a study by Larsen *et al* (Larsen Alf et al., 2014) found no significant difference in hypercholesterolemia incidence between patients with MINOCA or MI-CAD. However, in a large study including 322,523 patients, blood cholesterol levels in patients with MINOCA were lower than those in patients with MI-CAD (Smilowitz Nathaniel et al., 2017). In a study in China, it was concluded that LDL-C was negatively associated with MINOCA onset, and the levels of LDL-C in the MINOCA group was lower in the univariate analysis compared with the MI-CAD group, which was statistically significant (Abdu Fuad et al., 2019).

However, further studies found that the independent risk factors for adverse cardiac events were not the same in the STE and NSTE populations of patients with MINOCA, with higher LDL-C levels observed in patients NSTE (Lin et al., 2023). Xu *et al* (Xu et al., 2020) also demonstrated that total cholesterol was only a predictor of NSTE MINOCA disease onset, not STE. A *meta*-analysis indicated that reducing LDL-C levels was effective in reducing the incidence of cardiovascular disease and stroke, while higher LDL-C levels were an independent risk factor for MACE in the STE MINOCA group (Baigent et al., 2010). The administration of statins to patients with MINOCA reduces LDL-C levels and stabilizes and controls coronary plaque progression with a beneficial prognostic impact (Choo et al., 2019). Another study has found that the different mechanisms of MINOCA negate any benefits of patients taking DAPT (Dual Antiplatelet Therapy) or statin medications (Stefanescu et al., 2017). These contradictory findings leave the role of statin drugs in the treatment of MINOCA inconclusive. Current research also tends to suggest that MINOCA patients are not the primary focus of secondary prevention measures, thus resulting in a higher risk of recurrent myocardial infarction (Nordenskjöld et al., 2019).These studies suggest that cholesterol levels may play different roles in patients with STE or NSTE MINOCA. A Previous study have reported higher short-term mortality rates in patients with STEMI and higher long-term mortality rates in patients with NSTEMI, which was also observed in the MINOCA population (Nordenskjöld et al., 2018). It can therefore be inferred that abnormal cholesterol metabolism may have an effect on long-term mortality in patients with MINOCA, but this conclusion needs further validation.

*Association of Lp(a) and MINOCA prognosis*. Lp(a) is a plasma lipoprotein formed by the covalent association of lipoprotein B100 and lipoprotein A (Yaxin et al., 2023). Epidemiological data indicate that 20–30 % of the global population has elevated Lp(a) levels, which significantly increases the risk of cardiovascular events, including in young individuals with no other risk factors (Michael et al., 2023). Further studies have confirmed a correlation between Lp(a) levels and the prognosis of patients with coronary heart disease, with higher Lp(a) levels being associated with poorer prognosis (Xu et al., 2020; Baigent et al., 2010; Choo et al., 2019). The role of Lp(a) in increasing residual cardiovascular risk is independent of LDL-C and other risk factors (Xu et al., 2020). However, the significance of Lp(a) in MINOCA has only recently been recognized, and research in this area remains limited. In a 2021 prospective study of 1,179 patients with MINCOA, Gao *et al* (Side et al., 2021) were the first to evaluate the impact of Lp(a) levels on the long-term prognosis of patients with MINOCA treated with statins, and suggested that improving Lp(a) levels may enhance the prognosis of this population. However, another study suggested that elevated Lp(a) was an independent predictor of poor prognosis in patients with MINOCA, with the role of statins in improving prognosis lacking sufficient evidence (Andrea et al., 2023).

The relationship between elevated Lp(a) levels and increased cardiovascular risk is not fully understood, but several mechanisms have been proposed that primarily involve pro-inflammatory and prothrombotic effects. Given its structural similarity to LDL particles, Lp(a) can enhance foam cell formation, generate ROS and promote smooth muscle cell proliferation, thereby promoting atherosclerosis (Stefanescu et al., 2017). Additionally, Lp(a) can be recognized by inflammatory cells and trigger inflammatory pathways. Lp(a) also competes with plasminogen for binding sites, inhibiting fibrinolysis and promoting thrombus formation (Halima et al., 2023). A recent prospective multicenter study involving 1,042 patients with AMI found that patients with MINOCA were younger, more likely to be female, had a lower incidence of diabetes and Lp(a) $>$ 9 mg/dl and had higher high-density lipoprotein cholesterol (HDL-c) levels (Andrea et al., 2023). In conclusion, in patients with AMI, the absence of high Lp(a) and HDL-c levels are independent predictors of the absence of CAD, and high Lp(a) levels are also independent predictors of ischemic events or death. Despite these findings, the pathophysiological mechanisms of MINOCA remain a topic of debate.

*Serum cystatin C (CysC) levels may affect the prognosis of MINOCA*. CysC, an endogenous tissue cysteine protease inhibitor, primarily functions to maintain the balance between proteases and inhibitors (Nordenskjöld et al., 2018). Inflammatory cytokines that are related to atherosclerosis formation promote the production of tissue proteases, and elevated CysC levels can disrupt this balance (Yaxin et al., 2023). This disruption can lead to increased degradation of the arterial elastic lamina and extracellular matrix, promoting the formation and progression of coronary atherosclerosis (Yaxin et al., 2023). Elevated serum CysC levels have been closely linked with stable CAD, ACS, NSTEMI and

STEMI (Azadeh et al., 2023; Lena et al., 2023). In 2021, Lu *et al* (Ya-Wen et al., 2021) found that CysC could be used to assess the severity of coronary lesions in patients with CAD, with higher CysC levels being an independent risk factor for CAD progression. Another study found a positive correlation between serum CysC levels and the degree of coronary lesions in patients with MINOCA, with high CysC levels being an independent risk factor for adverse events in these patients (Brolin Elin et al., 2018).

A number of clinical studies have found a positive correlation between serum CysC and CRP (Nordenskjöld et al., 2019; Nordenskjöld et al., 2018; Yaxin et al., 2023). In addition, in a previous tudy, a significant correlation between serum CysC and TNF was noted (Cheng et al., 2009). A study by Leung et al (Leung-Tack et al., 1990) found that serum CysC and its fragments could promote the phagocytosis and chemotaxis of neutrophils, exacerbating the inflammatory response. The most crucial aspect in the development of cardiovascular diseases is the remodeling of the extracellular matrix. Under normal circumstances, serum CysC maintains a dynamic balance with tissue proteases (Kavindi et al., 2023). When an inflammatory response occurs, VSMCs excessively secrete tissue proteases under the stimulation of inflammatory factors (Marycarmen et al., 2023). This leads to an increase in mitochondrial outer membrane permeability in vascular endothelial cells, and the mitochondria release apoptosis-inducing factors that promote cell apoptosis, leading to vascular endothelial damage. Then, platelets adhere to the damaged endothelium and various inflammatory factors in the blood form a positive feedback loop, further accelerating the development of atherosclerosis (Fig. 3) (Yiwei et al., 2023). As tissue proteases disrupt the vascular environment, the concentration of serum CysC also increases (Andrea et al., 2023). High concentrations of serum CysC can inhibit the solubilizing effect of tissue proteases, reducing tissue protein degradation, protecting arterial endothelium and preventing damage from inflammatory reactions (Andrea et al., 2023). This halts further damage to the vascular intima and inhibits the progression of atherosclerosis. However, although serum CysC secretion increases during inflammation, it remains relatively deficient compared with the increase in tissue protease secretion at arterial injury sites (Yaxin et al., 2023; Michael et al., 2023; Side et al., 2021). When serum CysC is relatively insufficient, tissue proteases remain upregulated, causing degradation of the extracellular matrix and collagen accumulation, and leading to extracellular matrix remodeling (Michael et al., 2023; Side et al., 2021). Additionally, many researchers have proposed new explanations the involvement mechanism of CysC in MINOCA: i) Vascular endothelial cell damage and dysfunction: During the sulfhydryl oxidation process, serum CysC produces a series of free radicals (such as superoxide anions, hydrogen peroxide and hydroxyl radicals) causing protein damage, enzyme release, receptor activity and functional impairment (Ward Nathan, 2023). Free radicals also promote the oxidation of LDLs, forming foam cells. The accumulation of foam cells forms lipid stripes and lipid plaques, accelerating the progression of atherosclerosis and narrowing the arterial lumen (Lei et al., 2023). ii) Serum CysC can directly induce the proliferation and migration of VSMCs and interfere with VSMC function through signal transduction pathways (Azadeh et al., 2023). iii) High serum CysC levels can alter coagulation factor functions, promoting platelet adhesion and aggregation, which leads to thrombosis (Lena et al., 2023). iv) Vascular contraction dysfunction: Nitric oxide is a potent endothelium-derived vasodilator and has strong antiplatelet properties (Ya-Wen et al., 2021). Damage to vascular endothelial cells by serum CysC can reduce nitric oxide production, causing vascular contraction, further endothelial damage, platelet aggregation, plaque formation and cascading positive feedback responses, accelerating atherosclerotic plaque formation and progression (Sylwia et al., 2022). v) Elevated serum CysC can also act through the CD40 pathway, an immune-inflammatory regulatory pathway. CD40 ligand induces the expression of matrix metalloproteinases in plaque macrophages and VSMCs, leading to plaque rupture (Klas and Arne, 2004).

## 5. Conclusion

MINOCA, accounting for 5–10 % of AMI cases, poses a high risk of long-term adverse events despite past assumptions of a better prognosis than obstructive MI-CAD. Particularly susceptible are women, due to societal and physiological aspects. The onset and prognosis significantly relate to cardiometabolic risk factors including glucose, lipid metabolic disorders, and varying serum CysC levels. Factors affecting prognosis are summarized in Table 2. Current research, although limited, suggests that these complex prognostic factors may provide targets for enhancing MINOCA treatment outcomes. Further exploration could uncover novel approaches to this cardiovascular condition.

## CRediT authorship contribution statement

**Mowei Kong:** Writing – original draft. **Zhenying Pei:** Writing – review & editing, Conceptualization. **Yuyu Xie:** Writing – review & editing. **Yu Gao:** Writing – original draft. **Jun Li:** . **Guoxiang He:** .

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

## Acknowledgements

Not applicable.

*Funding*

No funding was received.

*Availability of data and materials*

Not applicable.

*Authors' contributions*

MK wrote the manuscript, and ZP, YX, YG JL and GH reviewed and revised the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

*Ethical approval and consent to participate*

Not applicable.

*Patient consent for publication*

Not applicable.

## References

Abdu Fuad, A., Liu, Lu, Abdul-Quddus, Mohammed, et al., 2019. Myocardial infarction with non-obstructive coronary arteries (MINOCA) in Chinese patients: Clinical features, treatment and 1 year follow-up. Int. J. Cardiol. 287, 27–31.

Abdu Fuad, A., Liu, L.u., Abdul-Quddus, M., et al., 2019. Myocardial infarction with non-obstructive coronary arteries (MINOCA) in Chinese patients: Clinical features, treatment and 1 year follow-up. Int. J. Cardiol. 287, 27–31.

Abdu Fuad, A., Jassur, Galip, Penglong, Qi, et al., 2023. Association of stress hyperglycemia ratio and poor long-term prognosis in patients with myocardial infarction with non-obstructive coronary arteries. Cardiovasc. Diabetol. 22, 11.

Abdul-Quddus, M., Abdu Fuad, A., Liu, L.u., et al., 2021. Hyperuricemia Predicts Adverse Outcomes after Myocardial Infarction with Non-Obstructive Coronary Arteries. Front Med (Lausanne) 8, 716840.
Abhishek, M., 2017. Dhoble Abhijeet, Takotsubo Cardiomyopathy. N. Engl. J. Med. 377, e24.
Agewall, S., Beltrame, J.F., Reynolds, H.R., Niessner, A., Rosano, G., et al., 2017. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur. Heart J. 38 (3), 143–153.
Agewall, S., Beltrame, J.F., Reynolds, H.R., et al., 2017. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur. Heart J. 38 (3), 143–153.
Andersson, H.B., Pedersen, F., Engstrøm, T., Helqvist, S., Jensen, M.K., Jørgensen, E., Kelbæk, H., Räder, S.B.E.W., Saunamäki, K., Bates, E., Grande, P., Holmvang, L., Clemmensen, P., 2018. Long-term survival and causes of death in patients with ST-elevation acute coronary syndrome without obstructive coronary artery disease. Eur. Heart J. 39 (2), 102–110.
Andrea, K., María, P.L.A., Blanco-Colio Luis, M., et al., 2023. Absence of High Lipoprotein(a) Levels Is an Independent Predictor of Acute Myocardial Infarction without Coronary Lesions. J. Clin Med 12, undefined.
Antonio, M.R., Nicola, C., Francesca, G., et al., 2022. Precision medicine versus standard of care for patients with myocardial infarction with non-obstructive coronary arteries (MINOCA): rationale and design of the multicentre, randomised PROMISE trial. EuroIntervention 18, e933–e939.
Aryan, L., Younessi, D., Zargari, M., et al., 2020. The Role of Estrogen Receptors in Cardiovascular Disease. Int. J. Mol. Sci. 21 (12), 4314.
Azadeh, Mottaghi, Farzaneh, Alipour, Nazanin, Alibeik, et al., 2023. Serum cystatin C and inflammatory factors related to COVID-19 consequences.BMC. Infect. Dis. 23, 339.
Baigent, C., Blackwell, L., Emberson, J., et al., 2010. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170, 000 participants in 26 randomised trials. Lancet 376, 1670–1681.
Bainey, K.R., Welsh, R.C., Alemayehu, W., Westerhout, C.M., Traboulsi, D., Anderson, T., Brass, N., Armstrong, P.W., Kaul, P., 2018. Population-level incidence and outcomes of myocardial infarction with non-obstructive coronary arteries (MINOCA): Insights from the Alberta contemporary acute coronary syndrome patients invasive treatment strategies (COAPT) study. Int. J. Cardiol. 1 (264), 12–17.
Barbara, R., Francesca, A., Francesco, R., et al., 2019. Epigenetic Modification in Coronary Atherosclerosis: JACC Review Topic of the Week. J. Am. Coll. Cardiol. 74, 1352–1365.
Beltrame, J.F., 2013. Assessing patients with myocardial infarction and nonobstructed coronary arteries (MINOCA). J. Intern. Med. 273 (2), 182–185.
Brolin Elin, B., Stefan, A., Kerstin, C., et al., 2018. Plasma biomarker levels and non-obstructive coronary artery disease determined by coronary computed tomography angiography. Clin. Physiol. Funct. Imaging 38, 246–253.
Bucholz, E.M., Butala, N.M., Rathore, S.S., Dreyer, R.P., Lansky, A.J., Krumholz, H.M., 2014. Sex differences in long-term mortality after myocardial infarction: a systematic review. Circulation 130 (9), 757–767.
Bye Bailey, A., Jarrid, Jack, Alexandra, Pierce, et al., 2023. Combined PI3K and MAPK inhibition synergizes to suppress PDAC. bioRxiv undefined: undefined.
Chao-Jie, H.e., Chun-Yan, Z.u., Yu-Juan, Z.u., et al., 2020. Effect of exercise-based cardiac rehabilitation on clinical outcomes in patients with myocardial infarction in the absence of obstructive coronary artery disease (MINOCA). Int. J. Cardiol. 315, 9–14.
Cheng, J., Zhao, D., Zeng, Z., et al., 2009. The impact of demographic and risk factor changes on coronary heart disease deaths in Beijing, 1999–2010. BMC Public Health 9, 30.
Choo, E.H., Chang, K., Lee, K.Y., et al., 2019. Prognosis and predictors of mortality in patients sufering myocardial infarction with non-obstructive coronary arteries. J. Am. Heart Assoc. 8, e011990.
Choo, E.H., Chang, K., Lee, K.Y., Lee, D., Kim, J.G., et al., 2019. Prognosis and predictors of mortality in patients suffering myocardial infarction with non-obstructive coronary arteries. J. Am. Heart Assoc. 8, e011990.
Ciliberti, G., Finocchiaro, G., Papadakis, M., et al., 2020. Myocardial Infarction With Nonobstructed Coronary Arteries and Sudden Cardiac Death: A Clinical and Pathological Perspective. Circ. Arrhythm. Electrophysiol. 13 (7), e008302.
Cobi, A., Gagandeep, S., Kuljit, S., 2022. Comparing pharmacotherapy in MINOCA versus medically managed obstructive acute coronary syndrome. Heart Vessels 37, 705–710.
Del, B.M.G., Montone, R.A., Iannaccone, G., 2021. Diagnostic work-up and therapeutic implications in MINOCA: need for a personalized approach. Future Cardiol. 17 (1), 149–154.
Desiderio, F., Whady, H., Gersh Bernard, J., et al., 2003. Relative cost comparison of treatments for coronary artery disease: the First Year Follow-Up of MASS II Study. Circulation null, II21-3.
Dreyer Rachel, P., Rosanna, T., Curtis Jeptha, P., et al., 2020. Myocardial infarction with non-obstructive coronary arteries as compared with myocardial infarction and obstructive coronary disease: outcomes in a Medicare population. Eur. Heart J. 41, 870–878.
Driskill Jordan, H., Duojia, P., 2023. Control of stem cell renewal and fate by YAP and TAZ. Nat. Rev. Mol. Cell Biol. undefined: undefined.
Elias, M.A., Gianluca, I., Elena, D., et al., 2023. Human Epicardial Adipose Tissue Expresses Glucose-dependent Insulinotropic Polypeptide, Glucagon and Glucagon-Like Peptide 1 Receptors as Potential Targets of Pleiotropic Therapies.Eur. J Prev Cardiol undefined: undefined.
Evbayekha Endurance, O., Okobi Okelue, E., Oyintoun-Emi, O., et al., 2022. Myocardial infarction with non-obstructive coronary arteries (MINOCA): A clinical conundrum. Cureus 14, e32108.
Fangdi, Z., Yong, L.i., Shijie, Z., et al., 2022. DP1 (Prostaglandin D Receptor 1) Activation Protects Against Vascular Remodeling and Vascular Smooth Muscle Cell Transition to Myofibroblasts in Angiotensin II-Induced Hypertension in Mice. Hypertension 79, 1203–1215.
Feng, Y., Madungwe, N.B., da Cruz Junho, C.V., Bopassa, J.C., 2017. Activation of G protein-coupled oestrogen receptor 1 at the onset of reperfusion protects the myocardium against ischemia/reperfusion injury by reducing mitochondrial dysfunction and mitophagy. Br. J. Pharmacol. 174 (23), 4329–4344.
Giancarla, Scalone, Giampaolo, Niccoli, Filippo, Crea, 2019. Editor's Choice-Pathophysiology, diagnosis and management of MINOCA: an update. Eur. Heart J. Acute Cardiovasc. Care 8, 54–62.
Halima, Siddiqui, Nikita, Deo, Rutledge Malcolm, T., et al., 2023. Plasminogen Receptors Promote Lipoprotein(a) Uptake by Enhancing Surface Binding and Facilitating Macropinocytosis. Arterioscler. Thromb. Vasc. Biol. undefined: undefined.
Hiroaki, Shimokawa, 2014. 2014 Williams Harvey Lecture: importance of coronary vasomotion abnormalities-from bench to bedside. Eur. Heart J. 35, 3180–3193.
Hsue Priscilla, Y., Bittner Vera, A., John, B., et al., 2015. Impact of female sex on lipid lowering, clinical outcomes, and adverse effects in atorvastatin trials.Am. J. Cardiol. 115, 447–453.
Hui-Xin, W., Mittleman Murray, A., Constanze, L., et al., 2006. Depressive symptoms, social isolation, and progression of coronary artery atherosclerosis: the Stockholm Female Coronary Angiography Study. Psychother. Psychosom. 75, 96–102.
Kavindi, K.Y., Liyanage, D.S., Omeka, W.K.M., et al., 2023. Identification, expression profiling, and functional characterization of cystatin C from big-belly seahorse (Hippocampus abdominalis). Fish Shellfish Immunol. 138, 108804.
Kilanowski-Doroh Isabella, M., McNally Alexandra, B., Tristen, W., et al., 2023. Ovariectomy-Induced Arterial Stiffening Differs from Vascular Aging and is Reversed by GPER Activation. bioRxiv undefined: undefined.
Klas, P., Arne, H., 2004. Truncated thioredoxin: physiological functions and mechanism. Antioxid. Redox Signal. 6, 53–61.
Larsen Alf, I., Tomey Matthew, I., Roxana, M., et al., 2014. Comparison of outcomes in patients with ST-segment elevation myocardial infarction discharged on versus not on statin therapy (from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction Trial). Am. J. Cardiol. 113, 1273–1279.
Lei, D., Sander, K., Rinke, S., 2023. Triacylglycerol uptake and handling by macrophages: From fatty acids to lipoproteins. undefined Prog. Lipid Res., 101250
Lena, L., Garmo, H.G., Arne, Å., et al., 2023. Calprotectin and CRP as biomarkers of cardiovascular disease risk in patients with chronic kidney disease: a follow-up study at 5 and 10 years. Scand. J. Clin. Lab. Invest. 83, 258–263.
Leung-Tack, J., Tavera, C., Martinez, J., Colle, A., 1990. Neutrophil chemotactic activity is bymodulated human cystatin C, an inhibitor of cysteine proteases. Inflammation 14 (3), 247–258.
Lin, C., Yinghong, F., Zhen, F., et al., 2023. Long-Term Outcomes and Predictors of Patients with ST Elevated versus Non-ST Elevated Myocardial Infarctions in Non-Obstructive Coronary Arteries: a Retrospective Study in Northern China. PeerJ 11, e14958.
Lisa, Canton, Damiano, Fedele, Luca, Bergamaschi, et al., 2023. Sex and age-related differences in outcomes of patients with acute myocardial infarction: MINOCA versus MIOCA. Eur. Heart J. Acute Cardiovasc. Care undefined: undefined.
Luo, T., Liu, H., Kim, J.K., 2016. Estrogen Protects the Female Heart from Ischemia/Reperfusion Injury through Manganese Superoxide Dismutase Phosphorylation by Mitochondrial p38β at Threonine 79 and Serine 106. PLoS One 11 (12), e0167761.
Luying, Jiang, Jingbo, Liu, Zhenjia, Yang, et al., 2023. The effect of type 2 diabetes mellitus on multiple obstructive coronary artery disease. Echocardiography undefined: undefined.
Marlene, R., Alexander, L., Eriselda, M., et al., 2022. Physical Activity and Risk of Major Diabetes-Related Complications in Individuals With Diabetes: A Systematic Review and Meta-Analysis of Observational Studies. Diabetes Care 45, 3101–3111.
Marycarmen, A.M., Olivia, R., Bastrup Joakim, A., et al., 2023. Vascular smooth muscle-specific YAP/TAZ deletion triggers aneurysm development in mouse aorta.JCI. Insight undefined: undefined.
Mehmet, Y., Namrita, A., Aarushi, S., et al., 2022. Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA). Front Cardiovasc Med 9, 1032436.
Michael, S., Esther, R., Wouter, J.J., et al., 2023. Relating Lipoprotein(a) Concentrations to Cardiovascular Event Risk After Acute Coronary Syndrome: A Comparison of Three Tests. Circulation undefined: undefined.
Montone Rocco, A., 2021. Meucci Maria Chiara, De Vita Antonio, Lanza Gaetano A, Niccoli Giampaolo Coronary provocative tests in the catheterization laboratory: Pathophysiological bases, methodological considerations and clinical implications. Atherosclerosis 318, 14–21.
Montone Rocco, A., Ik-Kyung, J., Beltrame John, F., et al., 2021. The evolving role of cardiac imaging in patients with myocardial infarction and non-obstructive coronary arteries. Prog. Cardiovasc. Dis. 68, 78–87.
Nadine, G., Michael, K., Alexander, N., et al., 2022. Metabolic alterations in a rat model of takotsubo syndrome. Cardiovasc. Res. 118, 1932–1946.
Nakamura, M., Nishikawa, H., Mukai, S., et al., 2001. Impact of coronary artery remodeling on clinical presentation of coronary artery disease: an intravascular ultrasound study. J Am Coll Cardiol 37, 63–69.
Nauta, S.T., Deckers, J.W., van Domburg, R.T., Akkerhuis, K.M., 2012. Sex-related trends in mortality in hospitalized men and women after myocardial infarction between 1985 and 2008: equal benefit for women and men. Circulation 126 (18), 2184–2189.
Nelson, W., Jordan, F., Nishan, A., et al., 2020. Intensive LDL Cholesterol-Lowering Treatment beyond Current Recommendations for the Prevention of Major Vascular

Events: a Systematic Review and Meta-Analysis of Randomised Trials including 327 037 Participants. Lancet Diabetes Endocrinol 8, 36–49.
Nimrat, G., Onur, D., 2022. Jansen Evert Et Al. Are Acute Type A Aortic Dissections Atherosclerotic? Front Cardiovasc Med 9:, 1032755.
Nordenskjöld Anna, M., Eggers Kai, M., Tomas, J., et al., 2019. Circadian onset and prognosis of myocardial infarction with non-obstructive coronary arteries (MINOCA). PLoS One 14, e0216073.
Nordenskjöld, A.M., Baron, T., Eggers, K.M., Jernberg, T., Lindahl, B., 2018. Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease. Int. J. Cardiol. 261, 18–23.
Nordenskjöld, A.M., Lagerqvist, B., Baron, T., et al., 2019. Reinfarction in Patients with Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA): Coronary Findings and Prognosis. Am. J. Med. 132 (3), 335–346.
Orth-Gomér, K., Horsten, M., Wamala, S.P., et al., 1998. Social relations and extent and severity of coronary artery disease. The Stockholm Female Coronary Risk Study. Eur. Heart J. 19, 1648–1656.
O'Sullivan Jack, W., Ashley Euan, A., Elliott Perry, M., 2023. Polygenic risk scores for the prediction of cardiometabolic disease. Eur. Heart J. 44, 89–99.
Pasquale, P., Alberto, F., Luca, B., et al., 2021. Impact of admission hyperglycemia on short and long-term prognosis in acute myocardial infarction: MINOCA versus MIOCA. Cardiovasc. Diabetol. 20, 192.
Paula, G.-L., Marta, Á.-V., Rubén, R.-S., et al., 2023. Role of miR-15a-5p and miR-199a-3p in the Inflammatory Pathway Regulated by NF-Kb in Experimental and Human Atherosclerosis. Clin Transl Med 13, e1363.
Planer, D., Mehran, R., Ohman, E.M., White, H.D., Newman, J.D., et al., 2014. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. Circ. Cardiovasc. Interv. 7 (3), 285–293.
Planer, D., Mehran, R., Ohman, E.M., White, H.D., Newman, J.D., Xu, K., Stone, G.W., 2014. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. Circ. Cardiovasc. Interv. 7 (3), 285–293.
Poznyak Anastasia, V., Larisa, Litvinova, Paolo, Poggio, et al., 2022. Effect of Glucose Levels on Cardiovascular Risk. Cells 11, undefined.
Rahul, C., Michael, B., Novelli Enrico, M., et al., 2022. Sex-related differences in clinical outcomes among patients with myocardial infarction with nonobstructive coronary artery disease: A systematic review and meta-analysis. Int. J. Cardiol. 369, 1–4.
Roshanzamir, S., Showkathali, R., 2013. Takotsubo cardiomyopathy a short review. Curr. Cardiol. Rev. 9 (3), 191–196.
Safdar, B., Spatz, E.S., Dreyer, R.P., Beltrame, J.F., Lichtman, J.H., Spertus, J.A., Reynolds, H.R., Geda, M., Bueno, H., Dziura, J.D., Krumholz, H.M., D'Onofrio, G., 2018. Presentation, Clinical Profile, and Prognosis of Young Patients With Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): Results From the VIRGO Study. J. Am. Heart Assoc. 7 (13), e009174.
Shively Carol, A., Musselman Dominique, L., Willard Stephanie, L., 2009. Stress, depression, and coronary artery disease: modeling comorbidity in female primates. Neurosci. Biobehav. Rev. 33, 133–144.
Side, Gao, Haobo, Xu, Wenjian, Ma, et al., 2022. Remnant Cholesterol Predicts Risk of Cardiovascular Events in Patients With Myocardial Infarction With Nonobstructive Coronary Arteries. J. Am. Heart Assoc. 11.
Side, G., Wenjian, M.a., Sizhuang, H., et al., 2021. Effect of Lipoprotein (a) Levels on Long-term Cardiovascular Outcomes in Patients with Myocardial Infarction with Nonobstructive Coronary Arteries. Am. J. Cardiol. 152, 34–42.
Sivasinprasasn, S., Palee, S., Chattipakorn, K., Jaiwongkum, T., Apaijai, N., Pratchayasakul, W., Chattipakorn, S.C., Chattipakorn, N., 2019. N-acetylcysteine with low-dose estrogen reduces cardiac ischemia-reperfusion injury. J. Endocrinol. 242 (2), 37–50.
Smilowitz Nathaniel, R., Mahajan Asha, M., Roe Matthew, T., et al., 2017. Mortality of Myocardial Infarction by Sex, Age, and Obstructive Coronary Artery Disease Status in the ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines). Circ Cardiovasc Qual Outcomes 10, e003443.
Songzan, Chen, Yang, Xu, Tian, Fangkun, et al., 2023. Smoking and coronary artery disease risk in patients with diabetes: A Mendelian Randomization Study. Front. Immunol. 14, 891947.
Steagall, R.J., Yao, F., Shaikh, S.R., Abdel-Rahman, A.A., 2017. Estrogen receptor α activation enhances its cell surface localization and improves myocardial redox status in ovariectomized rats. Life Sci. 1 (182), 41–49.
Stefanescu, S.A.C., Kereiakes Dean, J., Cutlip Donald, E., et al., 2017. Myocardial Infarction Risk After Discontinuation of Thienopyridine Therapy in the Randomized DAPT Study (Dual Antiplatelet Therapy). Circulation 135 (18), 1720–1732.
Sylwia, M., Sonia, K., Polderdijk Stéphanie, G.I., et al., 2022. Parallel Imaging of Coagulation Pathway Proteases Activated Protein c, Thrombin, and Factor Xa in Human Plasma. Chem Sci 13, 6813–6829.
Tamis-Holland Jacqueline, E., Hani, J., Reynolds Harmony, R., et al., 2019. Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. Circulation 139, e891–e908.
Tedy, S., Abdullah, S., Nicolas, N., et al., 2022. Role of RhoA and Rho-associated kinase in phenotypic switching of vascular smooth muscle cells: Implications for vascular function. Atherosclerosis 358, 12–28.
van Helden, Josef, Evliyaoglu, Osman, Andreas, Küberl, Weiskirchen, Ralf, 2020. Disorders of the glucose metabolism correlate with the phenotype and the severity in women with polycystic ovary syndrome. Clin. Endocrinol. 93 (No.1), 44–51.
Virani, S.S., Alonso, A., Benjamin, E.J., Bittencourt, M.S., Callaway, C.W., et al., 2020. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation 141 (9), e139–e596.
Ward Nathan, P., 2023. Cys-regulation: oxidized CHK1 controls cross-compartment circuit of chemoresistance. Trends Cancer 9, 700–702.
Xu, B., Abdu, F.A., Liu, L., et al., 2020. Clinical outcomes and predictors of ST-elevation versus non-ST-elevation myocardial infarction with non-obstructive coronary arteries. Am. J. Med. Sci. 360, 686–692.
Xu, X., Bao, H., Strait, K., Spertus, J.A., Lichtman, J.H., D'Onofrio, G., Spatz, E., Bucholz, E.M., Geda, M., Lorenze, N.P., Bueno, H., Beltrame, J.F., Krumholz, H.M., 2015. Sex differences in perceived stress and early recovery in young and middle-aged patients with acute myocardial infarction. Circulation 131 (7), 614–623.
Ya-Wen, L.u., Yi-Lin, T., Ruey-Hsing, C., et al., 2021. Serum creatinine to cystatin C ratio is associated with major adverse cardiovascular events in patients with obstructive coronary artery disease. Nutr Metab Cardiovasc Dis 31, 1509–1515.
Yaxin, W., Gabriella, B., Huang, Y.u., et al., 2023. Determinants of Incident Atherosclerotic Cardiovascular Disease Events among Individuals with Type 2 Diabetic Microvascular Complications in the UK: a Prospective Cohort Study. Diabetol Metab Syndr 15, 178.
Yeh, R.W., Sidney, S., Chandra, M., Sorel, M., Selby, J.V., Go, A.S., 2010. Population trends in the incidence and outcomes of acute myocardial infarction. N. Engl. J. Med. 362 (23), 2155–2165.
Yiwei, Y., Cao, Xu, Yueyue, Yide, et al., 2023. CARMA3 Deficiency Aggravates Angiotensin II-Induced Abdominal Aortic Aneurysm Development Interacting Between Endoplasmic Reticulum and Mitochondria. Can. J. Cardiol. undefined: undefined.
Zhang, S., Zhang, X., Wu, S., et al., 2022. Analysis of clinical features and the outcome of in-hospital mortality of myocardial infarction with non-obstructive coronary arteries. J. Zhonghua Xin Xue Guan Bing Za Zhi 50, 873–880.
Zhi, O., Jian, Z., Junyi, S., et al., 2023. The Cell Origins of Foam Cell and Lipid Metabolism Regulated by Mechanical Stress in Atherosclerosis. Front Physiol 14, 1179828.