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Contents

Monthly Volume 12 Number 10 October 26, 2020

## MINIREVIEWS



## ORIGINAL ARTICLE

### Retrospective Study



## META-ANALYSIS

*World Journal of Cardiology*

**Monthly Volume 12 Number 10 October 26, 2020**

## Contents

## ABOUT COVER

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*MINIREVIEWS*

# Electronic cigarettes — myocardial infarction, hemodynamic compromise during pregnancy, and systolic and diastolic dysfunction: Minireview

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## Abstract

The aim of this study was to review the most recent literature on the safety of electronic cigarettes (ECs) in the context of cardiovascular disease and in the context as a tool for smoking cessation and recreational purposes. The format of this review begins with relevant research from the basic sciences and follows through with a pertinent review of clinical trials. Daily use of ECs has implications in myocardial infarction (MI) with an odds ratio of 1.70 compared to healthy, nonsmokers and even worse risk for MI with dual use of combustible cigarettes together with EC with an odds ratio of 4.62. Studies measuring cardiac function with echocardiography reported both systolic and diastolic dysfunction along with reduced ejection fractions. Platelet aggregation, endothelial function, and hemodynamics during pregnancy were all but some of the pernicious cardiovascular implications of EC exposure. Though more studies need to be done on the topic of EC use and cardiovascular disease, the majority of studies considered in this review concluded some level of harm albeit in some instances less than that of traditional combustible cigarettes. ECs are toxic to human beings and their harmful effects cannot be overlooked. There is some favorable evidence of efficacy in smoking cessation though mixed with concern of chronic EC use. It will take decades to collect data for chronic EC use on long term sequelae, such as lung cancer. Though more and more reports of acute lung injury and hospitalizations related to EC use have been reported. Due to undergoing investigations of possible harm and life threatening complications of EC use, we cannot recommend ECs as safer or a more efficacious method of smoking cessation to traditional nicotine replacement therapies. A notable consideration for much of the literature reviewed are that standardization of EC use is difficult as device generation and battery voltage, frequency of use, and contents of EC

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liquid are just some of the vast complicating factors that limit the ability to effectively compare data.

**Key Words:** Electronic cigarettes; Vaping; Cardiovascular effects; Electronic nicotine delivery; Angiogenesis; Nicotine replacement therapies



**Core Tip:** Electronic cigarette (EC) use is rapidly expanding to cigarette-native users including adolescents with little known available studies on long term use in both respiratory and cardiovascular systems. As most recent studies have focused on respiratory implications of EC use, there is much research to be done on cardiovascular ramifications. This literature review focuses on the most recent publications relating to EC use and oxidant formation, thrombogenesis, and myocardial infarctions, and examines the safety profile of ECs in smoking cessation and recreational use.

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## INTRODUCTION

Electronic cigarettes (ECs, E-cigarettes, E-cigs, personal vaporizers, vape pens) are recreational devices used to vaporize a solvent mixture to inhale as a cigarette alternative. As the rate of tobacco cigarette (TC) use has dropped in the United States relative to the rest of the world, industries have heavily marketed the use of ECs as the "safer" alternative. According to the surgeon general, smoking rates had reached historic lows in 2014[1]. The CDC reported that from 2017 to 2018 EC use (defined as at least 1 d of use in 30 d) amongst high school students and middle school students had increased 78% and 48%, respectively[2]. Approximately 20% of current high school students say that they have tried ECs likely because they feel they are safe[3]. Many of the claims advocating ECs as healthier alternatives to combustible cigarettes are sponsored by profit-driven tobacco companies whose assertions in the determination of EC safety profile needs to be studied.

Their rise to popularity can be attributed to a variety of factors including but not limited to unsubstantiated claims of higher safety profile compared to traditional combustion cigarettes, arguable smoking cessation efficacy, and limited market regulations. As large tobacco companies continue to enter the market, concerns about the short term and long term safety of ECs continues to trend as a popular topic[4,5].

EC devices vary in design but all share essential hardware basics consisting of a rechargeable lithium battery, a vaporization chamber, and an interchangeable liquid cartridge. Formulations of EC liquids include both tobacco-based and nontobacco mixtures. Of importance to our study, nicotine delivery to the human body is affected by various factors, such as the type of device used, voltage of battery, resistance, and chemical composition of solvent. Thus, studies on first-generation ECs reported delivery of low concentrations of nicotine to the bloodstream unlike newer generation devices equipped with high-capacity batteries[4-6]. One study by Farsalinos *et al*[8] showed a 35% to 72% increase in nicotine delivery with newer generations of ECs relative to first-generation devices.

ECs introduce new complexities to studying the side effect profile that prior combustible cigarette use did not entail. The broad variability of ECs arises from the various nicotine concentrations present in e-liquids, various volumes of e-liquids per product, different carrier compounds, additives, flavors, and battery voltages[4,5]. Figure 1 shows the main effects of TC smoke on the cardiovascular system[9]. Many of these effects could be relevant to ECs as well.

Given that cardiovascular disease accounts for 30% of smoking-related deaths[4] and the recent explosion of the use of ECs, it is important to review the current literature

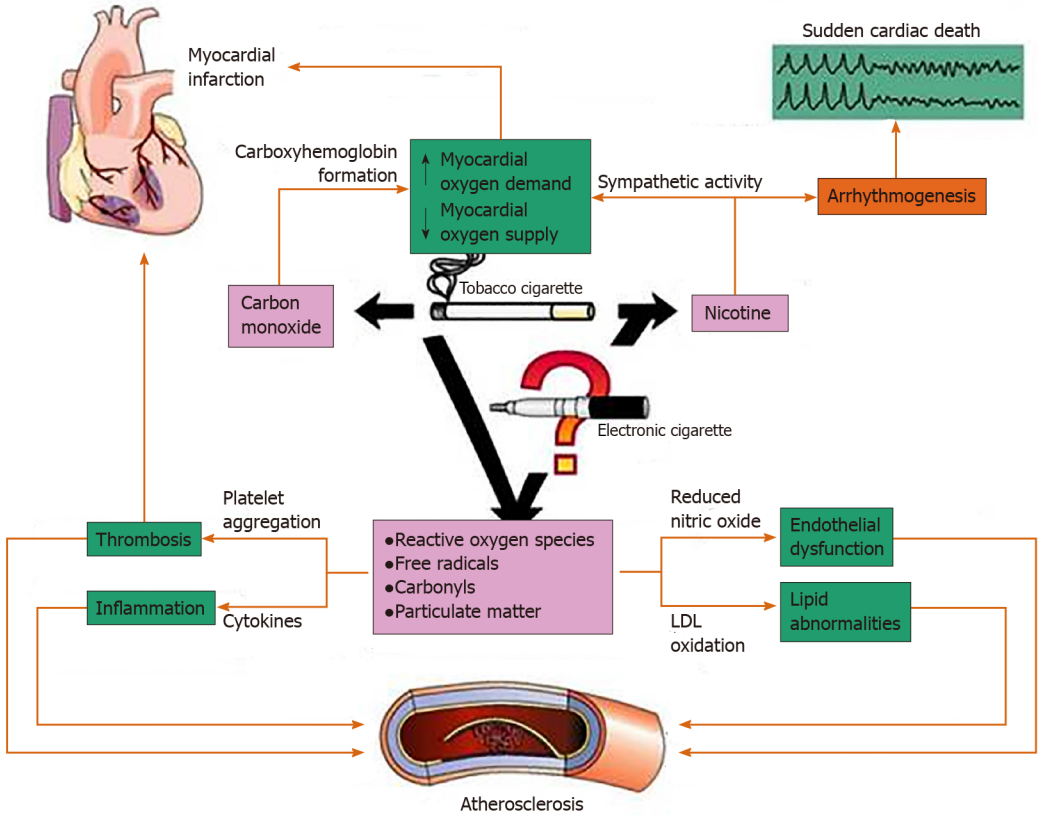


**Figure 1 Effects of tobacco cigarette smoke on the cardiovascular system.** Citation: MacDonald A, Middlekauff HR. Electronic cigarettes and cardiovascular health: what do we know so far? *Vasc Health Risk Manag* 2019; 15: 159-174. Copyright© The Authors 2019. Published by Dove Medical Press Limited.

relating to ECs and the cardiovascular system.

## MYOCARDIAL INFARCTION AND CARDIAC FUNCTIONAL CHANGES

A joint study[10] from Charles Drew University and University of California, Los Angeles used apolipoprotein-E knockout mice to study cardiovascular effects of ECs on the heart. These mice were elected as they have been used to study the cardiovascular effects of conventional cigarettes. Mice were grouped and exposed to either aerosolized saline (used as a baseline control), ECs sans nicotine (0%), or ECs with 2.4% nicotine for 12 wk. One of the aims of the study was to use the 0% nicotine group to determine the relationship, if any, of propylene glycol and glycerol on the formation of free radicals in a heat dependent manner. The study used the commercially available E-cig brand bluCig PLUS and a specialized EC delivery system for the mice similar to human ECs. The 0% nicotine and 2.4% nicotine groups were exposed to bluCig solvents, specifically the Gold Leaf Tobacco (0% nicotine) and Classic Tobacco (2.4% nicotine), which varied only in nicotine content. This study used echocardiography and reported that mice exposed to ECs with 2.4% nicotine had decreased left ventricular fractional shortening and ejection fraction compared with 0% nicotine ECs, though they found no differences in the saline, 0%, and 2.4% groups in the following parameters: peak early diastolic, E/A ratio, and atrial filling velocity. University of California, Los Angeles researchers looked at RNA sequence changes of tissue in the left ventricle of mice in the 2.4% and 0% and aerosolized nicotine groups using an Agilent 2100 Bioanalyzer. Of the 24054 genes analyzed, 109 of them showed at least a 1.5 fold variability (48 upregulated, 61 downregulated) with a $P$ value of $< 0.05$ in the 2.4% aerosolized nicotine group relative to no changes seen in the saline group. The 2.4% subgroup again was associated with expression of inflammatory molecules Col5a3, TNFRSF12A, and selectin E.

Ventricular transcriptomatic analysis revealed changes in genes associated with metabolism, circadian rhythm, and inflammation on mice exposed to ECs with 2.4% nicotine while transmission electron microscopy showed cardiomyocytes with

structural irregularities suggestive of cardiomyopathy. In the same group of mice, researchers saw increased oxidative stress, mitochondrial DNA mutations, and atherosclerotic lesions compared with saline aerosol-treated mice.

A large cross-sectional study from George Washington University published in 2018 was one of the first of its kind to report that daily EC use increased the odds of having a myocardial infarction (MI) with an odds ratio of 1.79, which was relatively less than associated TC smoking (odds ratio: 2.72) though still of significant concern[7]. Study data was collected from 2014 to 2016 by the National Health Interview Survey by random selection of United States households and subsequent in-person interviews of adults over the age of 18. The study found that daily dual use of EC and traditional combustible cigarettes had significantly higher risk for MI relative to never smokers (odds ratio: 2.72 × 1.70 = 4.62). The limitations of this study were that the study was a self-reporting survey posing concerns for recall bias, and equally as important there was no differentiation between solvent nicotine presence or concentration, type of device used, and a clearly defined meaning of "daily use."

Farsalinos *et al*[8] recently published a study shedding light on the little known effects of EC use and cardiovascular health. They conducted a study on 36 healthy persons who heavily smoked TC and compared them to 40 healthy, ex-TC smokers now using ECs at a comparable rate for 1 mo. Echocardiographic examinations were performed before and after using the EC device with "medium-strength" nicotine concentration. The study used echocardiography to measure acute changes in cardiac function and found no change in left ventricular function after EC use but did find changes in diastolic function after just one EC use[8]. Echocardiography studies focused on mitral flow diastolic velocities, deceleration time, isovolumetric relaxation time, and corrected heart rate[8]. Diastolic velocities were specifically measured by averaging the lateral, septal, anterior, and inferior insertion sites of the mitral leaflets. Some limitations of this study were a small sample size of 76 subjects and a lack of unhealthy participants. Further, the scope of the study was limited to acute changes and little can be said about the chronic effects of EC use from this experiment.

A cross-sectional study published in the American Journal of Preventive medicine had significant data regarding the association between EC use and myocardial infarction. Alzahrani *et al*[7] stratified EC and TC users as never before, former, some days, or daily users taking into account demographics and pre-existing health conditions such as hypertension, dyslipidemia, and diabetes. The study population was based on the 2014 and 2016 National Health Interview Survey with participants aged ≥ 18 years from randomly sampled United States households. Significantly, data unequivocally suggested an increased risk for MI with an odds ratio of 1.7 in both adjusted and unadjusted groups of daily EC users compared with subjects that had never used ECs before when all confounding variables were accounted for such as previous history of cigarette use, gender, *etc*. Moreover, participants who were dual users of ECs and combustible cigarettes had a total odds of 4.62 of having had an MI compared to those who had never smoked and never used ECs. This suggests a synergistic pernicious effect that dual usage has on cardiovascular health. In summary this study concluded that daily EC use was associated with a higher risk of MI after confounding factors are accounted for including traditional combustible cigarettes and other risk factors.

We summarized the major studies about effects of ECs on cardiac functional changes and associated risks of MI in Table 1.

## THROMBOGENESIS/PLATELET AGGREGATION

TCs have long been known to be associated with platelet aggregation and thrombogenesis[5,7,9,11]. One *in vivo* study evaluated platelet function while under incubation with ECs, TCs, and pure nicotine extracts and showed that platelet aggregation and adhesion receptors were upregulated in relation to nicotine concentration in a dose dependent manner[5,9]. Two types of ECs were used: All-in-one devices, 1.2% or 1.8% nicotine by volume (Njoy and OneJoy, respectively); and reloadable cartridge devices, 0, 12, and 18 mg of nicotine (eGo, OKC Vapes, and Desert Sands Flavor, respectively). Researchers mimicked puffing times of 5 min (time to smoke traditional cigarette) during their extraction of EC vapors. Extracts were stored in HEPES buffer and later exposed to healthy platelets. Results showed activation of platelet CD41 (GP11b) after exposure to both combustible tobacco smoke extracts and EC vapor extracts compared to controls of no smoke exposure. gC1qR, cC1qR, CD42b, GPIBa, and CD62P (P-selectin) also showed significant upregulation, and researchers

**Table 1 Effects of electronic cigarettes on the risk of myocardial infarction and cardiac functional changes from electronic cigarettes**

| Name of the study | Type of the study | Results | Comments |
|---|---|---|---|
| Chronic intermittent electronic cigarette exposure induces cardiac dysfunction and atherosclerosis in apolipoprotein-E knockout mice | Animal model randomized control study with intervention | ECs with 2.4% nicotine had decreased left ventricular ejection fraction and had increased atherosclerotic lesions compared to ECs without nicotine and saline groups. Mice exposed to 2.4% nicotine vapor had increased atherosclerotic lesions on aorta as well | Mice model with limited implication to humans |
| Association between electronic cigarette use and myocardial infarction | Cross-sectional; study was based on self-reporting surveys | Increased odds ratio (1.79) of having MI with ECs and even higher odds ratio (4.62) with dual use of ECs and combustible cigarettes relative to never smokers | Number of surveys in 2014 was 36697 and 33028 in 2016 |
| Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: Comparison with the effects of regular cigarettes | Interventional, case-control | Electronic cigarettes caused delayed myocardial relaxation, no effect on systolic function | Small study with total of 76 subjects; the study does not predict long term effects |
| Association between electronic cigarette use and myocardial infarction | Cross-sectional through surveys | Daily EC use increased the odds of having MI (OR = 1.79) while daily TC smoking had a higher correlation of MI (OR = 2.72) | Large surveys: 36697 in 2014 and 33028 in 2016 |

ECs: Electronic cigarettes; MI: Myocardial infarction; OR: Odds ratio; TC: Tobacco cigarette.

also found an increase of platelet aggregation rate[5]. Interestingly, pure nicotine seemed to exacerbate platelet dysfunction in a dose-dependent manner. The study also measured deposition of complement products (C1q, C3b, C4d, and C5b-9) on the surface of platelets but was unable to show any correlation with exposure to any of the extracts. In the same study researchers at Stony Brook University showed a similar response in humans and by measuring CD40L and P-selectin platelet activation markers. After TC and EC use, an increase in activity in both of the aforementioned was observed. Another recently published study in the Journal of the American Heart Association reported a rapid increase in the number of circulating endothelial progenitor cells after EC use by examining the *in vitro* effects of adhesion and aggregation in healthy human volunteers[14].

Aldehydes such as formaldehyde and acrolein have long been suspected to play roles in human toxicology[9,11,12]. Acrolein is found in high concentrations in automobile exhaust, industrial waste, and tobacco smoke, which are generally thought to be produced by burning of fossil fuels exogenously and endogenously by lipid peroxidation[12]. Gaseous acrolein is one of the suspected agents in EC smoke that contributes to increased thrombogenesis, while another agent in EC smoke, formaldehyde, was seen to increase total platelet count in mice[9,11]. Sithu *et al*[12] showed that both acute and chronic acrolein levels correlated with increased platelet-fibrinogen formation, ADP-induced platelet aggregation, induction of platelet-leukocyte aggregates, and PF4 Levels.

One significant study from Osei *et al*[13] at Johns Hopkins focused on dual usage of ECs and TCs and the subsequent effects on the cardiovascular system. This was a cross-sectional telephone survey study that consisted of 449092 participants of whom 15863 (3.5%) were current EC users, 2.9% were dual users (EC + TC), and 10% of the participants had cardiovascular disease. This was a self-reported study where cardiovascular disease was defined as a composite of coronary heart disease, myocardial infarction, or stroke. Remarkably, dual smokers had a 36% higher odds of cardiovascular disease (odds ratio: 1.36) along with reports of premature cardiovascular disease in women in comparison to traditional cigarette smokers who had never used ECs[13].

## ARTERIOSCLEROSIS AND ENDOTHELIAL DAMAGE

A study from Stanford led by Lee *et al*[5] used stem-cell-derived endothelial cells to study the effects of EC use. The study included the flavors of fruit, tobacco, sweet tobacco with caramel and vanilla, sweet butterscotch, cinnamon, and menthol and nicotine concentrations of 0, 6, and 18 milligrams per milliliter. Of major significance, they found that the cells lost viability even in the absence of nicotine. Results varied from the different flavors with the cinnamon flavor having the highest adverse reactions, including decreased cell viability, increased reactive oxygen species (ROS)

levels, caspase 3/7 activity, and low-density lipoprotein uptake, activation of oxidative stress-related pathway, and impaired tube formation and migration, which confirmed their hypothesis of endothelial dysfunction. Further they found activation of macrophages, which caused downstream activation of interleukin-1B and increased ROS. Lee *et al*[3] found that nicotine had a dose-dependent effect on many of the measured parameters including cytotoxicity, ROS generation, and apoptotic activities.

An interesting review article on vascular calcification and ECs comes from a recent publication in the Journal for the American Heart Association that looked at human, rat, and cell culture studies. First, a review on the definitions of atherosclerosis *vs* arteriosclerosis that this article focused on: Atherosclerosis is characterized by accrual of lipids, penetration of macrophages, and fibrotic lesions within plaques with ensuing rupture and thrombus formation; and arteriosclerosis is transformation of the arteriole wall by either hardening, thickening, or loss of elasticity. Of significance, this scholarly review of literature concluded that nicotine-containing vaping facilitates and perhaps induces osteogenic transdifferentiation and calcification of the tunica media wall of vascular smooth muscle cells by means of inflammation, endothelial dysfunction, and production of ROS. This process is believed to be a key event in the calcification of the tunica media of the vessel wall. Nicotine facilitates transdifferentiation of vascular smooth muscle cells by activation of three major pathways: NF-κB; macrophages and monocytes; and subsequently TNFα, interleukin-6 and VCAM-1. These all lead to an inflammatory state in the vasculature that can cause both acute cardiovascular compromise and chronic degradation of contractile properties of the vascular smooth muscle cells[14].

As concerns arise regarding the lack of regulation on EC products, it is important to recall that the flavoring additives alone can be toxic to humans. While combustible cigarettes are limited to menthol for flavoring, ECs remain unregulated with a wide range of flavorings available on the market. Fetterman *et al*[19] used freshly isolated endothelial cells from nonsmoking, healthy participants and measured nitric oxide production and vasodilation at baseline and after exposure to heated flavorings. The flavoring additives were heated to a temperature of 37 C using a tank device similar in function to an EC device and subsequently exposed to the endothelial cells for 90 min. The flavorings vanillin, cinnamaldehyde, eugenol, acetylpyridine, and menthol impaired nitric oxide production and increased expression of proinflammatory mediators and interleukin-6, suggesting that these flavors are injurious to the endothelium.

In a previously referenced article[10], mice were exposed to an EC delivery system mimicking real use in a laboratory setting to measure the formation of atherosclerotic lesion formation. They used oil red O staining and contrasted that with a hematoxylin and fast green stain and found that rats exposed to 2.4% nicotine EC vapor had increased lesions at the aortic root as quantified by Image-Pro Plus in comparison to saline treated mice. To be exact, saline treated mice had lesions that measured 53.6 ± 7.5 × $10^5$ μm$^2$ *vs* a much larger lesion in 2.4% treated mice of 103.9 ± 12.9 × $10^5$ μm$^2$ with a *P* value of less than 0.01. More information on the methods of this particular experiment is mentioned above.

One opposing view regarding cardiovascular effects of ECs comes from Cossio *et al*[15]. In a small study consisting of sixteen young, healthy tobacco product naïve participants, they measured acute responses to "vaping trials" using flavored ECs with either 0% or 5.4% nicotine for 6 min. The vaping protocol was a total of 6 min in length consisting of 4 s inhalations every 20 s, which corresponded to 18 puffs in total. Subjects were monitored during their trial to ensure they were puffing at a standardized rate. Measurements were done at baseline, immediately post, 1 h, and 2 h post-EC exposure. There were no noteworthy changes in heart rate, systolic and diastolic blood pressure, endothelial function (*via* flow-mediated dilation), or arterial stiffness (*via* cardio-ankle vascular index) during the trials. The study is limited in that the reported data represented acute changes to only one bout of EC use and does not account for multiple bouts per day, which is characteristic of many EC users.

We summarized the major studies about the effects of ECs on arteriosclerosis and endothelial damage in Table 2.

## SMOKING CESSATION

The potential use of ECs in the area of smoking cessation therapy must be weighed against potential subsequent chronic use of ECs along with EC specific toxicities that remain to be studied extensively. As of September 24, 2019, 46 state health agencies

**Table 2 Arteriosclerosis and endothelial damage**

| Name of the study | Type of the study | Results | Comments |
|---|---|---|---|
| Modeling cardiovascular risks of ECs with human-induced pluripotent stem cell-derived endothelial cells | Randomized interventional on human endothelial cells; cells were exposed to EC flavoring products with and without nicotine | Flavoring e-liquids caused endothelial dysfunction even without nicotine; nicotine had a dose-dependent effect on cytotoxicity, reactive oxygen species generation, and apoptotic activities | *In vitro* study with limited implications |
| Flavorings in tobacco products induce endothelial cell dysfunction | Intervention study on human endothelial cells obtained from smokers and nonsmokers | The flavorings vanillin, cinnamaldehyde, eugenol, acetylpyridine, and menthol impaired nitric oxide production and increased expression of proinflammatory mediators and interleukin-6 | Small study; the endothelial cells obtained by biopsy from 3 groups of 6 to 9 subjects |
| Vascular effects of a single bout of electronic cigarette use | Interventional nonrandomized study on healthy volunteers | There were no significant changes in heart rate, systolic and diastolic blood pressure, endothelial function (*via* flow-mediated dilation), and arterial stiffness (*via* cardio-ankle vascular index) throughout the experiments | Small study on 16 volunteers; the study was limited to acute changes post smoking one bout of ECs; flow mediated dilation and cardio-ankle vascular index may not be sensitive enough |

ECs: Electronic cigarettes.

have reported 805 patients with cases of lung injury associated with use of EC products to the Centers for Disease Control and Prevention and per the same report from the Centers for Disease Control and Prevention, 12 EC-related deaths have been confirmed in 10 states[24]. The efficacy of ECs in cessation of smoking TCs continues to be a debated topic with mixed results. Safety profile and superiority of ECs in relation to nicotine replacement products (NRTs) in smoking cessation are two areas of interest on the issue. A recent study published in the New England Journal of Medicine in February gives some insight into this topic.

Hajek *et al*[16] designed a two-group randomized, controlled trial with 886 participants to evaluate ECs as a means of smoking cessation relative to traditional NRTs. Smokers were divided into two treatment groups: EC users and NRTs. Subjects were treated for 3 mo with their respective cessation method and followed up in 1 year with a biochemical test (expired carbon-monoxide levels), and these values were compared to their baseline carbon-monoxide levels prior to initiation of treatment. EC users were given "starter packs" consisting of second generation refillable ECs with 18 mg per milliliter of nicotine though participants were free to purchase their own preferred brand and flavoring during the duration of the study. The NRT group was given their preferred choice of patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtab with the option of interchanging one for another. Both groups received weekly behavioral support for at least 4 wk from local clinicians. The abstinence rate at the 1-year mark was 18% in the EC group and 9.9% in the NRT group (relative risk, 1.83; 95% confidence interval: 1.30 to 2.58; $P < 0.001$). However, it is important to note that of those that were able to abstain from smoking at the year mark, EC users were more likely to be continually using their EC at the 52 wk mark than NRTs (80% *vs* 9%, respectively)[16]. The superiority of ECs to NRTs in smoking cessation is in contrast to the Cochrane study in 2016, which had inconclusive results of potency of ECs to NRTs in smoking cessation[6].

A recent review published in August 2019 by Worku *et al*[17] concluded that the few studies showing success in the role of ECs in smoking cessation were offset by the fact that the most common EC user was a dual user of both ECs and traditional combustible cigarettes and the increased susceptibility of users, particularly youth, to future use of cigarettes[18]. Youth are particular targets of the EC campaigns as the appeal for traditional cigarettes has lessened in recent years. Therefore, companies have aimed to revive the smoking industry by marketing the devices as trendy and modern. A University of California, Los Angeles review found three studies indicating that high school students who were EC users had increased interest relative to never-before-smokers to initiate use of cigarettes supporting the notion that ECs are a gateway to cigarettes and other combustible tobacco products such as hookah[20].

## HEMODYNAMICS AND PREGNANCY

Youth are not the only subgroup that are especially at risk of potential harms.

Pregnant females are also a population of concern. A survey study published in 2015 surveyed 184 persons, 68 of whom were 18-20-years-old, 55 were 21-30-years-old, and 61 were 31-plus-years-old. The study found that all ages perceive ECs as significantly less pernicious than combustible cigarettes including relating to lung cancer, harm during pregnancy, and addictive properties[21]. Multiple studies suggest that the negative fetal effects of tobacco are specifically linked to nicotine, an alarming finding in the context of increased usage of ECs during pregnancy due to false safety claims[21,23].

A Texas based study in May 2019 used lab rats to study how EC aerosol exposure during fetal development jeopardized vascular hemodynamic function and attributed to growth defects[22]. The study used pregnant Sprague-Dawley rats and divided them into three groups: Controls, juice-fed, and juice plus nicotine fed and used a custom engineered vaping system to simulate the EC paradigm. Researchers compounded an inhouse e-liquid with various nicotine concentrations to use in the study with an 80:20 propylene glycol to glycerol ratio, which is similar to that found in popular e-liquid brands. The rats undertook vaping treatment for 2 h a day, 5 d days per week from gestation day (GD)5 until GD 21 and gave birth on GD 22. It is important to note that the researchers exposed the nicotine rat group to 10% nicotine throughout the duration of the study. The study utilized mass spectrometry to identify and quantify blood nicotine levels. Results were significant as they found the juice plus nicotine group had a decreased fetal weight of 46.56% and a decrease of 23.83% in crown-rump length compared to controls. Again, fetal hemodynamics were compromised as both uterine and umbilical artery blood flow between the control group and nicotine group were significantly decreased (uterine artery 49.50%, $P = 0.05$; umbilical artery 65.33%, $P = 0.01$). These values were measured using a Doppler ultrasound and measured peak-to-peak times for three waveforms to pass. Although this study brings interesting insight into gestational hemodynamic compromise in rats, we are unable to draw any definitive implications regarding human gestation for obvious ethical concerns. Given the data presented in this study, we strongly admonish the use of EC during any stage of human gestation.

## CONCLUSION

ECs remain a threat to cardiovascular health as studies thus far unanimously support the notion that ECs pose at least some level of risk. Misleading marketing geared towards youth and a general misconception about the safety profile of ECs are of particular concern as these products remain generally unregulated and unstudied. Atherosclerosis, free radical formation, diastolic functional changes, RNA and mDNA sequence changes, and incidence of MI are only some of the changes implicated thus far in ongoing research on the topic of ECs. Further tangential vascular concerns include fetal compromise due to significant umbilical and uterine artery blood flow restriction from EC use in rat models. Though a minority of studies show EC as posing less of a threat to cardiovascular health in relation to traditional combustible cigarettes, there is a need for more studies, particularly ones that focus on chronic use. The vast majority of literature reviewed concluded some level of harm, and multiple studies showed a significant synergistic risk when smokers concomitantly used ECs with combustible cigarettes, which greatly increased the risk for MI relative to either used individually. This literature review concludes at least some level of risk to endothelial and platelet function as well as compromised hemodynamics during rat-model gestation. After thorough review of the current literature, we are unable to endorse ECs as a safe alternative to smoking cessation especially in the context of cardiovascular disease and ongoing reports of acute lung injury and lethal consequences with EC use.

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ORIGINAL ARTICLE

Retrospective Study

# Upper body peripherally inserted central catheter in pediatric single ventricle patients

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## Abstract

### *BACKGROUND*

There is risk of stenosis and thrombosis of the superior vena cava after upper extremity central catheter replacement. This complication is more serious among patients with single ventricle physiology, as it might preclude them from undergoing further life-sustaining palliative surgery.

### *AIM*

To describe complications associated with the use of upper extremity percutaneous intravenous central catheters (PICCs) in children with single ventricle physiology.

### *METHODS*

A single institution retrospective review of univentricular patients who underwent superior cavopulmonary anastomoses as their stage 2 palliation procedure from January 2014 until December 2018 and had upper body PICCs placed at any point prior to this procedure. Clinical data including ultrasonography, cardiac catheterization, echocardiogram reports and patient notes were used to determine the presence of thrombus or stenosis of the upper extremity and cervical vessels. Data regarding the presence and duration of upper extremity PICCs and upper extremity central venous catheter (CVC), and use of anticoagulation were recorded.

### *RESULTS*

Seventy-six patients underwent superior cavopulmonary anastomoses, of which 56 (73%) had an upper extremity PICC at some point prior to this procedure. Median duration of PICC usage was 24 d (25%, 75%: 12, 39). Seventeen patients

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(30%) with PICCs also had internal jugular or subclavian central venous catheters (CVCs) in place at some point prior to their superior cavopulmonary anastomoses, median duration 10 d (25%, 75%: 8, 14). Thrombus was detected in association with 2 of the 56 PICCs (4%) and 3 of the 17 CVCs (18%). All five patients were placed on therapeutic dose of low molecular weight heparin at the time of thrombus detection and subsequent cardiac catheterization demonstrated resolution in three of the five patients. No patients developed clinically significant venous stenosis.

*CONCLUSION*
Use of upper extremity PICCs in patients with single ventricle physiology prior to super cavopulmonary anastomosis is associated with a low rate of catheter-associated thrombosis.

**Key Words:** Thrombosis; Central venous catheters; Catheterization peripheral; Univentricular heart; Children



**Core Tip:** There is a wide variation in practice in terms of the preferred central venous access site and catheter-type for patients who undergo surgery for single ventricle heart disease. Thrombosis is a serious concern in patients with single ventricle physiology. This study aims to describe the use of upper body percutaneously inserted central catheters in patients with single ventricle physiology prior to their superior cavopulmonary anastomosis procedure at our institution. Our study shows that upper body percutaneous intravenous central catheters are associated with a low rate of clinically significant catheter-related thrombosis.

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## INTRODUCTION

Children with critical congenital heart disease (CHD) often require a central venous catheter (CVC) in the medication administration, fluid resuscitation, nutrition and hemodynamic monitoring prior to surgical repair and for post-operative care management. A subset of children with CHD can require central venous access for a longer period of time[1,2]. The use of central venous catheters (CVCs) or percutaneously inserted central catheters (PICCs) for prolonged periods can result in complications including venous stenosis and thrombosis, especially in neonates[3,4]. Central venous thrombosis is a cause of considerable morbidity and mortality in children who undergo surgery for CHD[5,6]. Patients who undergo surgery for CHD are at high risk of developing thrombosis due to a hypercoagulable state often related to cardiopulmonary bypass and blood product transfusions[1,7,8].

There are several options for CVCs location including umbilical in neonates, femoral, internal jugular, or subclavian vein, transthoracic intracardiac catheters, and PICCs[9]. Considerable variation exists between centers in the most commonly used catheters and sites, and no formal recommendations have been published to guide current practice[9-11].

Infants with single ventricle physiology need to have patent superior vena cava and upper-extremity veins to ensure adequate passive pulmonary blood flow[12]. Stenosis or thrombosis of these central veins can delay surgery and, in some patients, preclude further palliation surgeries. Due to these concerns about obstruction of upper extremity veins many institutions discourage the use of upper extremity CVCs or PICCs in this patient population. However, data on the rate of venous thrombosis in children with single ventricle physiology in whupper extremity CVCs are placed are

limited[8,13,14]. In our practice, the use of upper extremity PICCs in this patient population is common.

We aim to describe our use of upper extremity PICCs in children with single ventricle physiology who have undergone superior cavopulmonary anastomosis as their stage two palliation surgery.

## MATERIALS AND METHODS

### Patients

This study was approved by the Institutional Review Board at our institution. This is a retrospective cohort study of pediatric patients undergoing cardiac surgery at our institution over a 5-year period–January 2014 to December 2018. Patients who underwent superior cavopulmonary anastomoses (Hemi-Fontan or bidirectional Glenn procedure) were identified from our institutional pediatric cardiac surgical database and data was extracted from chart reviews of the electronic medical records. Patients who required cervical extracorporeal membrane oxygenation support at any point prior to their superior cavopulmonary anastomosis procedure and patients who did not undergo a first stage palliation procedure were excluded from the study.

### Institutional protocols

All patients at our institution undergo diagnostic cardiac catheterization prior their superior cavopulmonary anastomosis for surgical planning purposes. Routine screening for the presence of CVC- or PICC-associated thromboses however is not performed, studies are ordered based on the discretion of the primary care team. All patients had a diagnostic cardiac catheterization to assess hemodynamics prior to the second stage pallation surgery.

Location and type of central venous access is not protocolized. For most patients, an umbilical venous catheter is placed in neonates with CHD at birth. If a patient continues to need stable intravenous access beyond 48 h of life, a PICC is placed in the intervention radiology suite and the umbilical venous catheter removed. Intraoperatively, most patients receive a double lumen intra-cardiac, right atrial catheter is placed. For some patients, an internal jugular or subclavian CVC is placed as an additional venous access site. The ongoing need for a central venous access is assessed daily during the multidisciplinary morning rounds. For patients who are deemed to require central venous access for a prolonged period to time postoperatively, which includes most of the patients with single ventricle physiology who undergo stage 1 palliation procedures, a PICC is placed and right atrial catheters and other CVCs are removed. A heparin infusion (2 U/mL) is administered as a carrier fluid for all central venous access lumens while they are in place.

Beginning in January 2016, central venous catheter-related thrombus prophylaxis protocol in our cardiac intensive care unit was implemented. For patients who were deemed to require their central venous access for 72 h or more, low molecular-weight heparin (LMWH) is started within 48 h post-operatively or within 12 h after the placement of central venous access for non-surgical patients. The dose is adjusted by a designated clinical pharmacist based on Anti-Xa activity (goal range: 0.25-0.49 IU/mL). Prophylactic LMWH protocol is delayed in for significant post-operative bleeding, concern for high risk of bleeding, use of another agent for therapeutic anticoagulation, compromised renal function (creatinine clearance < 30 mL/min/1.73 $m^2$), or concern for heparin-induced thrombocytopenia. LMWH is initiated at 0.75 mg/kg/dose every 12 h for patients who were less than 2 mo old and 0.5 mg/kg/dose for patients who were greater than 2 mo old.

### Data collection

Patient characteristics including demographic data, diagnoses, and first stage palliation procedures were collected. Data regarding type and duration of the central venous access, number of catheters, and use of anticoagulation after the cardiac surgery were also collected. We also collected information regarding central venous access utilized during any hospital admissions during the inter-stage period between stage 1 palliation procedures and superior cavopulmonary anastomosis. Outcome data regarding thrombosis was collected from vascular ultrasound, computerized tomography, fluoroscopy, echocardiogram and cardiac catheterization studies obtained prior to superior cavopulmonary anastomosis.

### *Statistical analysis*

Data are presented using descriptive statistics. Categorical data are presented as frequency with percentage and continuous variables are presented as median with (25%, 75%) unless otherwise noted. Chi square test was used to compare the rate of complications between the group of patients with PICCs and CVCs.

## RESULTS

We reviewed 76 patients who underwent cardiac catheterization prior undergoing superior cavopulmonary anastomoses as their stage 2 palliation procedure (hemi-Fontan or bidirectional Glenn). Patient characteristics are shown in (Table 1). The median age at first stage palliation surgery was 9 d (25%, 75%: 6, 15). Thirty (39%) patients were female and 35 (46%) patients had hypoplastic left heart syndrome. The distribution of the primary cardiac defects is shown in (Figure 1).

All patients had at least one CVC or PICC placed prior to their second stage procedure. The types of CVCs and PICCs used are summarized in (Figure 2). Fifty-six patients (73%) had an upper extremity PICC at some point prior to their superior cavopulmonary anastomosis with a median duration of 24 d (25%, 75%: 12, 39). Seventeen patients who had PICCs also had an upper extremity CVC (internal jugular or subclavian vein) in place at some point prior to superior cavopulmonary anastomosis with a median duration 10 d (25%, 75%: 8, 14). No patient had an upper extremity PICC and CVC in place simultaneously. Sixty-eight patients (89%) received aspirin and 68 patients (89%) received LMWH prophylaxis while PICCs or CVCs were in place.

Venous thrombus was identified in 5 patients (7%), all of which were seen on upper extremity vascular ultrasound. Three patients had hypoplastic left heart syndrome and underwent the Norwood operation, one patient had tricuspid atresia and underwent pulmonary artery band placement, and one patient had double outlet right ventricle and underwent pulmonary artery band placement. No thrombi were detected *via* other radiologic studies or cardiac catheterization. In total, upper extremity ultrasounds were obtained in 11 (14%) patients due to suspicion for thrombus. Thrombus was detected in association with 2 of the 56 PICCs (43.6%) and 3 of the 17 CVCs (18%) and the incidence of thrombosis was significantly different between the PICCs *vs* CVCs ($P < 0.04$). Thrombosis was identified at a median of 5 d (Range: 4-18 after their first stage palliation surgery and a median of 9 d (Range: 7-16) after placement of PICC or CVC. All 5 patients were switched from prophylactic LMWH dose to therapeutic LMWH after identification of thrombosis and subsequent cardiac catheterization demonstrated thrombus resolution in 3 of 5 patients. The presence of thrombosis in two patients delayed their surgery and, in one patient, precluded the patient from having the second stage surgery. These two patients had PICCs and chorionic villi sampling prior the cardiac catheterization. None of the other 71 patients were found to have thrombosis on cardiac catheterization. Characteristics of the patients with upper extremity thrombus are shown in (Table 2).

## DISCUSSION

At our institute, we utilize upper extremity PICCs in most of our single ventricle physiology patients. This cohort demonstrates that the practice of using upper body PICC lines has a low rate of thrombosis among single ventricle physiology patients. There is a large range of reported incidence of venous thrombosis after cardiac surgery in the literature. A prior study from our institute identified a rate of thrombosis of 6% among all patients who underwent cardiac surgery which similar is to this cohort[1]. Manlhiot *et al*[2], reported thrombosis in 11% of pediatric patients with CHD[2]. In another case series with 89 umbilical venous catheters and femoral central venous catheters, the incidence of the thrombosis among single ventricle patient was high as 42%[15]. In a third study, Miller *et al*[4] reported no cases of thrombosis in 156 right internal jugular vein catheters in patients who underwent Glenn or Fontan operations[4].

Upper body venous thrombosis is a major concern for single ventricle patients because it could preclude them from further palliative operations in the future. It is important to weigh the risks versus the benefits when deciding the location and type of central venous catheter. In general, pediatric patients will require a deep sedation or

**Table 1 Characteristics of the patients in the cohort**

| Variable | Patients |
|---|---|
| Birth weight in kgs (mean) | 3.13 |
| Age at first palliation surgery in days (IQR) | 9 (6, 15) |
| Female sex, *n* (%) | 30 (39) |
| Non-hispanic white, *n* (%) | 48 (64) |
| Prematurity, *n* (%) | 10 (15) |
| HLHS, *n* (%) | 46% |

HLHS: Hypoplastic left heart syndrome.

**Table 2 Haracteristics of the five patients with upper extremity thrombus detected on ultrasonography or cardiac catheterization**

| Diagnosis | First stage operation | Age at surgery (in days) | Age at diagnosis thrombus (in days) | Type of venous access | Anti-coagulation prior to thrombus | Resolution of thrombus |
|---|---|---|---|---|---|---|
| DORV | PA band | 6 | 10 | Subclavian | No | Yes |
| HLHS | Hybrid | 20 | 25 | Subclavian | Yes | Yes |
| HLHS | Norwood | 14 | 18 | UE PICC | No | Yes |
| Tricuspid atresia | PA band | 9 | 27 | UE PICC | No | No |
| HLHS | Norwood | 9 | 18 | Subclavian | Yes | No |

DORV: Double outlet right ventricle; HLHS: Hypoplastic left heart syndrome; UE: Upper extremity; PA: Pulmonary artery; PICC: Percutaneous upper intravenous central catheters.

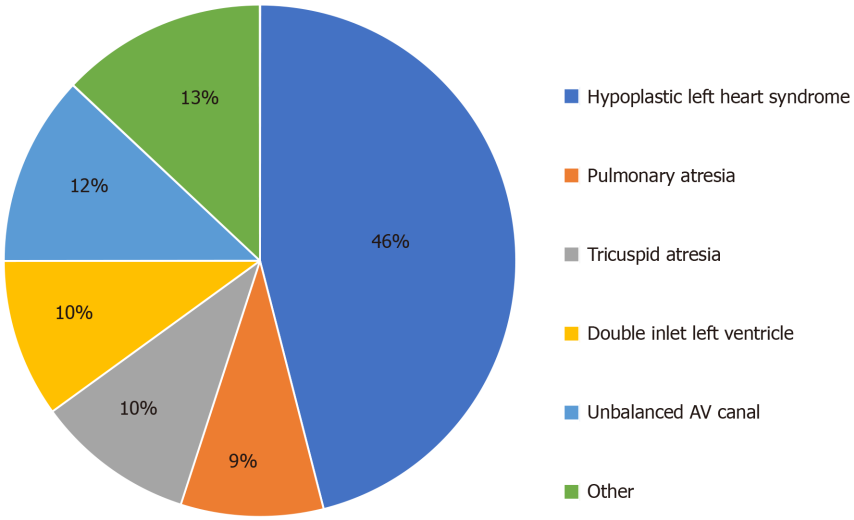


**Figure 1 Pie chart summarizing primary cardiac diagnoses, represented as percentages.**

mechanical ventilation during central venous catheter replacement. In our institute, PICCs are placed in interventional radiology suite, if a patient's condition allows for a transfer. Patients receive local anesthetic and minimum sedation for placement with a high success rate.

Obtaining venous access for pediatric patients who undergo congenital heart surgery can be challenging and might take a significant amount of time after induction of anesthesia or require surgical replacement in some cases. As a result, having a PICCs replaced prior to the surgery will facilitate the preoperative process and save operating room time along. Upper extremity venous access will be at the head of the

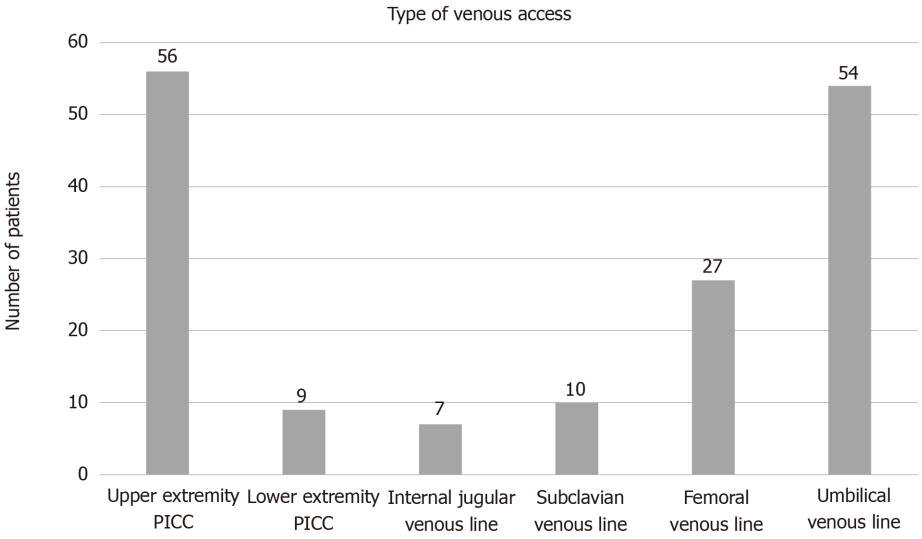


**Figure 2 Bar graph illustrating the different types of central venous access utilized for patients with single ventricle physiology prior to their superior cavopulmonary anastomosis.** Upper extremity percutaneous intravenous central catheters were most frequently used.

operation table for easy access by the pediatric cardiac anesthesia team. Moreover, most of the single ventricle patients will require several diagnostic or interventional cardiac catheterization over the course of their life, upper extremity PICCs will decrease the number of the femoral venous access attempts.

There is limited data comparing safety and complication rate of PICCs over CVCs in children. Most of the studies have focused on complications with PICCs in neonates and children with leukemia[8,16]. There are few studies published that compare the rates of infection and thrombosis in the hospitalized pediatric patients with PICCs versus CVCs. Noonan *et al*[17] recently published their experience of the 2709 venous catheters, 126 PICCs and 1583 CVCs. They reported that the rates of central line-associated blood steam catheters (CLABSIs) and venous thromboembolism were higher among patients with PICCs[17]. Data measuring the different complications between PICCs and CVCs among patients with congenital heart disease is very sparse. In this cohort, we did not report the incidence of the CLABSIs, as we have a very low CLABSI rate at our institute with over 800 CLABSI free days during the timeframe of this study.

The majority of patients (60%) who developed thrombosis had upper body CVCs at some point in addition to the PICCs. There was resolution of thrombosis on subsequent cardiac catheterization prior to the second stage palliative after treating them with low-molecular-weight heparin in 60% (3/5) of patients with thrombosis. There were two patients who had PICCs without additional CVC who developed non-occlusive thrombosis, which resolved prior to the cardiac catheterization. There was no one excluded from the second stage from the group who had only PICCs due to the present of the thrombosis. Another interesting finding from our cohort was that patients who were diagnosed with catheter-related thrombosis developed it in close proximity to the first stage palliation surgery. This suggests that the immediate post-operative period is prothrombotic and early anticoagulation, once the risk of bleeding is reasonable, may be beneficial.

This is a retrospective study at the single center. We do not perform routine upper body ultrasound for thrombosis detection. Imaging for thrombosis identification was directed by symptoms prior second stage cardiac catheterization which might underestimate the rate. Additionally, patients had to survive until pre-stage II diagnostic cardiac catheterization in order to be assessed for the outcomes. The majority of our patients were receiving anti-coagulation which might contribute to this low rate of thrombosis. There is no controlled evaluation for other important clinical indicators like anticoagulation practices or rate of CLABSIs

## CONCLUSION

In this retrospective study of children with single ventricle physiology, the placement of percutaneously inserted central catheter in the upper extremity is a reliable way to achieve long-lasting central venous access and associated with a low risk of clinically

significant stenosis or thrombosis.

## ARTICLE HIGHLIGHTS

### *Research background*

There is risk of stenosis and thrombosis of the superior vena cava after upper extremity central catheter replacement. This complication is more serious among patients with single ventricle physiology, as it might preclude them from undergoing further life-sustaining palliative surgery. Data on the rate of venous thrombosis in children with single ventricle physiology with upper extremity central venous catheters are limited. Also, there is a wide variation in practice regarding the choice of central access in this population across the centers.

### *Research motivation*

To study the risk of using upper body percutaneously inserted central catheter (PICC) in single ventricle patients. The results of this study could be used to develop a multicenter study to determine the risk and benefit of using this type and location of the catheter in this population.

### *Research objectives*

To describe the incidence of thrombosis associated with the use of PICCs in patients with single ventricle physiology.

### *Research methods*

We retrospectively reviewed the charts of patients with single ventricle physiology who underwent second stage palliation surgery. Data regarding the type and duration of central venous access were collected in addition to the data regarding thrombosis or stenosis.

### *Research results*

We reviewed a total of seventy-six patients underwent superior cavopulmonary anastomoses, of which 56 (73%) had an upper extremity PICC at some point prior to this procedure. Median duration of PICC usage was 24 d (25%, 75%: 12, 39). Seventeen patients (30%) with PICCs also had internal jugular or subclavian central venous catheters (CVCs) in place at some point prior to their superior cavopulmonary anastomoses with a median duration of 10 days (25%, 75%: 8, 14). Thrombus was detected in association with 2 of the 56 PICCs (4%) and 3 of the 17 CVCs (18%) and the incidence of thrombosis was significantly different between the PICCs *vs* CVCs ($P < 0.04$). All five patients were placed on therapeutic dose of low molecular weight heparin at the time of thrombus detection and subsequent cardiac catheterization demonstrated resolution in three of the five patients. No patients developed clinically significant venous stenosis.

### *Research conclusions*

The placement of PICC in the upper extremity in children with single ventricle physiology was associated with low risk of clinically significant stenosis or thrombosis and provide a reliable way to have long-lasting central venous access.

### *Research perspectives*

Further research and multicenter studies specifically looking at the incidence of complications with upper body PICCs in single ventricle patients are warranted.

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ORIGINAL ARTICLE

Retrospective Study

# Risk score for predicting abdominal complications after coronary artery bypass grafting

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**Author contributions:** Belov DV wrote the manuscript and performed data analysis; Garbuzenko DV contributed to the conception and design of the study, acquisition, analysis and interpretation of data, and wrote the manuscript; Abramovskikh KA contributed to writing the manuscript, drafting the conception and design of the study; Arefyev NO contributed to analysis of data, and wrote and revised the manuscript; all authors have read and approved the final manuscript.

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**Informed consent statement:** Each "Patient's Medical Record" contained an "Informed voluntary consent to the processing of

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## Abstract

*BACKGROUND*

Although early abdominal complications after coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) are rare, the associated mortality remains high.

*AIM*

To develop a risk score for the prediction of early abdominal complications after CABG with CPB.

*METHODS*

This retrospective study was performed in the Federal State Budgetary Establishment "Federal Center of Cardiovascular Surgery" of the Ministry of Health of Russia (the city of Chelyabinsk) and included data of 6586 patients who underwent CABG with CPB during 2011-2017. The risk factors taken for evaluation were compared between patients with early abdominal complications ( $n$ = 73) and without them ($n$ = 6513). We identified the most important risk factors and their influence on the development of early abdominal complications after CABG with CPB.

personal data" filled out and signed by the patient, where the patient gave permission to use his/her personal data for conducting scientific research.

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*RESULTS*

Gender and the presence of postinfarction cardiosclerosis, chronic kidney disease, or diabetes in the anamnesis did not affect the occurrence of abdominal complications. The leading risk factors of the early abdominal complications after CABG with CPB were multifocal atherosclerosis, extracorporeal membrane oxygenation, intra-aortic balloon pump, atrial fibrillation, perioperative myocardial infarction, and the need for resternotomy in the postoperative period. The average value of the predicted probability was 0.087 ± 0.015 in patients with early abdominal complications after CABG with CPB and 0.0094 ± 0.0003 in patients without these complications. The percentage of correct classification turned out to be 98.9%. After calculating a score for each of the leading risk factors, we counted a total score for each particular patient. The highest risk was noted in patients with a total score of 7 or more.

*CONCLUSION*

The developed score predicts the risk of early abdominal complications after CABG with CPB and makes it possible to stratify patients by risk groups.

**Key Words:** Coronary artery bypass grafting; Cardiopulmonary bypass; Abdominal complications; Risk factors; Risk score



**Core Tip:** Although early abdominal complications after coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) are rare, the associated mortality remains high. We developed a score for the prediction of early abdominal complications after CABG with CPB. The leading risk factors were multifocal atherosclerosis, extracorporeal membrane oxygenation, intra-aortic balloon pump, atrial fibrillation, perioperative myocardial infarction, and the need for resternotomy in the postoperative period. A risk score that involves these factors makes it possible to stratify patients, which is important for timely treatment and diagnosis and, ultimately, will help to reduce postoperative mortality.

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## INTRODUCTION

Abdominal complications in patients who underwent coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) are rare (1.1%) but associated with high mortality, which reaches 90%[1,2]. Predicting the risk of their development may be one of the ways to solve this problem.

One way to reduce mortality in this category of patients is to predict the risk of abdominal complications[3]. Our aim was to develop a score for predicting early abdominal complications after CABG with CPB.

## MATERIALS AND METHODS

### *Patients*

We retrospectively analyzed individual medical records of 6586 patients who underwent CABG with CPB in the Federal Center of Cardiovascular Surgery of the Ministry of Health of Russia (the city of Chelyabinsk) during 2011-2017. Cases of acute cholecystitis, acute pancreatitis, acute mesenteric ischemia, intestinal necrosis, and acute intestinal obstruction that developed prior to discharge of the patient were

referred to as early abdominal complications.

Some patients had postinfarction cardiosclerosis, chronic kidney disease, or type 1 or type 2 diabetes in the anamnesis.

Diabetes was diagnosed using one of the following diagnostic criteria: (1) Classic symptoms of diabetes (polyuria, polydipsia, ketonuria, and rapid weight loss) and a random venous plasma glucose concentration of ≥ 11.1 mmol/L; (2) Fasting glucose concentration of ≥ 7.0 mmol/L in venous plasma or ≥ 6.1 mmol/L in whole blood; and (3) 2-h plasma glucose concentration of ≥ 11.1 mmol/L during a 75-g oral glucose tolerance test.

In each case, measurement of glucose concentration was repeated on a second occasion to confirm the diagnosis[4].

Chronic kidney disease was diagnosed if either of the following was present for > 3 mo: Glomerular filtration rate of < 60 mL/min/1.73 m$^2$; One or more markers of kidney damage: (1) Albuminuria (ACR ≥ 30 mg/g), (2) Urine sediment abnormalities, (3) Electrolyte and other abnormalities due to tubular disorders, (4) Abnormalities detected by histology, (5) Structural abnormalities detected by imaging, and (6) History of kidney transplantation[5].

Each medical record contained a completed and signed informed voluntary consent of the patient to the processing and use of his/her personal data and written consent to treatment. Information that was taken into account to evaluate the risk factors for abdominal complications is presented in Table 1.

### *Assessment of risk factors and statistical analysis*

The anamnestic risk factors and the risk factors that occurred within 2 d from the date of surgery were taken for evaluation and compared between patients with early abdominal complications ($n$ = 73) and without them ($n$ = 6513), and the relative risks (RRs) were calculated. Statistical data processing was performed using Statistica 10.0 (Statsoft, Tulsa, OK, United States) and SPSS 23.0 (IBM Corp., Armonk, NY, United States). In order to describe the risks, contingency tables were used to calculate the RR and the odds ratio.

An integrated score for assessing the risk of early abdominal complications was created on the basis of the above-mentioned factors by using multivariate logistic regression analysis. The presence or absence of complications was a dependent variable, while the above-mentioned factors were independent variables. Then, the obtained risk score was evaluated by using a receiver operating characteristic (ROC) curve analysis. The presence or absence of early abdominal complications was an outcome variable. The ordinate axis (sensitivity) corresponded to the true positive rate; the abscissa axis (1-specificity) corresponded to the false positive rate. It is generally supposed that the area under the ROC curve that is in the range of 0.9-1.0 should be considered as an indicator of the highest informativeness of the diagnostic method. The range of 0.8-0.9 is good, 0.7-0.8 is acceptable, 0.6-0.7 is weak, and 0.5-0.6 is extremely weak.

## RESULTS

In order to determine the probability of early abdominal complications after CABG with CPB, the RRs of their development were analyzed according to the presence and absence of the factors included in the study. Gender and the presence of postinfarction cardiosclerosis, chronic kidney disease, or type 1 or type 2 diabetes in the anamnesis did not affect the occurrence of abdominal complications.

At the same time, abdominal complications most often occurred in patients with extracorporeal membrane oxygenation (RR = 38.7), intra-aortic balloon pump (RR = 29.3), and acute myocardial infarction diagnosed after surgery (RR = 21.9). In addition, the development of early abdominal complications was possible in patients who had the following risk factors: Resternotomy (RR = 14.1); ischemic and hemorrhagic brain stroke (RR = 9.4); atrial fibrillation (RR = 8.2); multifocal atherosclerosis, namely the presence of hemodynamically significant stenoses, not only in coronary arteries but also in the brachiocephalic arteries, arteries of the upper and lower extremities, and renal arteries (RR = 4.0); CPB with the duration of more than 125 min (RR = 3.19); a combination of CABG with valve correction (RR = 3.4); aortic clamping time of more than 70 min (RR = 2.5); and age over 70 years (RR = 2.3) (Table 2).

Based on the data obtained, a multivariate logistic regression model analysis was done in order to create an integrated score for assessing the risk of early abdominal complications after CABG with CPB. The presence or absence of complications was a

**Table 1 Indicators for the evaluation of the risk factors for abdominal complications**

| Factor | Indicator | Mean (95%CI) or *n* (%) |
|---|---|---|
| Male sex | 1–Presence/0-Absence | 5164 (78.4) |
| Age in years | Number | 61 (56 to 66) |
| Weight, kg | Number | 82 (73 to 93) |
| Height, cm | Number | 169 (161 to 174) |
| Body mass index, kg/m$^2$ | Number | 29.27 (26.35 to 32.56) |
| Left ventricular ejection fraction, % | Number | 55.69 (47.74 to 61) |
| Post-infarction cardiosclerosis | 1–Presence/0-Absence | 4429 (67.2) |
| Cerebrovascular accident in the anamnesis | 1–Presence/0-Absence | 359 (5.5) |
| Chronic kidney disease | 1–Presence/0-Absence | 917 (13.9) |
| Multifocal atherosclerosis | 1–Presence/0-Absence | 673 (10.2) |
| Diabetes | 1–Presence/0-Absence | 1452 (22) |
| The duration of cardiopulmonary bypass in min | Number | 77 (60 to 107) |
| Aortic clamping time in min | Number | 41 (31 to 61) |
| Combination of coronary artery bypass grafting with valve correction | 1–Presence/0-Absence | 1049 (15.9) |
| Resternotomy | 1–Presence/0-Absence | 294 (4.5) |
| Postoperative bleeding requiring resternotomy | 1–Presence/0-Absence | 182 (2.8) |
| Other reasons for resternotomy | 1–Presence/0-Absence | 100 (1.52) |
| Atrial fibrillation in the postoperative period | 1–Presence/0-Absence | 695 (10.6) |
| Intra- and postoperative myocardial infarction | 1–Presence/0-Absence | 90 (1.37) |
| Intra- and postoperative cerebrovascular accident | 1–Presence/0-Absence | 74 (1.12) |
| Intra-aortic balloon pump | 1–Presence/0-Absence | 13 (0.19) |
| Extracorporeal membrane oxygenation | 1–Presence/0-Absence | 30 (0.45) |

CI: Confidence interval.

dependent variable and the six most significant risk factors were independent variables (Table 3).

It was found that the most significant independent risk factors were extracorporeal membrane oxygenation, intra-aortic balloon pump, and resternotomy in the postoperative period, followed by atrial fibrillation, perioperative acute myocardial infarction, and multifocal atherosclerosis. The average value of the predicted probability was 0.087 ± 0.015 in patients with early abdominal complications after CABG with CPB and 0.0094 ± 0.0003 in patients without these complications. The percentage of correct classification turned out to be 98.9%.

To facilitate the use of this model in practice, each factor was assigned a specific score reflecting its contribution to the total risk of early abdominal complications after CABG with CPB (Table 4).

To evaluate the probability of early abdominal complications for each patient, we calculated the exact predicted probability by using the created logistic regression model and the sum of scores. Next, both of them were compared by using a ROC analysis. The criterion "presence/absence" of complications was used as an outcome variable (Table 5 and Figure 1).

The data presented in Figure 1 indicates that the ROC-curve for the indicator "sum of scores" almost coincides with that for the predicted probability and has a good diagnostic value [area under the curve (referred to as the AUC) = 0.805 ± 0.033, $P < 0.001$].

After the ROC curve analysis, we found it reasonable to divide the curve into four segments that would reflect the low, moderate, high, and very high risk (Table 6).

We also prospectively evaluated our scale in a group of patients who underwent CABG with CPB in 2018. The identification of a high and very high risk group for

**Table 2 Qualitative risk factors of abdominal complications and relative risk of abdominal complications**

| Factor | Patients with the presence of a studied factor | | Patients with the absence of a studied factor | | Relative risk | *P* value |
|---|---|---|---|---|---|---|
| | *n* | Risk of abdominal complications, *n* (%) | *n* | Risk of abdominal complications, *n* (%) | | |
| Extracorporeal membrane oxygenation | 30 | 11 (36.67) | 6556 | 62 (0.95) | 38.7 | < 0.001 |
| Intra-aortic balloon pump | 13 | 4 (30.77) | 6573 | 69 (1.05) | 29.3 | < 0.001 |
| Perioperative myocardial infarction | 90 | 17 (18.89) | 6496 | 56 (0.86) | 21.9 | < 0.001 |
| Resternotomy | 294 | 29 (9.86) | 6292 | 44 (0.7) | 14.1 | < 0.001 |
| Cerebrovascular accident in the perioperative period | 74 | 7 (9.46) | 6512 | 65 (1.0) | 9.4 | < 0.001 |
| Atrial fibrillation in the postoperative period | 695 | 36 (5.18) | 5891 | 37 (0.63) | 8.2 | < 0.001 |
| Multifocal atherosclerosis | 673 | 23 (3.42) | 5913 | 50 (0.85) | 4.0 | < 0.001 |
| Combination of coronary artery bypass grafting with valve correction | 1049 | 29 (2.76) | 5537 | 44 (0.79) | 3.4 | < 0.001 |
| Cardiopulmonary bypass with the duration of more than 125 min | 1238 | 31 (2.5) | 5348 | 42 (0.79) | 3.19 | < 0.001 |
| Aortic clamping time of more than 70 min | 1374 | 29 (2.11) | 5212 | 44 (0.84) | 2.5 | < 0.001 |
| Age over 70 yr | 830 | 18 (2.17) | 5756 | 55 (0.96) | 2.3 | 0.0018 |
| Cerebrovascular accident in the anamnesis | 359 | 8 (2.23) | 6227 | 65 (1.04) | 2.1 | 0.037 |
| Chronic kidney disease | 917 | 14 (1.53) | 5669 | 59 (1.04) | 1.4 | 0.19 |
| Male sex | 5164 | 60 (1.16) | 1422 | 13 (0.91) | 1.3 | 0.43 |
| Postinfarction cardiosclerosis | 4429 | 48 (1.08) | 2157 | 25 (1.16) | 0.94 | 0.78 |
| Diabetes | 1452 | 10 (0.69) | 5134 | 63 (1.23) | 0.56 | 0.084 |

**Table 3 Coefficients of the model of multivariate logistic regression (Nagelkerke R Square = 0.966, *P* < 0.0001)**

| Risk factor | B ± SE | Exp (B) | *P* value |
|---|---|---|---|
| Multifocal atherosclerosis | 0.74 ± 0.28 | 2.10 | 0.001 |
| Extracorporeal membrane oxygenation | 2.323 ± 0.546 | 10.207 | < 0.001 |
| Intra-aortic balloon pump | 1.762 ± 0.887 | 5.824 | 0.047 |
| Resternotomy | 1.922 ± 0.316 | 6.833 | < 0.001 |
| Atrial fibrillation in the postoperative period | 1.62 ± 0.262 | 5.054 | < 0.001 |
| Perioperative myocardial infarction | 1.384 ± 0.415 | 3.991 | 0.001 |
| Constant | 5.508 ± 0.193 | 0.004 | < 0.001 |

B: Coefficient of regression; SE: Standard error.

abdominal complications contributed to early diagnosis in 14 patients. The number of lethal cases was 20 (27.4%) for 2011-2017 and decreased to 2 (14.3%) cases in 2018 ($P < 0.05$). Hence, the hospital mortality decreased to 52.2% in the group of patients with early abdominal complications.

The division of patients into risk groups according to the development of abdominal complications after CABG with CPB suggests a differentiated approach to their management in the postoperative period. Patients with a score of more than 7 according to our score require particular attention.

**Table 4 Distribution of scores assigned to the risk factors for abdominal complications**

| Risk factor | Score |
|---|---|
| Multifocal atherosclerosis | 3 |
| Extracorporeal membrane oxygenation | 10 |
| Intra-aortic balloon pump | 6 |
| Atrial fibrillation in the postoperative period | 5 |
| Perioperative myocardial infarction | 4 |
| The need to perform postoperative resternotomy (excluding patients with extracorporeal membrane oxygenation) | 7 |

**Table 5 Results of receiver operating characteristic curve analysis**

| Factor | AUC | SE (AUC) | 95%CI | *P* value |
|---|---|---|---|---|
| The exact predicted probability | 0.805 | 0.033 | 0.739-0.869 | < 0.001 |
| Total score | 0.805 | 0.033 | 0.740-0.871 | < 0.001 |

AUC: Area under the curve; CI: Confidence interval; SE: Standard error.

**Table 6 Distribution of patients according to the risk groups of abdominal complications after coronary artery bypass grafting with cardiopulmonary bypass**

| Risk group | Score | Risk of abdominal complications, % | *n* | The percentage of the risk group in the general population, % |
|---|---|---|---|---|
| Low risk of abdominal complications | 0 | 0.4 | 5072 | 77.0 |
| Moderate risk of abdominal complications | 1-6 | 1.2 | 1047 | 15.9 |
| High risk of abdominal complications | 7-12 | 9.4 | 421 | 6.4 |
| Very high risk of abdominal complications | ≥ 13 | 44 | 46 | 0.7 |

## DISCUSSION

Abdominal complications after CABG with CPB are found in 0.2%-5.5% of operated patients[6] and are accompanied by a mortality rate from 11% to 74%[7]. Therefore, it is relevant to identify risk factors for predicting the development of abdominal complications.

Long-term CPB is accompanied by a wide range of pathophysiological disorders, which include non-pulsating blood flow, activation of hormonal immunity, anticoagulation, hypothermia, decreased organ perfusion, redistribution of blood flow, threat of embolism, and hyperkalemia[6]. It is known that subphysiological blood flow, the release of endogenous vasoconstrictors, including angiotensin II, and the subsequent increase in systemic vascular resistance during CPB may lead to abdominal ischemia, especially if atherosclerotic lesions are present[8,9].

An increase in aortic clamping time may lead to low cardiac output and/or release of inflammatory mediators[10]. In addition, if CABG is combined with valve surgery, the risk of mesenteric embolism increases[11].

In patients with postoperative bleeding that requires a resternotomy and in the case when a ventilation time is more than 24 h, there is a decrease in cardiac output and in mean arterial pressure and an increase in vascular resistance of internal organs, which induce temporary hypoperfusion[12]. These disorders of splanchnic hemodynamics are exacerbated by the activation of the renin-angiotensin-aldosterone system and increased levels of catecholamines.

Severe acute perioperative myocardial infarction is accompanied by a decrease in cardiac output, systemic hypotension with the centralization of blood circulation, and a decrease in mesenteric perfusion[13,14]. They are also facilitated by the following factors: (1) Vasopressors that are used to treat myocardial infarction[15]; (2)

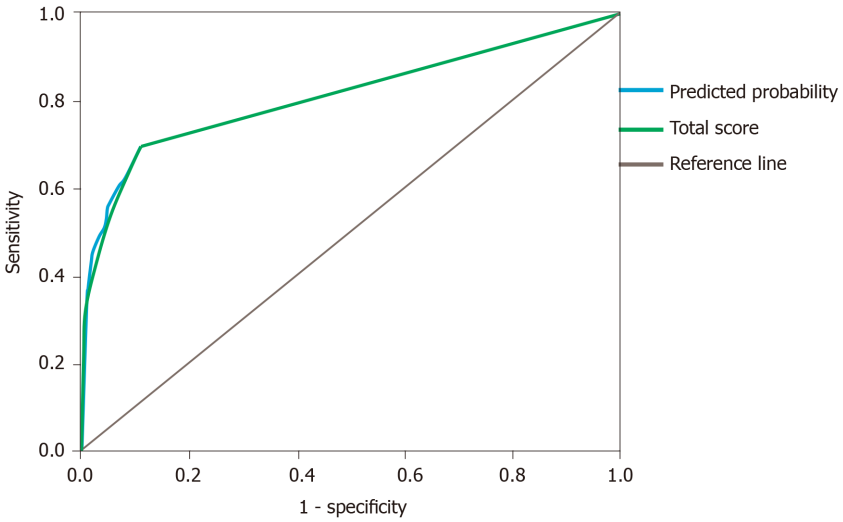


**Figure 1 Receiver operating characteristic curve for the predicted probability and the sum of scores.**

Prolongation of CPB and mechanical ventilation[16]; (3) Resternotomy for reshunting[6,8,17]; (4) Extracorporeal membrane oxygenation[16,18]; and (5) Intra-aortic balloon counterpulsation, when there is thromboembolism of visceral arteries or their obstruction due to incorrect positioning[17,19].

Atrial fibrillation in the postoperative period contributes to the embolism of the mesenteric vasculature[12], which is also possible during manipulations on the aorta in multifocal atherosclerosis[10]. In the latter, hemodynamically insignificant stenoses in the superior mesenteric artery exacerbate the impairment of mesenteric perfusion caused by hypovolemia and hypotension. In addition, multifocal atherosclerosis may act as an independent risk factor of early abdominal complications in patients older than 70 years[18].

Comparing the literature data with the results of our own research, we identified the most significant risk factors and used them to develop a prognostic score, which had a good diagnostic value (AUC = 0.805 ± 0.033, $P < 0.001$). This score allows us to stratify patients with the risk for early abdominal complications after CABG with CPB, which is important for timely treatment and diagnosis and, ultimately, will help to reduce postoperative mortality[20].

## CONCLUSION

In conclusion, the leading risk factors for early abdominal complications after CABG with CPB in our study were multifocal atherosclerosis, extracorporeal membrane oxygenation, intra-aortic balloon pump, atrial fibrillation, acute perioperative myocardial infarction, and the need for performing postoperative resternotomy. According to the developed score, patients with a score of 7 or more had the highest risk of abdominal complications. The score makes it possible to predict the risk of early abdominal complications after CABG with CPB and to stratify patients with the risk for their development, which is important for timely treatment and diagnosis and, ultimately, will help to reduce postoperative mortality.

## ARTICLE HIGHLIGHTS

### *Research background*

Abdominal complications in patients who underwent cardiac surgery are rare but the associated mortality varies from 11.0% to 74.0%, which makes the problem relevant. One reason for high mortality rates is late diagnosis. Certain difficulties in diagnosing these complications are associated with the peculiarities of postoperative management and unclear clinical picture due to sedation, analgesia, prolonged mechanical ventilation, and the use of extracorporeal membrane oxygenation. Determining the risk factors for abdominal complications and identifying high-risk groups is an urgent

task that may help diagnose abdominal complications and reduce related mortality.

### Research motivation

The topic of this study is the identification of leading risk factors for abdominal complications in patients after coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) and the development of a prediction score based on perioperative predictors to reveal patients at a high risk of abdominal complications.

### Research objectives

The objectives of this study were to identify risk factors for abdominal complications according to clinical, laboratory, and imaging findings, to determine their rank influence on the development of early abdominal complications after CABG with CPB, and to develop a risk prediction score. The risk score makes it possible to perform early screening and to develop an algorithm of therapeutic and diagnostic measures for the prevention, early diagnosis, and treatment of this pathology.

### Research methods

The factors taken for evaluation were compared between patients with early abdominal complications ($n$ = 73) and without them ($n$ = 6513), and the relative risks were calculated. Statistical data processing was performed using Statistica 10.0 (Statsoft, Tulsa, OK, United States) and SPSS 23.0 (IBM Corp., Armonk, NY, United States). In order to describe the risks, contingency tables were used to calculate the relative risk and the odds ratio. An integrated score for assessing the risk of early abdominal complications was created on the basis of the above-mentioned factors by using multivariate logistic regression analysis. The presence or absence of complications was a dependent variable, while the above-mentioned factors were independent variables. Then, the obtained risk score was evaluated by using a receiver operating characteristic curve analysis. The presence or absence of early abdominal complications was an outcome variable. The ordinate axis (sensitivity) corresponded to the true positive rate; the abscissa axis (1-specificity) corresponded to the false positive rate. It is generally supposed that the area under the receiver operating characteristic curve that is in the range of 0.9-1.0 should be considered as an indicator of the highest informativeness of the diagnostic method. The range of 0.8-0.9 is good, 0.7-0.8 is acceptable, 0.6-0.7 is weak, and 0.5-0.6 is extremely weak.

### Research results

The leading risk factors of the early abdominal complications after CABG with CPB were multifocal atherosclerosis, extracorporeal membrane oxygenation, intra-aortic balloon pump, atrial fibrillation, perioperative myocardial infarction, and need for resternotomy in the postoperative period. After calculating a score for each of the leading risk factors, we counted a total score for each particular patient. The highest risk was noted in patients with a total score of 7 or more. Further research may be devoted to a prospective assessment of the proposed scale for the prediction of the risk of abdominal complications and the development of an algorithm for the management of high-risk patients.

### Research conclusions

The developed score predicts the risk of early abdominal complications after CABG with CPB and makes it possible to stratify patients by risk groups. It is important for timely treatment and diagnosis and, ultimately, will help to reduce postoperative mortality in this group of patients.

### Research perspectives

Future studies should prospectively assess the effectiveness of the proposed method, as well as to create a protocol for the prevention, early diagnosis, and treatment of abdominal complications in high-risk patients.

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META-ANALYSIS

# Safety and efficacy of soluble guanylate cyclase stimulators in patients with heart failure: A systematic review and meta-analysis

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## Abstract

### *BACKGROUND*

The utility of novel oral soluble guanylate cyclase (sGC) stimulators (vericiguat and riociguat), in patients with reduced or preserved ejection fraction heart failure (HFrEF/HFpEF) is currently unclear.

### *AIM*

To determine the efficacy and safety of sGC stimulators in HF patients.

### *METHODS*

Multiple databases were searched to identify relevant randomized controlled trials (RCTs). Data on the safety and efficacy of sGC stimulators were compared using relative risk ratio (RR) on a random effect model.

### *RESULTS*

Six RCTs, comprising 5604 patients (2801 in sGC stimulator group and 2803 placebo group) were included. The primary endpoint (a composite of cardiovascular mortality and first HF-related hospitalization) was significantly reduced in patients receiving sGC stimulators compared to placebo [RR 0.92, 95% confidence interval (CI): 0.85-0.99, $P$ = 0.02]. The incidence of total HF-related hospitalizations were also lower in sGC group (RR 0.91, 95%CI: 0.86-0.96, $P$ = 0.0009), however, sGC stimulators had no impact on all-cause mortality (RR 0.96, 95%CI: 0.86-1.07, $P$ = 0.45) or cardiovascular mortality (RR 0.94, 95%CI: 0.83-1.06,

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*P*= 0.29). The overall safety endpoint (a composite of hypotension and syncope) was also similar between the two groups (RR 1.50, 95%CI: 0.93-2.42, *P* = 0.10). By contrast, a stratified subgroup analysis adjusted by type of sGC stimulator and HF (vericiguat *vs* riociguat and HFrEF *vs* HFpEF) showed near identical rates for all safety and efficacy endpoints between the two groups at a mean follow-up of 19 wk. For the primary composite endpoint, the number needed to treat was 35, the number needed to harm was 44.

*CONCLUSION*
The use of vericiguat and riociguat in conjunction with standard HF therapy, shows no benefit in terms of decreasing HF-related hospitalizations or mortality.

**Key Words:** Vericiguat; Riociguat; Soluble guanylate cyclase; Heart failure; Guanylate cyclase stimulator



**Core Tip:** Recently soluble guanylate cyclase (sGC) stimulators (vericiguat and riociguat) have emerged as a novel treatment for heart failure with reduced or preserved ejection fraction. Data published in literature revealed no additional benefits to guideline-based medical therapy in reducing incidence of heart failure hospitalization and mortality with sGC stimulator use. Large scale studies are required to determine the efficacy of sGC stimulators in patients with heart failure.

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## INTRODUCTION

There are an estimated 6.5 million adults in the United States suffering from heart failure (HF) with the disease accounting for nearly 1 in every 8 deaths[1] Approximately 1 million[2,3] HF-related hospitalizations (HHF) occur annually, accounting[4] for over 6.5 million hospital days and $37.2 billion in costs every year[1]. This economic burden has risen dramatically over the past two decades, with the increasing prevalence of risk factors for HF adding to new cases and better therapies adding to increased life expectancy among HF patients[1].

Despite traditional pharmacologic management with beta-blockers, angiotensin-converting-enzyme inhibitors (ACEI) and mineralocorticoid receptor antagonists to reduce HF exacerbations and mitigate clinical progression, overall prognosis remains dismal[2]. This has led researchers to target alternative pathways involved in the pathogenesis of HF, with promising research focusing on soluble guanylate cyclase (sGC) and the natriuretic peptide system (NPS)[3,4].

Both pathways influence myocardial perfusion and ventricular function through their common second messenger: Cyclic guanosine monophosphate (cGMP). The therapeutic augmentation of NPS with a combination angiotensin receptor–neprilysin inhibitor (sacubitril) has proven to be immensely beneficial, to the extent that the pioneering PARADIGM trial was halted early given the clear benefits in terms reducing mortality [risk ratio (RR) 0.84, 95% confidence interval (CI): 0.76-0.93, *P* < 0.001] and hospitalization (by 21%, *P* < 0.001) compared to ACEI alone[5]. However, the use of conventional vasodilators (nitrites and nitrates) to achieve soluble GC activation has met with more mixed results, with the development of tolerance, hypotension and failure of treatment being reported[6]. These discouraging findings have been attributed to a relative deficiency of sGC due to reduced nitric oxide (NO) bioavailability and endothelial dysfunction in HF leading to impaired cyclic GMP generation[7].

Novel sGC stimulators (vericiguat and riociguat) have shown advances over traditional vasodilators[6], by augmenting the cGMP signaling pathway, independent

of NO and enhancing the effect of endogenous NO[2,8]. In contrast to the conventional therapeutic approach of antagonizing counterregulatory neurohormonal pathways, such as by phosphodiesterase inhibitors, or by addition of exogenous NO, sGC stimulators sensitize soluble GC to endogenous NO, thereby potentially having more efficacy for HF treatment[9].

In this regard, multiple clinical trials have attempted to explore the utility of vericiguat and riociguat in patients with HF[2,8]. The VICTORIA (vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial recently established that vericiguat in patients with HFrEF can reduce the risk of cardiovascular mortality and HF-related hospitalizations[2]. These findings, however, stand in contrast to previous trials that have not shown any consistent benefit with sGC stimulators. The ambiguity of current literature and the absence of any definite large-scale studies to determine the true merits of sGC stimulators in patients with HF, motivated us to perform this meta-analysis.

## MATERIALS AND METHODS

### Search strategy and data extraction

The MEDLINE (PubMed, Ovid), Embase, Clinicaltrials.org and Cochrane databases were queried with various combinations of medical subject headings (MeSH) to identify relevant articles. There were no language or time restrictions placed. Backward snowballing was performed to retrieve unidentified studies that were missed on the initial search. The MeSH used included two subsets: One for HF using the terms like "heart failure," "HFrEF," "HFpEF," "CHF," "cardiac failure," and the other for sGC using "guanylate cyclase stimulators," "sGC," "vericiguat," and "riociguat." The two subsets of MeSH were combined in a 1:1 combination using Boolean operators. Results from all possible combinations were downloaded into an EndNote library. All randomized control trials (RCT) until March 31, 2020, comparing the safety and efficacy of sGC in HF were evaluated for inclusion.

Patients with HFrEF and HFpEF [New York Heart Association (NYHA) class II-IV], on optimal guideline-based medical therapy requiring hospitalization or outpatient intravenous (IV) diuretics, were included in this study. Patients requiring IV inotropic support, in acute decompensated HF or requiring mechanical device support were excluded, so were patients using suboptimal doses of vericiguat (< 10 mg daily) or riociguat (< 2 mg daily), nitrates, alternative sGC stimulators or PDE inhibitors.

The primary efficacy endpoint was a composite of the first hospitalization for HF and death from cardiovascular causes. The secondary efficacy endpoints were the components of the primary outcome, total HF-related hospitalizations, cardiovascular and all-cause mortality. Safety endpoints included anemia, hypotension, syncope, and a composite of the later two. A detailed search map and definition of outcomes are given in the Supplementary Appendix.

### Data and quality analysis

The statistical analysis was performed using the Cochran–Mantel–Haenszel test on a random-effect model to calculate RR for the dichotomous outcomes of RCTs. The probability value of $P < 0.05$ was considered statistically significant. The "test for overall effect" was reported as the z value corroborating the inference from the 95%CI. Subgroup analysis based on the choice of sGC stimulator and type of HF was also performed. Higgins I-squared ($I^2$) statistical model was used to assess variations in outcomes of the included studies. $I^2$ less than 40% corresponded to low heterogeneity. Depending upon the strength of evidence for heterogeneity ($P$ value from the chi-square $\chi^2$ analysis), $I^2$ of 41 to 74% indicated moderate ($P \geq 0.05$) or moderate to severe ( $P \leq 0.05$) and $I^2$ of 75% or higher suggested substantial heterogeneity. Publication bias was illustrated graphically using a funnel plot. The methodological quality assessment of the included RCTs was performed using the Cochrane collaboration tool for the systematic review and meta-analysis, where each study was screened for five different types of bias (selection, performance, detection, attrition, and reporting bias). All statistical analysis was performed using the Cochrane Review Manager (RevMan) version 5.3.

### Quality of the included studies

The overall quality of the included RCTs was high (Figure 1). Due to adequate randomization and allocation concealment, the risk of selection bias was low. The risk of performance and detection bias were reduced with appropriate blinding of

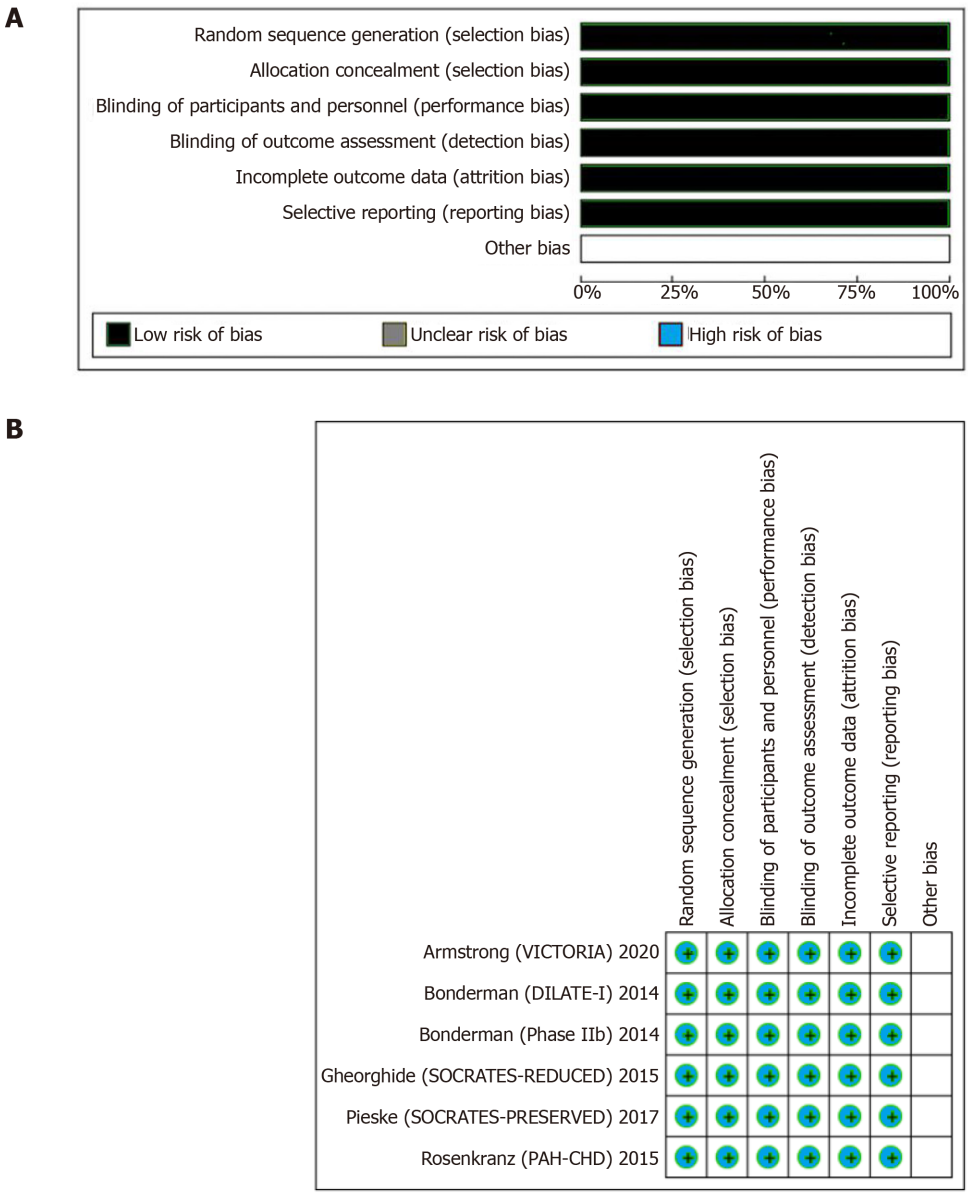


**Figure 1 Summary and detailed methodological quality of the included studies.** A: Summary of the included studies; B: Detailed methodological quality of the included studies.

participants and outcomes, respectively. Similarly, reporting bias across all studies was decreased due to an adequate description of the study results. The fact that most RCTs used an "intention to treat model" or had a minimal loss at follow-up, the risk of attrition bias was low.

## RESULTS

### *Search results and study characteristics*

The initial search revealed 1905 articles. After the removal of irrelevant and duplicate items, 43 studies were selected for full-text review. Of these, 37 articles were excluded based on our selection criteria, 6 articles (all RCTs) qualified for quantitative analysis[2,8,10-13]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is shown in Figure 2.

A total of 5604 patients, 2801 in the sGC stimulator group, and 2803 in the placebo group were included. The mean age of patients receiving sGC stimulator was 64 and for the placebo group 62 years; comprising 59% and 57% male patients, respectively. Three of the included trials used vericiguat (1.25, 2.5, 5, or 10 mg), and three RCTs used riociguat (0.5, 1, or 2 mg) in the experimental arm. Baseline characteristics of

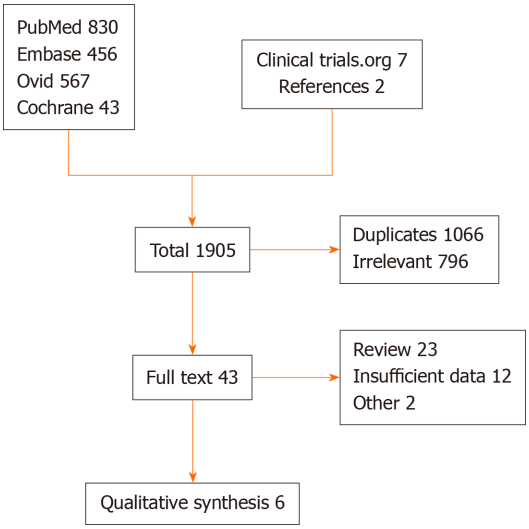


**Figure 2 Flow diagram of the included studies showing reasons for exclusion.**

treatment and placebo groups were comparable. Use of the concomitant guideline-directed HF medical therapy was also balanced between the two groups. The VICTORIA and the (soluble guanylate cyclase stimulator in heart failure patients with preserved and reduced EF) SOCRATES trials used vericiguat in HFrEF patients. These patients had a mean EF of 29% and NYHA class III-IV. The median baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were 2816 pg/mL and 3076 pg/mL, respectively. The SOCRATES-PRESERVED trial used the Kansas City cardiomyopathy questionnaire-clinical summary score to gauge symptomatic improvement in the HFpEF population. The DILATE-1 (acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure) investigated riociguat in the HFpEF population. The PAH-CHD (pulmonary arterial hypertension after correction of congenital heart disease) trial included younger patients with a mean 38 ± 15 years. The PAH-CHD and the LEPHT (left ventricular systolic dysfunction associated with pulmonary hypertension) had 100% and 97% of HF patients with NYHA II-III, respectively. The overall follow-up duration ranged from 12-43 wk, with a mean follow up of 19 wk. The detailed baseline characteristics, inclusion criteria, and definitions of outcomes are given in Supplementary Tables 1-3, respectively.

### *Pooled analysis of overall studies*

**Pooled efficacy endpoints:** Four studies comprising 5530 patients (2752 sGC stimulator and 2778 placebo) compared the primary composite endpoint (cardiovascular mortality plus first-time hospitalization) between the sGC stimulators and the control group. At a mean follow-up of 21-wk, a significantly lower rate of the primary endpoint was obtained with the use of sGC stimulator in HF patients (RR 0.92, 95%CI: 0.85-0.99, $P$ = 0.02) (Figure 3A). Similarly, compared to placebo, the rate of total HF-related hospitalizations was significantly lower (RR 0.91, 95%CI: 0.86-0.96, $P$ = 0.000.9) in patients on sGC stimulators. However, the incidence of cardiovascular and all-cause mortality remained identical in both groups at a mean follow up of 19-mo (RR 0.94, 95%CI: 0.83-1.06, $P$ = 0.29 and RR 0.96, 95%CI: 0.86-1.07, $P$ = 0.45, respectively) (Figure 3B). Six studies consisting of 5604 patients (2801 sGC stimulator and 2803 placebo) contributed to the later comparison (Figure 4). There was no heterogeneity among the outcomes of the included studies ($I^2$ = 0%).

**Pooled safety endpoints:** Six studies comprising 5596 patients (2793 sGC stimulator and 2803 placebo) were used to calculate the incidence of net adverse events of clinical interest (NAECI) (a composite of hypotension and syncope). The rate of NAECI was 1.5 times higher but statistically non-significant in patients receiving sGC stimulators compared to placebo (RR 1.50, 95%CI: 0.93-2.41, $P$ = 0.10) (Figure 3B). The incidence of hypotension (RR 1.47, 95%CI: 0.93-2.33, $P$ = 0.10) and syncope (RR 1.18, 95 CI: 0.90-1.55, $P$ = 0.24) were also numerically higher with the use of sGC stimulator use by 47% and 18% respectively; however, none of these differences reach the level of statistical significance. The incidence of anemia was significantly higher in sGC group (RR 1.33, 95%CI: 1.08-1.64, $P$ = 0.007). There was minimal heterogeneity among the studies

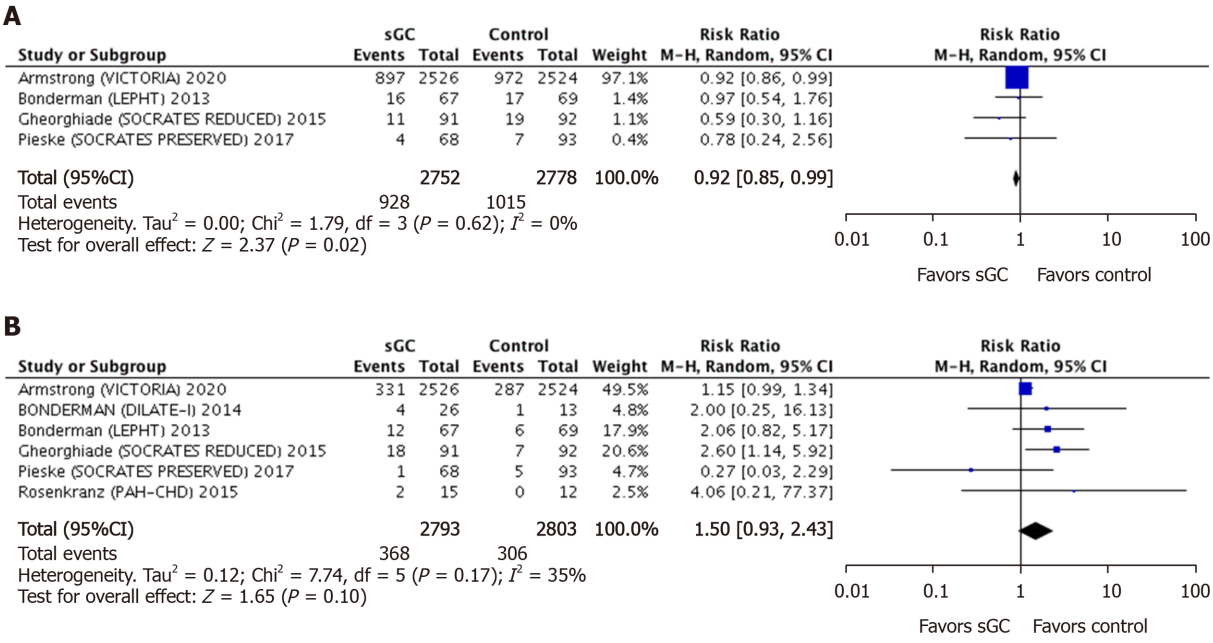


**Figure 3 Forest plot for the primary composite endpoint overall side-effects showing an individual and pooled risk ratio for randomized controlled trials comparing soluble guanylate cyclase stimulators to control.** A: Pooled composite endpoint; B: Overall side-effects. The pooled risk ratio (RR) with 95% confidence interval (CI) were calculated using random-effects models. Weight refers to the contribution of each study to the overall pooled estimate of treatment effect. Each square and horizontal line denotes the point estimate and 95%CI for each trial's RR, respectively. The diamonds signify the pooled RR; the diamond's centre denotes the point estimate and width denotes the 95%CI. CI: Confidence interval; sGC: Soluble guanylate cyclase.

comparing NAECI and hypotension ($I^2$ = 35% and $I^2$ = 20%, respectively) .

**Net clinical benefit:** The overall number needed to treat (NNT) for the primary composite endpoint by adding vericiguat to the standard guideline-directed HF therapy was 35 (95%CI: 18.7-332.2). The overall number needed to harm (NNH) for NAECI was 44 (95%CI: 25.2-180). The net clinical benefit (NCB) was 9, indicating futility. The overall NNT to prevent one death due to any-cause was 142 (95%CI: 36.3-74.2) and to prevent one death from cardiovascular cause was 111 (95%CI: 35.3-96.7). None of the NNT values was statistically significant, as evidenced by the cross-over of its CI with the NNH.

### *Subgroup sensitivity analysis*

A stratified analysis of prespecified subgroups adjusted on the type of HF (HFrEF and HFpEF) and choice of experimental regimen (vericiguat and riociguat) showed significant deviation from the pooled results. Two studies comprising 5233 patients (2616 sGC stimulator and 2617 placebo) contributed to the comparison of vericiguat and placebo agents in HFrEF patients. In contrast to the pooled results, there was no significant difference in the incidence of primary composite endpoint between patients receiving vericiguat and placebo for HFrEF (RR 0.84, 95%CI: 0.58-1.21, $P$ = 0.24). Similarly, the rate of primary composite endpoint remained identical across patients on placebo and those receiving riociguat for HFrEF (RR 0.97, 95%CI: 0.54-1.76, $P$ = 0.92) or HFpEF (RR 0.78, 95%CI: 0.24-2.56, $P$ = 0.68) (Supplementary Figure 1). Compared to placebo, there was no significant difference in the rate of total HF-related hospitalizations across HFrEF patients receiving vericiguat (RR 0.84, 95%CI: 0.60-1.20, $P$ = 0.34) or riociguat (RR 0.97, 95%CI: 0.54-1.76, $P$ = 0.92) and HFpEF patients on riociguat (RR 0.68, 95%CI: 0.18-2.64, $P$ = 0.58) (Supplementary Figure 2).

The incidence of all-cause mortality stratified by the type of sGC stimulators or type of HF mirrored the overall results. A similar rate of mortality was obtained between patients on placebo *vs* those on vericiguat (RR 0.96, 95%CI: 0.86-1.07, $P$ = 0.43) or riociguat (RR 1.97, 95%CI: 0.32-12.16, $P$ = 0.46) (Supplementary Figure 3). Both HFrEF (5369 patients, 2648 sGC stimulator and 2685 placebo) and HFpEF (200 patients, 94 sGC stimulator and 106 placebo group) followed the pooled results of all-cause mortality, showing a similar incidence of mortality between the two groups (RR 0.96, 95%CI: 0.86-1.07, $P$ = 0.44 and RR 1.45, 95%CI: 018-11.54, $P$ = 0.73, respectively) ( Supplementary Figure 4). Sensitivity analysis by the exclusion of PAH-CHD study also

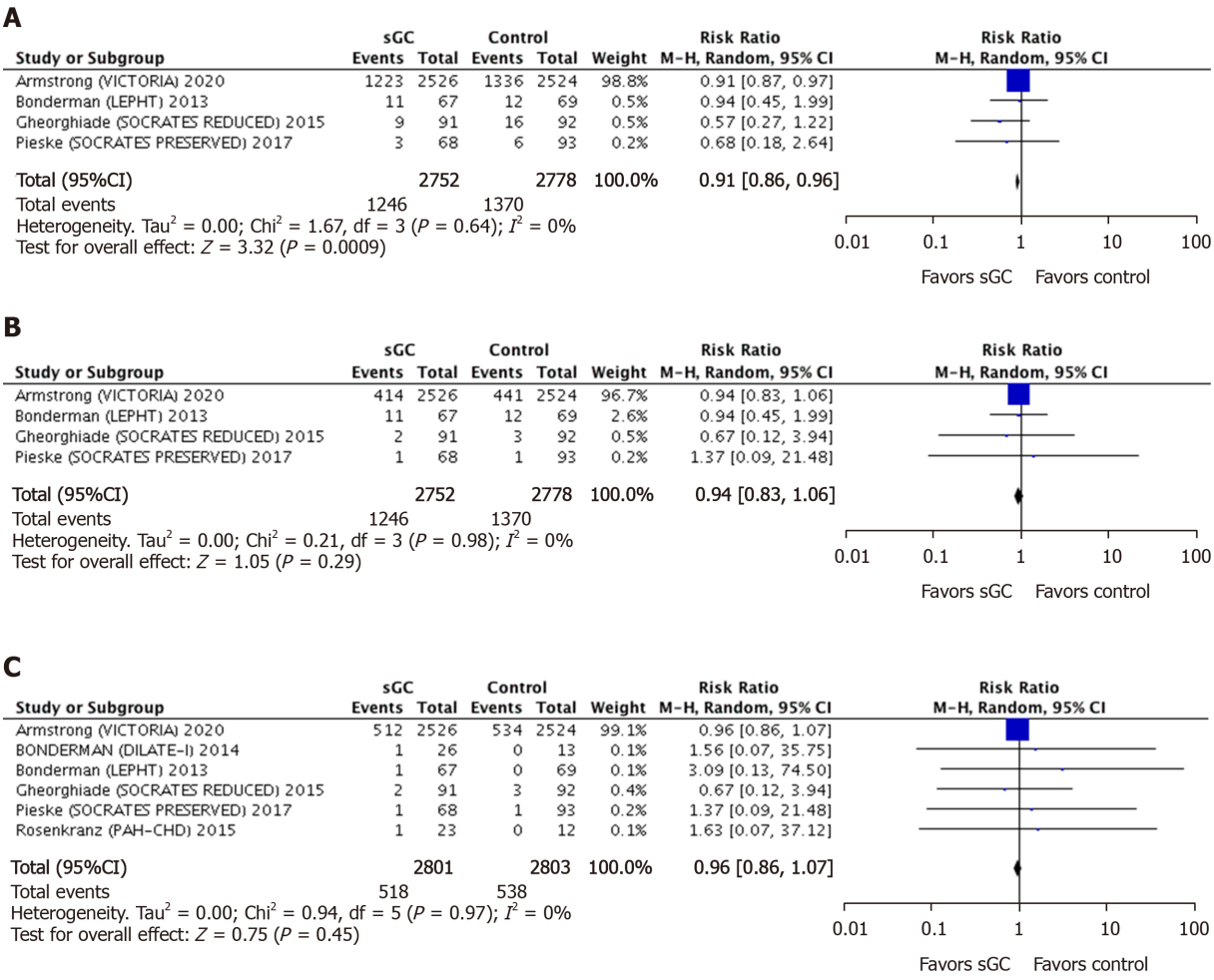


**Figure 4 Forest plot for hospitalizations, cardiovascular and all-cause mortality showing an individual and pooled risk ratio for randomized controlled trials comparing soluble guanylate cyclase stimulators to control.** A: Hospitalizations; B: Cardiovascular; C: All-cause mortality. CI: Confidence interval; sGC: Soluble guanylate cyclase.

did not alter the results of pooled analysis (RR 0.96, 95%CI: 0.86-1.07, $P$ = 0.45) ( Supplementary Figure 5).

### *Publication bias*

The funnel plot showed asymmetry, indicating the possibility of publication bias. (Figure 5) The vertical axis of the plot used standard error to estimate the sample size of the study, plotting large population studies on top and smaller at the bottom. The horizontal spread reflected the power and effect size of the included studies. One can argue that it is difficult to differentiate between "findings by chance" and "real asymmetry," as only six articles were assessed for potential publication bias. As pointed by Sterne *et al*[14]. in a study of fewer than ten articles, it is difficult to ascertain publication bias.

## DISCUSSION

To our knowledge, this is the largest study performed to assess the safety and efficacy of novel sGC stimulators (vericiguat and riociguat) in patients with HF. The results were drawn from 6 RCTs, comprising 5604 patients. In the combined analysis, among patients with high-risk HF (NYHA class II-IV), the addition of sGC stimulators to current guideline-based medical therapy showed a modest decrease in risk of the primary composite endpoint (first HF hospitalization plus cardiovascular death) by 8%. With a similar decrease in HF-related total hospitalization by 9%. However, these benefits were attenuated when the pooled results were matched based on the type of HF and choice of sGC stimulator. Neither vericiguat nor riociguat groups reached the threshold of statistical significance when the efficacy endpoints (hospitalization and

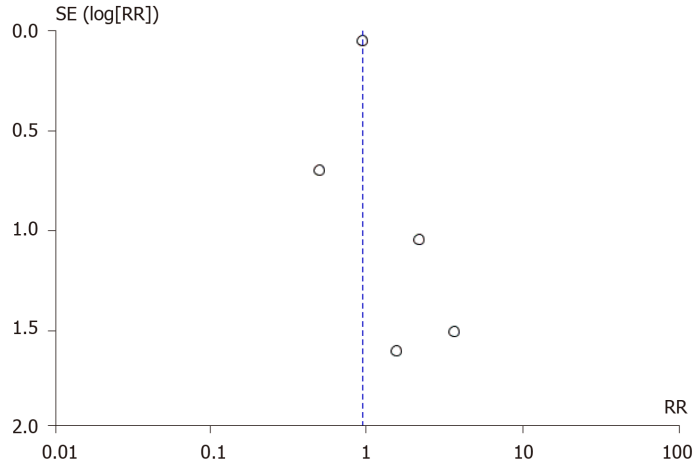


**Figure 5 Funnel plot showing possible publication bias.** RR: Risk ratio.

death) were stratified by HFrEF and HFpEF. Similarly, compared to the control group, both vericiguat and riociguat failed to lower the incidence of cardiovascular or all-cause mortality, irrespective of the type of HF or duration of follow-up. Moreover, the incidence of NAECI and its components (hypotension and syncope) in the intervention group were 1.5 times higher than the placebo group. Briefly, our analysis did not show the same positive findings seen in the recent VICTORIA trial and highlight the ambiguity in the use of sGC stimulators, until more definitive evidence is available ( Supplementary Figure 6).

It is interesting to compare our combined results with all included RCTs. The SOCRATES-PRESERVED and the SOCRATES-REDUCED trials used vericiguat in patients with HFpEF and HFrEF, respectively[10,11]. These trials were primarily designed to determine the optimal dose and tolerability of vericiguat. While on pooled analysis, the relative difference in the NT-proBNP levels was identical, the SOCRATES-REDUCED did show a significant dose-response relationship. Compared to placebo, a higher vericiguat dose of 10 mg was associated with greater reductions in NT-proBNP ($P$ = 0.02) and significant improvement in LVEF (+1.5% *vs* +3.7%, $P$ = 0.02) at 3 mo follow-up[11]. Similarly, the SOCRATES-PRESERVED trial showed a substantial improvement in the functional and symptomatic status of the HFpEF patients (increase in KCCQ-CSS by more than 5 points) on the 10 mg dose of vericiguat at 3 mo[10]. Both SOCRATES-PRESERVED and REDUCED trials used surrogate markers of disease severity and were relatively underpowered to gauge hard clinical outcomes (mortality and hospitalizations).

Three of the included RCTs compared the merits of riociguat against a placebo in both HFrEF and HFpEF patients. The PATENT-1 (the pulmonary arterial hypertension sGC-stimulator trial-1) and its long-term extension study PATENT-2 were unique in terms of inclusion criteria and assessment of outcomes. Riociguat was found to be associated with a decrease in the mean NT-proBNP levels, improved 6-minute walking distance (6MWD) and pulmonary vascular resistance (PVR) in patients with PAH-CHD[12]. Both LEPHT and DILATE-1 trials demonstrated a significant increase in the stroke volume ($P$ = 0.001 and $P$ = 0.04) in their respective HFrEF and HFpEF patient populations. However, there was no significant decrease in the mean pulmonary arterial pressure (PAP), the primary endpoint, even at the maximally tolerated dose of riociguat (2 mg)[8,13]. These trials were also underpowered to assess major clinical endpoints and had variability in dose-response outcomes, limiting their utility.

The more contemporary VICTORIA trial was adequately powered and specifically designed to measure clinically relevant outcomes[2]. The trial used a cox-regression-model to calculate a sample size of 5050 patients, who were hospitalized with the diagnosis of HFrEF. Both vericiguat and placebo groups in the trial were appropriately matched, minimizing ascertainment bias, but had a high rate of noncompliance and loss to follow-up. At a median follow-up of 10 mo, 24% of the vericiguat and 22% of the placebo arm had discontinued the trial regimen. While this amount of nonadherence was anticipated and an "intention to treat model" was used to reduce its impact on the overall results, the pooled difference in the primary composite endpoint was modest (RR 0.90, 95%CI: 0.82-0.98, $P$ = 0.02). The incidence of cardiovascular mortality was near identical in the vericiguat and placebo groups (12.9% *vs* 13.9%, $P$ = 0.83), indicating that the primary outcome was driven by the

lower rate of HF-related hospitalization in the vericiguat group (38.3% *vs* 42.4%, $P$ = 0.02)[2]. By contrast, our pooled analysis of vericiguat in HFrEF population showed no inter-group difference in both the incidence of the primary composite ($P$ = 0.34), cardiovascular mortality ($P$ = 0.29), and total HF-related hospitalizations ($P$ = 0.34). Nonetheless, mirroring our pooled results, the VICTORIA trial showed no significant difference in the incidence of all-cause mortality between vericiguat and the placebo groups (20.3% *vs* 21.2%, $P$ = 0.38). This underscores that the lower hospitalization rate in the vericiguat arm did not translate into clinical survival benefits. Together, these findings call for caution while interpreting the findings of the VICTORIA trial.

The present meta-analysis sought to address the overall discrepancies by systematically adjusting the definition of primary composite outcome and by excluding patients on the suboptimal dose of sGC stimulators. By design, our study prevents the influence of both known and unknown confounding factors due to the inclusion of high-quality studies. Our study showed no clinical benefits of sGC stimulator in terms of reducing mortality or HF-related hospitalization when the overall outcomes were stratified by type of HF and regimen of trial medication. These findings contrast with the most contemporary VICTORIA trial, which showed a decrease in the incidence of HF-related total hospitalizations and death from cardiovascular causes. Also unique was a demonstration of the consistent ineffectiveness of vericiguat and riociguat to reduce all-cause mortality across all included trials. Moreover, the calculation of the net clinical benefit may serve to inform clinical decision making, suggesting that sGC stimulators offer no benefits and could potentially be harmful.

### *Limitations*

Our study is constrained by the limitations of the included studies. Patient-level data were missing to measure the impact of non-compliance on overall clinical outcomes. Long term follow-up data was lacking in more than half of the included studies, limiting our ability to calculate their predictive effects. Some studies focused on non-clinical primary outcomes (pro-BNP, PAP) neglecting a significant amount of clinical complications such as myocardial infarction and mortality, reducing the precision of estimated complications. Due to the paucity of long-term follow-up data, it is unclear if these results could be extrapolated to patients with HFpEF. The ongoing DYNAMIC study might shed more light on the efficacy of sGC in patients with HFpEF[15].

It can also be argued that the assessment of the efficacy and safety of the sGC stimulators is a bivariate exercise, and summarizing it in a unidimensional variable (net clinical benefit) could be misleading. For example, a large number of relatively minor episodes of hypotension versus a small improvement in HF-related hospitalization rate may lead to a negative calculated Net Clinical Benefit (NCB). Still, given the vast disparity between the impact on the quality of life between an episode of hypotension versus HF-related hospitalization, it may falsely undervalue the benefit of therapy. Therefore, the NCB value should preferably be interpreted in the context of the nature of both adverse and beneficial events, without committing to value judgment. That being said, in our case, we found no significant beneficial effect of sGC stimulators and a higher incidence of adverse effects rendering this a moot point.

## CONCLUSION

Vericiguat and riociguat offer no additional benefits to current guideline-based medical therapy in terms of reducing the incidence of hospitalization or mortality in patients with HFpEF or HFrEF. Further larger-scale studies are needed to validate these findings.

## ARTICLE HIGHLIGHTS

### *Research background*

Despite treatment with traditional pharmacologic management, patients with heart failure (HF) have a dismal prognosis, with approximately 1 million HF-related hospitalizations (HHF) occurring annually, accounting for over 6.5 million hospital days and $37.2 billion each year.

### Research motivation

This has led researchers to study the efficacy of alternate drugs in preventing HF exacerbations, which include soluble guanylate cyclase (sGC) stimulators vericiguat and riociguat. Multiple clinical trials have attempted to explore the utility of vericiguat and riociguat in patients with HF. However, there a lack of large scale studies to determine the true merits of sGC stimulators in patients with HF.

### Research objectives

Therefore, we performed this meta-analysis to determine the efficacy and safety of sGC stimulators in HF patients.

### Research methods

The MEDLINE (PubMed, Ovid), Embase, Clinicaltrials.org and Cochrane databases were queried with various combinations of medical subject headings (MeSH) to identify relevant articles. All randomized control trials (RCT) until March 31, 2020, comparing the safety and efficacy of sGC in HF were evaluated for inclusion. The primary efficacy endpoint was a composite of the first hospitalization for HF and death from cardiovascular causes. The secondary efficacy endpoints were the components of the primary outcome, total HF-related hospitalizations, cardiovascular and all-cause mortality. The statistical analysis was performed using the Cochran–Mantel–Haenszel test on a random-effect model to calculate relative risk (RR) for the dichotomous outcomes of RCTs. The overall quality of the included RCTs was high.

### Research results

Six RCTs comprising 5604 patients (2801 sGC stimulator and 2803 placebo) were included. The primary endpoint (a composite of cardiovascular mortality and first HF-related hospitalization) was reduced in patients receiving sGC stimulators compared to placebo [RR 0.92, 95% confidence interval (CI): 0.85-0.99, $P$ = 0.02]. The incidence of total HF-related hospitalizations were also lower in sGC group (RR 0.91, 95%CI: 0.86-0.96, $P$ = 0.0009), however, sGC stimulators had no impact on all-cause and cardiovascular mortality (RR 0.96, 95%CI: 0.86-1.07, $P$ = 0.45) and (RR 0.94, 95%CI: 0.83-1.06, $P$ = 0.29), respectively. The overall safety endpoints (composite of hypotension and syncope) were also identical between the two groups (RR 1.50, 95%CI: 0.93-2.42, $P$ = 0.10). For the primary composite endpoint, the number needed to treat was 35, the number needed to harm was -44 and the overall net clinical benefit was -9.

### Research conclusions

Data published in literature revealed no additional benefits to guideline-based medical therapy in reducing incidence of HF hospitalization and mortality with sGC stimulator use. Large scale studies are required to determine the efficacy of sGC stimulators in patients with HF.

### Research perspectives

As it is unclear whether sGC stimulators have any additional benefit in improving the prognosis of HF patients due to a lack of substantial research, large scale studies are needed to determine their efficacy in reducing HF related hospitalization rates.

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