



# LIFESTYLE IN PREVENTION OF CARDIOVASCULAR DISEASE: WHAT IS THE ROLE OF NITRATE?

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## Abstract

## Review

**Background:** Cardiovascular disease (CVD) remains a common cause of death in the Netherlands. Risk factors for CVD include smoking, obesity, hypertension, high cholesterol and physical inactivity. Currently, prevention and treatment of CVD is based on changing lifestyle and/or the use of medication.

**Objective:** In this review we will first identify the current practice regarding prevention and treatment of CVD and after that it will further elaborate on the influence of diet on the blood pressure (BP).

**Results:** Two components are identified in the current approach for the prevention of CVD in the Netherlands: medicated and non-medicated interventions. Both reduce the risk of developing CVD in both people with or without previous CVD. However, medicated interventions can have their side effects. Lately, several studies have explored the effect of dietary nitrate supplementation on the BP. Results from these studies suggest that dietary nitrate intake can lower both systolic and diastolic BP in hypertensive and normotensive subjects. This tension-lowering effect of nitrate is found to be due to its conversion to nitric oxide (NO) via the nitrate-nitrite-NO pathway.

**Conclusion:** Lifestyle interventions may be a good alternative to medication and even a conceivable way to prevent CVD disease progression. Although only the short-term effects are studied, dietary nitrate could be considered as a promising new lifestyle intervention targeting hypertension, thereby lowering the risk of several diseases, such as CVD.

**KEYWORDS:** Non-medical, treatment, diet, nitric oxide

## Introduction

Almost 25% of total deaths in 2017 is caused by cardiovascular disease (CVD) in the Netherlands [1]. Additionally, 12% of healthcare costs were spent on CVD in the Netherlands in 2015 [2]. Thus, CVD is a threat to the health of many people. Therefore, multiple studies investigated why the incidence of CVD is so high and how this can be prevented or treated. A significant portion of these studies focused on the influence of lifestyle on CVD development and risk. According to the Dutch General Practitioners Society (NHG), there are a few risk factors for developing atherosclerotic plaques, known to be smoking, obesity, hypertension, high cholesterol and physical inactivity [3]. In 2015, diabetes and male gender were listed as additional risk factors [4]. Apart from diabetes and male gender, which are fixed factors, all the other risk factors can be altered. Within this review we will describe the traditional approach to treating and preventing CVD. After that, the focus will be on the influence of the diet on blood pressure (BP), an important risk factor for CVD.

## Current treatment and prevention of CVD

In the Netherlands, the prevention of CVD includes two main components. The first main component of CVD prevention is medication. The NHG guideline focuses on two factors, being lipids and BP [3]. For lipids, LDL-cholesterol (LDL-C) is the most important risk factor. According to the guideline, the target value for LDL-C should be less than 2.6 mmol/l for people with a high risk of CVD and the target value is even lower (less than 1.8 mmol/l) for people who have already undergone CVD and need to prevent another cardiovascular event [3]. In the United States of America, the same values are included in the Adult Treatment Panel III of the National Cholesterol Education Program [5]. However, a meta-analysis from 2010 suggests that further lowering of LDL-C would yield additional benefits, without an increased risk on side effects [6]. Statins are the most used

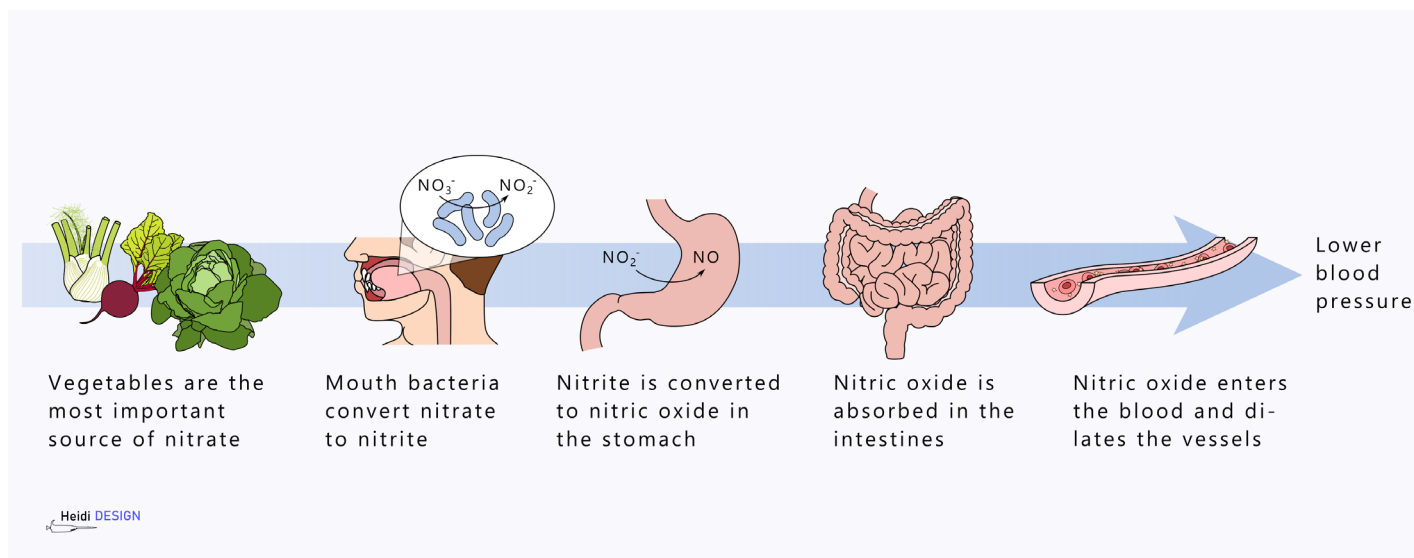
and most extensively studied cholesterol-lowering drug. A large meta-analysis from April 2019 concluded that statins are effective in preventing cardiovascular events in primary prevention, with atorvastatin being the most effective and safest [7].

The second important component in CVD prevention are non-medicated interventions, which are pieces of advice for the patients to improve their lifestyle in order to minimise the risk of CVD. Reduction of stress, depression and anxiety disorders; 150 minutes of moderate intensity exercise per week; quitting smoking; getting or keeping a healthy weight and eating healthy are listed in the NHG guideline as interventions to improve the risk factors [3].

## Hypertension as risk factor for CVD

The development of CVD is a complex interplay of interconnected factors. Hypertension is one of the risk factors for CVD, but most of the other risk factors are at the same time also risk factors for hypertension. Lowering the BP can be done in multiple ways. Consistent with the 2016 European Guidelines on cardiovascular disease prevention in clinical practice, the lifestyle changes that are mentioned, are recommended for patients with an increased risk of CVD [8]. When the risk of CVD is high, hypertension should be treated according to the Dutch guideline [3]. Currently, the target value should be set at a systolic blood pressure (SBP) lower than 140 mmHg [3]. Diuretics,  $\beta$ -blockers, calcium antagonists, ACE-inhibitors and angiotensin receptor blockers are all effective BP-lowering drugs and can be combined if one drug on its own does not yield the desired drop in BP [9]. This also prevents dose-related side effects.

Besides medication, hypertension can also be tackled by changing lifestyle factors. According to a study by El-Atat *et al.*, obesity control might eradicate 48% of hypertension in the Caucasian population [10]. Huang *et al.* also showed a 26% decrease in the incidence of hypertension associated



**Figure 1: The path nitrate takes in the body and the effect it has on the blood pressure.**

with long-term weight loss of 10 kg or more [11]. Accordingly, Becque *et al.* showed that 80% of obese adolescents indeed had an elevated BP [12]. Moreover, a meta-analysis from 2013 found that reducing salt intake to 4.4 grams per day leads to a significant drop in BP [13]. In the Netherlands, the recommended daily salt intake is currently set at a maximum of 6 grams per day [3]. Although this is beneficial to the BP, it is not ideal. According to Samadian *et al.*, it would be even better for the risk of hypertension to lower it even more to a maximum of 4 grams per day like in the United States of America [14].

## The diet: a promising new way to influence the BP

The Seven Countries study was the first to show that the risk of CVD could be altered by diet. This study identified an association between a low incidence of CVD and the Mediterranean Diet, a diet low in dairy products and meat and rich in fruit [15, 16]. Additionally, the Dietary Approaches to Stop Hypertension diet, a diet focusing on vegetables, fruits, lean meats and whole grains, also showed beneficial effects on BP [17, 18]. Later on, the protective effects of both diets on cardiovascular parameters were found to be partially due to the high nitrate and nitrite content [19-21]. More precisely, recent research has suggested that vegetables with a high nitrate content are the most protective against CVD [20-25]. Prominent dietary sources of nitrate are water and vegetables, with vegetables being the main source of dietary nitrate in humans, contributing up to 80% of the total nitrate intake [26]. Rocket, spinach and beetroot are examples of vegetables that are rich in nitrate (more than 2,500 mg/kg), whereas for example mushrooms and onions have a very low nitrate content (less than 200 mg/kg) [27, 28].

Lately, dietary nitrate as a promising new nutrient has gained rising interest. Numerous studies have already explored the effect of dietary nitrate supplementation on BP. In these studies, BP was found to be reduced after nitrate supplementation both acutely (ranging from 1 to 24 hours), as well as short term (ranging from 3 to 21 days) [29-43]. A review of Siervo *et al.* found that nitrate supplementation lowered systolic and diastolic BP up to 4.4 mmHg and 1.1 mmHg, respectively [21]. These BP lowering effects have been observed in both hypertensive and normotensive individuals [36, 44]. Moreover, an inverse relationship between nitrate dosage and SBP reduction was observed [45]. The finding that only a higher dosage

significantly reduced SBP suggests that a minimum amount of nitrate is needed to lower SBP [31]. For example, Hobbs *et al.* demonstrated that acute beetroot juice supplementation of 140, 350 and 700 mg provoked dose-dependent SBP reductions, with the latter two concentrations causing a significant decrease [36]. Likewise, Wylie *et al.* provided evidence that the similar type of supplementation caused a significant reduction in SBP when supplementing with 260 mg and a significant reduction in SBP and diastolic BP when supplementing with 520 mg of nitrate [46]. Moreover, Liu *et al.* investigated the acute effects of a meal rich in spinach containing 220 mg of nitrate and found a significant reduction in SBP [29]. Thus, these studies demonstrate that effects on the BP appear to occur after both nitrate supplementation and dietary nitrate consumption and that these decreases in BP are dose-dependent. Although most studies found only reductions in SBP and some did not even find a significant reduction in SBP and diastolic BP, there are plenty of studies that suggest that dietary nitrate has the potential to lower the BP [29, 30, 42, 47, 48]. However, currently there is a lack of studies investigating the long term effects (more than 4 weeks) of dietary nitrate on the BP, as only acute and short term effects on BP have been established [49, 50].

Once nitrate is in the body, it is converted to nitric oxide (NO) via the nitrate-nitrite-NO pathway (Figure 1). Nitrate from the diet concentrates in the salivary glands after which oral commensal bacteria reduce it to nitrite. Subsequently, nitrite in the saliva is further reduced to NO through enzyme activity [20, 26, 51]. NO mediates smooth muscle cell relaxation and vasodilation and because of these vasodilatory properties, dietary nitrate intake has the potential to reduce BP [52, 53].

## Nitrate and cancer?

The assumption that eating too much nitrate in the form of vegetables would increase the risk of cancer has been around for a long time and some worry about eating too much nitrate-rich vegetables. This assumption arose as the combination between NO and proteins from the diet can result in the formation of nitrosamines, which are substances that are classified as 'probably carcinogenic to humans' by the International Agency for Research on Cancer [54-58]. Later on, the Dutch Organisation for Applied Scientific Research found that especially the combination of fish and nitrate-rich vegetables into one meal can cause extra

nitrosamines to be formed [56]. For this reason, the Netherlands Nutrition Centre recommended not to eat nitrate-rich vegetables in combination with fish [54]. In response, the Dutch National Institute for Public Health and the Environment researched this question and concluded that the acute and long term exposure to these nitrosamines pose a negligible risk on cancer in humans [59]. Subsequently, the recommendation not to eat too much nitrate and definitely not to combine it into one meal with fish were withdrawn. To conclude, the worries about the harmful effects of consuming too much nitrate are unfounded and, therefore, one should not be concerned about eating too much nitrate-rich vegetables.

## Conclusion

In conclusion, for people with (pre)hypertension or with presence of cardiovascular risk factors, lifestyle interventions may be a plausible alternative to medication and even a conceivable way to prevent CVD progression. Especially the diet is an easy factor to influence and intervene in daily life. Since dietary nitrate has been observed to lower BP values in both normotensive and hypertensive individuals and due to the fact that acute and long term exposure to nitrosamines pose only a negligible risk on cancer, nitrate could be considered as a promising new lifestyle intervention targeting hypertension, thereby lowering the risk on several diseases, such as CVD. So, consuming a little bit extra beetroot or spinach would not hurt and could even benefit your BP!

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