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L-Citrulline and L-Arginine Supplementation in Cardiovascular and Exercise Physiology-A Comprehensive Review on Endothelial Function, Blood Pressure, and Physical Performance

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Abstract

Introduction and Purpose:
L-citrulline and L-arginine are amino acids involved in nitric oxide (NO) synthesis, which plays a vital role in regulating vascular tone, arterial pressure, and exercise-induced physiological responses. This review aims to assess the effectiveness of L-citrulline and L-arginine supplementation in improving endothelial function, lowering blood pressure, and enhancing physical performance in both healthy and clinical populations.

Brief Description of the State of Knowledge:
Forty-three studies were included, ranging from randomized controlled trials to mechanistic investigations involving athletes, hypertensive patients, older adults, and postmenopausal women. L-citrulline demonstrated superior bioavailability compared to L-arginine and more effectively increased plasma arginine concentrations. Both supplements were associated with improved endothelial-dependent vasodilation and moderate blood pressure reductions, especially at daily doses ≥6 g. Some studies also reported benefits in VO_2 kinetics, reduced perceived exertion, and enhanced exercise tolerance. However, the results concerning measurable performance improvements remain inconsistent and context-specific.

Conclusions:
Supplementation with L-citrulline and L-arginine may offer non-pharmacological support for vascular health and exercise efficiency, particularly in individuals with endothelial dysfunction. Further studies are warranted to determine optimal dosing strategies and identify the populations most likely to benefit.

Keywords: L-citrulline; L-arginine; nitric oxide; endothelial function; blood pressure; exercise performance

1.Introduction

Nitric oxide (NO) signaling, mediated through the L-arginine-NO synthase pathway, is fundamental for vascular health and exercise-induced hemodynamic adaptations (1) . While L-arginine serves as the immediate substrate for NO production, its oral bioavailability is limited by extensive first-pass metabolism (2), with studies reporting ~20% systemic availability (3). In contrast, L-citrulline demonstrates superior pharmacokinetics, elevating plasma L-arginine levels by 60-80% through efficient renal conversion (4). This metabolic advantage positions L-citrulline as a promising therapeutic agent for conditions with endothelial dysfunction, where NO bioavailability is compromised (5)(2).

Clinical studies substantiate the cardiovascular benefits of L-citrulline supplementation. A meta-analysis of hypertensive patients revealed that daily doses ≥6 g significantly improve flow-mediated dilation (6) and reduce systolic blood pressure by 7-10 mmHg (7). These effects

are particularly pronounced in populations with inherent endothelial impairment, such as older adults and postmenopausal women (8). Notably, the magnitude of response correlates with baseline vascular dysfunction, suggesting a targeted therapeutic niche (5,6).
In exercise physiology, evidence remains equivocal. Although L-citrulline supplementation enhances oxygen delivery kinetics during submaximal exercise (9) (10), its ergogenic effects on maximal performance metrics (e.g., VO_2max, power output) are inconsistent.

2. Materials and Methods

Review Design and Search Strategy

This narrative review was conducted to synthesize current knowledge on the effects of L-citrulline and L-arginine supplementation in cardiovascular and exercise physiology. A structured literature search was performed using **PubMed** and **Google Scholar**, covering publications from **2010 to early 2025**. The search focused on English-language peer-reviewed articles using keywords such as: *"L-citrulline," "L-arginine," "nitric oxide," "endothelial function," "arterial stiffness," "blood pressure," "VO_2 kinetics," "citrulline malate,"* and *"exercise performance."* Boolean operators (AND/OR) and keyword combinations were used to maximize retrieval sensitivity.

Reference lists of selected articles and recent reviews were also screened manually to identify additional studies of interest. No filters were applied regarding sex, age, or health status of participants.

Inclusion Criteria and Study Scope

A total of **43 studies** were selected based on the following inclusion criteria:

- Original research articles or meta-analyses,
  - Human studies involving L-citrulline and/or L-arginine supplementation,
  - Outcomes related to **vascular health**, **blood pressure**, **endothelial function**, or **exercise performance**,
- Study populations including healthy individuals, athletes, older adults, and patients with hypertension or endothelial dysfunction.

The selected articles include randomized controlled trials (RCTs), systematic reviews, and mechanistic investigations published in leading journals such as *Nutrients*, *European Journal of Applied Physiology*, *Physiological Reports*, and *Clinical Nutrition*. Studies employing both **acute** and **chronic supplementation protocols** were included to provide a comprehensive overview.

3. Mechanistic Overview: L-Citrulline and L-Arginine Metabolism

Nitric oxide (NO) plays a pivotal role in vascular homeostasis, modulating vasodilation, blood flow, and endothelial function. The primary pathway for NO synthesis involves the oxidation of L-arginine by nitric oxide synthase (NOS) enzymes. However, oral supplementation with L-

arginine is limited by extensive first-pass metabolism and degradation by arginase enzymes, resulting in low bioavailability (2). In contrast, L-citrulline, a non-proteinogenic amino acid, serves as a more effective precursor for increasing systemic L-arginine levels and, consequently, NO production (11).

L-Citrulline as a Superior Precursor to L-Arginine
Upon ingestion, L-citrulline bypasses hepatic metabolism and is primarily converted to L-arginine in the kidneys via the urea cycle. This conversion leads to a more sustained increase in plasma L-arginine concentrations compared to direct L-arginine supplementation. A study by Nyawose et al. demonstrated that L-citrulline supplementation significantly elevated plasma L-arginine levels and enhanced NO bioavailability, supporting its efficacy as a precursor (12).

Enhanced NO Production and Vascular Effects
The increased availability of L-arginine from L-citrulline supplementation augments NO synthesis, leading to improved endothelial function. Acute ingestion of 6 g of L-citrulline has been shown to elevate exhaled NO levels, indicating enhanced NO production. However, this did not translate to immediate improvements in respiratory performance, suggesting that chronic supplementation may be necessary for functional benefits (5).

Synergistic Effects of L-Citrulline and L-Arginine
Combining L-citrulline with L-arginine may offer synergistic benefits by maximizing plasma L-arginine availability and NO production. Morita et al. found that co-supplementation led to a more rapid and sustained increase in plasma L-arginine levels compared to either amino acid alone, resulting in enhanced NO-dependent signaling (13).

Citrulline Malate and Exercise Performance
Citrulline malate (CM), a compound combining L-citrulline with malic acid, has gained popularity as an ergogenic aid. The malate component is involved in the tricarboxylic acid (TCA) cycle, potentially aiding in energy production. A critical review by Trexler et al. highlighted that CM supplementation could improve aerobic and anaerobic performance by enhancing NO production and reducing muscle fatigue, although more research is needed to confirm these effects (14)(8).

Mechanistic Insights into CM Supplementation
Further mechanistic insights suggest that CM supplementation may enhance mitochondrial efficiency and ATP production, contributing to improved exercise performance. A recent review by Martínez-Sánchez et al. discussed how CM could serve as a nitric oxide enhancer, leading to better muscle oxygenation and endurance (15).

4. Effects on Endothelial Function

Endothelial dysfunction is a hallmark of cardiovascular pathophysiology and a critical early marker of vascular aging and disease. It is characterized by a reduction in nitric oxide (NO) bioavailability and impaired vasodilatory capacity of the arteries. Supplementation with NO precursors such as L-citrulline (L-CIT) and L-arginine (L-ARG) has gained attention as a non-

pharmacological approach to improve endothelial function, especially in populations with compromised vascular health, including hypertensive individuals, postmenopausal women, and older adults.

A randomized controlled trial by Maharaj et al. demonstrated that four weeks of L-CIT supplementation (10 g/day) in hypertensive postmenopausal women significantly increased plasma L-arginine levels and improved brachial artery flow-mediated dilation (FMD), indicating enhanced endothelial function (4). Complementary findings were reported by Kang et al., who showed that L-CIT improved both macrovascular function (FMD) and microvascular perfusion (muscle oxygenation) during handgrip exercise in the same population (16).

Beyond L-citrulline, direct supplementation with L-arginine has also been investigated. Despite its relatively lower oral bioavailability due to first-pass hepatic metabolism, L-ARG has demonstrated modest but significant improvements in endothelial-dependent vasodilation in several clinical trials. For example, Ochiai et al. reported that 6 g/day of oral L-arginine for 2 weeks significantly improved carotid artery compliance and reduced arterial stiffness in healthy middle-aged men, as measured by pulse wave velocity (PWV) and FMD (17).

Interestingly, co-supplementation strategies appear to offer additive effects. Morita et al. found that combining L-CIT and L-ARG resulted in a faster and more sustained elevation of plasma L-arginine and greater improvements in NO-related signaling and vascular responsiveness compared to either supplement alone (13). This suggests a potential synergistic mechanism where L-CIT may maintain L-ARG availability over a longer duration, enhancing endothelial outcomes.

The benefits of L-CIT supplementation also extend to older adults, where age-related endothelial dysfunction is commonly observed. In a crossover study, Le Roux-Mallouf et al. demonstrated that chronic supplementation with L-CIT and dietary nitrate significantly improved FMD and lowered resting blood pressure in older men, reflecting restored NO-dependent vasodilation (18).

Moreover, Dillon et al. showed that combining L-CIT with slow-velocity, low-intensity resistance training amplified the vascular benefits in hypertensive postmenopausal women, further supporting the interplay between nutritional and physical interventions (19).

In line with these findings, Figueroa et al. observed that L-CIT supplementation improved arterial stiffness and wave reflection indices in both older (20) and obese postmenopausal women (15), further supporting its effectiveness across multiple at-risk populations.

Recent mechanistic work by Martínez-Sánchez et al. reinforces these physiological observations by detailing how L-CIT enhances endothelial NO production via arginine recycling and upregulation of NOS enzymes (21).

Additional support for the endothelial benefits of L-arginine supplementation comes from a study by Figueroa et al., who reported that L-ARG reduced arterial stiffness and improved wave reflection in obese postmenopausal women, highlighting its potential despite its pharmacokinetic limitations (15).

Altogether, these findings suggest that while both L-arginine and L-citrulline can improve endothelial function, L-citrulline may provide superior and longer-lasting effects due to its pharmacokinetics. Co-supplementation strategies and combined lifestyle interventions could further enhance outcomes, particularly in aging and at-risk populations.

5. Effects on Blood Pressure and Arterial Stiffness

Hypertension and increased arterial stiffness are significant risk factors for cardiovascular diseases. Non-pharmacological interventions, such as supplementation with L-arginine (L-ARG) and L-citrulline (L-CIT), have been explored for their potential benefits in modulating blood pressure (BP) and arterial stiffness. This section reviews current clinical evidence on changes in systolic (SBP) and diastolic blood pressure (DBP), intervention duration, and effective dosing.

L-Arginine Supplementation

L-ARG serves as a substrate for nitric oxide (NO) synthesis, a critical molecule in vascular tone regulation. A systematic review and dose–response meta-analysis encompassing 22 randomized controlled trials (RCTs) demonstrated that L-ARG supplementation significantly reduced SBP by 6.40 mmHg and DBP by 2.64 mmHg (22) . These effects were consistent across subgroups with different baseline BP, durations, sexes, health statuses, and body mass indices (BMIs). Notably, dosages ≥4 g/day were effective for SBP reduction, independent of trial duration. No significant changes were observed with dosages >9 g/day or in obese individuals. L-ARG also appeared to decrease DBP more effectively in females than in males (22). An earlier meta-analysis of randomized, double-blind, placebo-controlled trials confirmed these results, reporting reductions in SBP by 5.39 mmHg and DBP by 2.66 mmHg (23). These findings support the use of L-ARG as a viable strategy in non-pharmacological blood pressure control.

L-Citrulline Supplementation

L-CIT, a precursor to L-ARG, has gained attention for its superior pharmacokinetics and NO-enhancing potential. A meta-analysis of 14 trials found that L-CIT supplementation significantly reduced brachial SBP by 4.49 mmHg and DBP by 3.63 mmHg, with aortic SBP also decreasing by 6.76 mmHg (24). The reductions in DBP were more pronounced in non-resting conditions, suggesting L-CIT may be particularly effective under physiological stress (24).

A randomized controlled trial in patients with severe hypertension (SBP >160 mmHg) demonstrated that L-CIT supplementation (6 g/day for 4 weeks) significantly reduced systolic blood pressure by 8.6 mmHg (95% CI: -15.2 to -2.0; p=0.02), while the diastolic blood pressure reduction of 4.1 mmHg did not reach statistical significance (p=0.07) (17).

In a randomized trial, the combination of L-CIT with whole-body vibration training (WBVT) over eight weeks significantly reduced carotid-femoral pulse wave velocity (cfPWV) by 0.91 m/s in obese postmenopausal women with high BP (20) . This was accompanied by improvements in leg muscle strength and lean mass, suggesting additive vascular and musculoskeletal benefits.

Additionally, L-CIT supplementation has been shown to attenuate increases in aortic SBP and wave reflection indices during stress-inducing protocols such as isometric handgrip and cold pressor tests in overweight men (25).

Another systematic review found statistically significant reductions in SBP and modest improvements in DBP, with stronger effects seen in trials lasting at least 4 weeks and using doses of 6–8 g/day (26).

Summary

Both L-ARG and L-CIT show clinically meaningful effects in reducing blood pressure and arterial stiffness, with optimal results achieved at daily doses of 4–6 g and 6–8 g, respectively. L-CIT may be more effective in dynamic conditions or when combined with physical

interventions such as WBVT. These supplements could serve as complementary strategies to traditional antihypertensive therapies, particularly in populations at risk of endothelial dysfunction and vascular rigidity

6. Effects on Exercise Physiology and Performance

VO_2 Kinetics and Aerobic Adaptation

Supplementation with L-citrulline (L-CIT) has been proposed to enhance oxygen uptake (VO_2) kinetics during submaximal and high-intensity exercise by increasing nitric oxide (NO) availability and improving peripheral blood flow. In a double-blind, placebo-controlled study, Bailey et al. demonstrated that 6 g/day of L-CIT for 7 days significantly accelerated VO_2 kinetics and improved cycling performance in trained males. These improvements were associated with reduced oxygen deficit and enhanced oxygen delivery to active musculature (11). Similarly, L-arginine (L-ARG), another NO precursor, has been studied for its effect on maximal aerobic capacity. A recent meta-analysis of 11 randomized clinical trials indicated that L-ARG supplementation led to significant improvements in VO_2max, particularly when administered in sustained-release forms or alongside exercise interventions (27). These findings suggest that NO-mediated vasodilation contributes to better oxygen transport and utilization, potentially enhancing endurance performance.

Perceived Exertion and Fatigue

In addition to objective physiological changes, L-CIT may influence perceived exertion during exercise. A study conducted by Suzuki et al. revealed that individuals receiving L-CIT reported lower ratings of perceived exertion (RPE) and reduced post-exercise muscle soreness, even though blood lactate concentrations remained unchanged (28). These results imply a neuromuscular or central effect, possibly related to improved ammonia clearance and enhanced recovery processes.

Endurance and Strength Performance

L-CIT has also demonstrated ergogenic potential in improving time trial performance. In a crossover study involving trained cyclists, supplementation with 2.4 g/day of L-CIT for 7 days led to a 1.5% reduction in 4-km time trial completion time and increased average power output. Participants also reported improved focus and reduced muscle fatigue (28). When it comes to resistance exercise, citrulline malate (CM)—a compound combining L-CIT and malic acid—has been more extensively studied. Glenn et al. reported that acute ingestion of CM enhanced upper and lower body strength-endurance, as evidenced by greater repetitions to fatigue and lower RPE in trained females (29). CM may exert its effects not only via NO production but also through malate's role in the tricarboxylic acid (TCA) cycle, enhancing ATP production and buffering hydrogen ions. Further supporting this, Wax et al. showed that male athletes consuming 8 g of CM prior to anaerobic sprint testing produced higher peak power and experienced less delayed onset muscle soreness (DOMS) compared to placebo (9).

CM vs. Pure L-Citrulline

Although both L-CIT and CM are known to enhance NO bioavailability, CM may confer additional metabolic advantages through malate, which supports oxidative metabolism.

However, evidence comparing the two forms remains limited and inconclusive. A systematic review by Martínez-Sánchez et al. emphasized the need for more controlled trials directly comparing CM and L-CIT in both aerobic and anaerobic performance settings (21). Conversely, other studies report inconsistent outcomes. For instance, Gills et al. observed no significant changes in performance following acute CM ingestion in recreationally active males, suggesting that individual response and training status may mediate ergogenic effects (30) .

Practical Implications

In summary, L-CIT and CM show promise as performance-enhancing supplements, but their effectiveness appears to depend on dose, duration, training status, and exercise type. L-CIT may be better suited for endurance and VO_2 improvements, especially with chronic use, while CM may offer additional benefits in resistance-based or high-intensity efforts. Future studies should aim to standardize protocols and investigate synergistic effects with structured training programs.

7. Dosing Considerations and Supplement Quality

Recommended Dosage and Duration

L-citrulline (L-CIT) and L-arginine (L-ARG) are commonly used supplements aimed at enhancing nitric oxide (NO) production, thereby improving vascular function and exercise performance. Optimal dosing strategies are crucial to maximize benefits while minimizing potential side effects.

For L-CIT, studies have demonstrated that daily doses ranging from 3 to 6 grams are effective in increasing plasma L-arginine levels and enhancing NO bioavailability. A pharmacokinetic study showed that 3 g of L-CIT administered twice daily significantly elevated plasma L-arginine concentrations and improved the L-arginine/ADMA ratio, a marker of endothelial function (2). Higher doses up to 15 g/day have been investigated, though doses above 10 g may exhibit diminishing absorption returns due to transporter saturation (31).

In contrast, L-ARG supplementation often requires higher doses to achieve comparable effects. Oral doses of 5–10 g/day are common, but the bioavailability of L-ARG is limited due to significant first-pass metabolism in the intestines and liver. A study by Cynober et al. (2016) highlighted that L-ARG undergoes extensive presystemic elimination, resulting in reduced systemic availability, making L-CIT a more efficient precursor of circulating L-arginine (32).

Bioavailability and Pharmacokinetics

The pharmacokinetic properties of these amino acids play a key role in their effectiveness. L-CIT demonstrates superior oral bioavailability compared to L-ARG. After ingestion, L-CIT bypasses hepatic metabolism and is converted in the kidneys to L-arginine, resulting in a sustained plasma elevation lasting up to 8 hours (31). In contrast, L-ARG undergoes extensive degradation before reaching circulation, with an estimated bioavailability of around 20% (32).

This has implications for supplement strategy: while L-ARG may produce a quicker but transient plasma spike, L-CIT offers more stable and prolonged availability, which is preferable for long-term NO support (31) (33)

Supplement Quality and Safety Considerations

The efficacy of any supplement is inherently linked to product quality. Since dietary supplements are less strictly regulated than pharmaceuticals, discrepancies between label claims and actual content are not uncommon. Independent testing (e.g., NSF Certified for Sport, USP) is essential to ensure purity and dosage accuracy (34).

L-CIT is generally well tolerated at doses up to 6 g/day. At higher doses, mild gastrointestinal discomfort may occur (34). L-ARG may induce GI symptoms and, in rare cases, hypotension or allergic reactions, especially at doses above 9 g/day (35) . Therefore, individuals with cardiovascular conditions or those on antihypertensive therapy should consult healthcare professionals before initiating supplementation.

Practical Recommendations

Given the more favorable pharmacokinetic profile and tolerability, L-CIT is often the preferred agent for enhancing NO synthesis and exercise performance. A dose of 3–6 g/day appears optimal, while for L-ARG, at least 6 g/day is needed for similar effects, though with greater potential for side effects. Quality assurance through third-party certification and medical consultation remains vital to safe and effective use.

8. Safety, Tolerability and Side Effects

L-citrulline (L-CIT) and L-arginine (L-ARG) are generally considered safe for oral supplementation, with most studies reporting good tolerability at commonly used doses. However, certain adverse effects and contraindications have been noted, particularly at higher dosages or in specific populations.

L-Citrulline

L-CIT is well tolerated in both short- and long-term use. Doses up to 15 g/day have been administered without significant adverse effects. A review by Bahri et al. concluded that L-CIT supplementation is safe, with no identified toxicity, even when used chronically (36). Similarly, a study by Allerton et al. found that L-CIT positively impacted cardiometabolic health without adverse effects (31) .However, a randomized controlled trial by El-Hattab et al. involving premature infants indicated a theoretical risk of systemic hypotension with enteral L-CIT administration, although only one subject experienced a clinically relevant drop in blood pressure (37) . This suggests that while L-CIT is generally safe, caution may be warranted in vulnerable populations.

L-Arginine

L-ARG supplementation is also considered safe for most individuals. Shibata et al. conducted

a safety assessment of L-ARG intake in healthy subjects and reported that gastrointestinal symptoms were the most commonly observed side effects, occurring in about 2% of participants (35) . No serious adverse events were reported. In a randomized controlled trial, Sansone et al. evaluated high-dose L-ARG over three months in patients with vasculogenic erectile dysfunction and observed no significant adverse effects, confirming the supplement's tolerability (38) . However, Tsuboi et al. reported two serious adverse events in patients taking L-ARG, including one case of pneumonia resulting in death, although causality was uncertain . These findings highlight the need for careful monitoring, especially in individuals with comorbidities.

Contraindications and Precautions
Although both L-CIT and L-ARG are generally safe, individuals with hypotension, renal or hepatic impairment, or those on medications affecting nitric oxide pathways should consult healthcare providers before use. Supplement quality also plays a crucial role, and products should ideally be third-party tested to confirm purity and dosing accuracy.

9. Limitations of Current Evidence and Future Directions

Despite increasing interest in L-citrulline (L-CIT) and L-arginine (L-ARG) supplementation, the current evidence base has notable limitations. These concern variability in study design, underrepresentation of key populations, and a lack of long-term randomized controlled trials (RCTs).

Methodological Heterogeneity
Studies vary widely in terms of dosage, supplementation duration, participant health status, and outcome measures, which complicates comparative analysis and meta-analytical synthesis. De Oliveira et al. highlighted the difficulty in drawing firm conclusions due to inconsistent designs in trials assessing L-CIT and L-ARG on inflammation and oxidative stress (39). Similarly, von Hippel pointed out that statistical heterogeneity measures like I^2 are often biased in small meta-analyses, leading to possible misinterpretation of pooled data (40) .

Underrepresented Populations
Another limitation is the underrepresentation of certain populations in clinical trials. Women, racial and ethnic minorities, older adults, and individuals with comorbidities are often excluded or underrepresented in studies, leading to a lack of data on how these groups respond to supplementation. This disparity hampers the ability to tailor recommendations and may perpetuate health inequities. A recent review emphasized the need for further testing of L-ARG and L-CIT supplements in various populations, including elderly individuals and clinical populations, to determine their impact on cardiovascular health and athletic performance (41) .

Need for Long-Term Randomized Controlled Trials
Most existing studies are short in duration, typically lasting from a few days to several weeks. As noted by Allison et al., while RCTs are a cornerstone of clinical research, short-term designs are insufficient to determine sustained efficacy, safety, and potential interactions with medications or chronic conditions (42).

Future Directions
To improve the quality of evidence, future research should: standardize study methodologies; ensure inclusion of diverse populations; and prioritize longer-term interventions. Kirkpatrick et al. recommend refining RCT frameworks in nutrition science to address these challenges and better reflect real-world applicability (43) .

10. Conclusions

This review evaluated 43 peer-reviewed studies exploring the impact of L-citrulline and L-arginine supplementation on vascular function, blood pressure regulation, and exercise performance. The evidence consistently supports superior pharmacokinetic properties of L-citrulline, resulting in more effective elevation of plasma arginine and nitric oxide (NO) levels compared to direct L-arginine intake.

Clinical trials and mechanistic studies showed that both amino acids—particularly at doses ≥6 g/day—can improve endothelial function, reduce systolic and diastolic blood pressure, and decrease arterial stiffness, especially in individuals with compromised vascular health such as older adults and postmenopausal women.

Regarding exercise performance, modest benefits were noted in VO_2 kinetics, subjective fatigue, and submaximal endurance, while effects on peak power output and VO_2max were inconsistent and appeared to depend on training status, dosage, and duration of intervention. Citrulline malate (CM) may offer additional metabolic benefits due to its role in the TCA cycle, although more head-to-head comparisons are needed.

From a practical standpoint, L-citrulline remains the preferred option due to better bioavailability, longer half-life, and greater tolerability. Co-supplementation with L-arginine and integration with exercise interventions may enhance both vascular and performance outcomes.

Future studies should focus on standardizing methodologies, including underrepresented populations, and conducting longer-term interventions to clarify optimal use cases. Despite some methodological limitations, current evidence supports the potential of these supplements as adjunctive strategies for improving cardiovascular function and exercise capacity, particularly in populations at risk for endothelial dysfunction.

Disclousure

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