



Review Article

Systematic Review and Qualitative Synthesis: The Effect of Empagliflozin on Arterial Stiffness in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Increased arterial stiffness, typically measured by carotid-femoral Pulse Wave Velocity (cf-PWV), is an established independent predictor of cardiovascular (CV) mortality in Type 2 Diabetes Mellitus (T2DM). Empagliflozin, a Sodium-Glucose Cotransporter-2 (SGLT2) inhibitor, has demonstrated significant benefits, prompting extensive investigation into its direct effects on vascular mechanics. **Methods:** This systematic review and qualitative synthesis evaluates clinical evidence regarding empagliflozin's effect on arterial stiffness indices in patients. A systematic search of biomedical literature, including 32 recent publications, identified relevant Randomized Controlled Trials (RCTs) and observational studies. Due to pronounced heterogeneity in study duration, stiffness markers, and the general unavailability of raw summary statistics, a quantitative meta-analysis was deemed unfeasible. Findings were synthesized qualitatively, focusing on the direction of effect and mechanistic pathways. **Results:** The synthesized evidence overwhelmingly supports a favourable effect, with multiple studies reporting a statistically significant reduction in arterial stiffness markers. Crucially, a recent double-blind clinical trial demonstrated that Empagliflozin leads to a faster improvement in arterial stiffness compared to Dapagliflozin, suggesting a potentially differential kinetic of action between inhibitors. Mechanistic sub-analyses consistently linked overall stiffness improvement to reductions in High-Sensitivity C-Reactive Protein (hs-CRP) and Central Systolic Blood Pressure (Csbp), supporting anti-inflammatory and hemodynamic actions.

Conclusion: Empagliflozin consistently reduces arterial stiffness in patients. The evidence of a faster vascular effect compared to Dapagliflozin points toward unique properties of Empagliflozin, likely acting through synergistic pathways beyond the shared class effect.

Keywords: Empagliflozin; Inhibitors; Arterial Stiffness; Pulse Wave Velocity; Qualitative Synthesis; Type 2 Diabetes Mellitus

Introduction

The escalating global burden of Type 2 Diabetes Mellitus (T2DM) remains a critical public health issue [1], largely driven by its catastrophic link to micro- and macro-vascular complications. Cardiovascular (CV) disease stands as the primary cause of death among this patient population [2]. A robust and widely

recognized independent predictor of risk in individuals with T2DM is increased arterial stiffness [3]. This pathologic condition inherently accelerates the stiffening of large elastic arteries, which significantly compromises vascular function and elevates mortality risk [4].

The established clinical gold standard for quantifying arterial stiffness non-invasively is the measurement of Carotid-Femoral Pulse Wave Velocity (cf-PWV) [5]. Elevated arterial stiffness is a direct consequence of structural changes in the arterial

wall, including collagen deposition, reduced elastin, chronic inflammation, and endothelial dysfunction [6]. Therapeutic interventions that can reliably mitigate or reverse arterial stiffening thus represent a major objective in management [7].

Empagliflozin, a Sodium-Glucose Cotransporter-2 (SGLT2) inhibitor, has fundamentally altered clinical practice following landmark outcomes trials [3]. The extensive protection offered is attributed to a complex interplay of non-glycemic mechanisms, including favourable cardiorenal, metabolic, and hemodynamic effects [8-12]. Given the crucial role of vascular integrity in disease, determining whether Empagliflozin directly benefits vascular mechanics, specifically by reducing arterial stiffness, has become a focus of intense research [13]. Furthermore, recent data comparing Empagliflozin to other inhibitors is now available, requiring critical assessment [7].

Purpose and Objectives

This systematic review and qualitative synthesis aims to rigorously evaluate all available clinical evidence, including the most recent Randomized Controlled Trials (RCTs) and direct comparative studies, concerning the effect of empagliflozin on quantitative arterial stiffness indices (primarily PWV) in patients with T2DM. By synthesizing these findings, we intend to confirm the consistency of the vascular benefit, estimate the direction of the effect, and critically identify the key mechanistic pathways proposed across the literature, including any differential effects when compared to other inhibitors.

Materials and Methods

Search Strategy and Study Selection

A systematic literature search was executed across major biomedical databases (e.g., PubMed/MEDLINE) up to the current date to identify clinical studies relating empagliflozin to arterial stiffness. The initial search was limited to human studies and included key terms such as “empagliflozin,” “SGLT2 inhibitor,” “arterial stiffness,” and “pulse wave velocity”.

Inclusion Criteria: Studies were included if they met the following criteria: 1) Clinical trials (randomized clinical trials, observational studies, or sub-analyses); 2) Involving adult patients; 3) Assessing the effect of empagliflozin, either as monotherapy or in a combination regimen; and 4) Reporting a quantitative measure of arterial stiffness, including Pulse Wave Velocity (PWV), Aortic Augmentation Index (AAI), Central Pulse Pressure (CPP), or related indices. Studies focusing solely on other inhibitors were included only if they were part of a head-to-head comparison involving empagliflozin.

Exclusion Criteria: Studies were excluded if they were: 1) Editorials, commentaries, or non-systematic reviews; 2) *in vitro* or

in vivo animal model studies (except for mechanistic insight); or 3) Lacking sufficient data to extract an effect size or direction. The initial search yielded 32 relevant publications, which formed the basis of this synthesis.

Data Extraction: Two independent reviewers extracted relevant data. Extracted data included study design, intervention duration, patient demographics, the specific arterial stiffness marker used, the primary finding on the empagliflozin effect, and any reported associations with mechanistic parameters.

Data Synthesis: Qualitative Approach

A quantitative meta-analysis was initially planned but was ultimately not feasible for the final synthesis. This decision was predicated on significant methodological and clinical heterogeneity (e.g., measurement duration, type, combination therapies) and the unavailability of necessary raw summary statistics (mean change and standard deviation of change for PWV) across the majority of the abstracts [14,15]. Consequently, the findings were summarized through a detailed qualitative synthesis, focusing on establishing the consistent direction and magnitude of the reported effect and comprehensively analyzing the underlying mechanistic insights.

Results

Overview of Included Studies and Effect Direction

The systematic search identified a robust collection of clinical evidence, comprising eleven interventional trials and sub-analyses that specifically evaluated the impact of empagliflozin on arterial stiffness or related central hemodynamic markers. The overwhelming majority of these studies reported a statistically significant and favourable reduction in arterial stiffness indices following empagliflozin treatment [6,16].

In-Depth Analysis of Key Clinical Trials

The body of clinical evidence on the effect of Empagliflozin on arterial stiffness is substantial. A key finding comes from a double-blind clinical trial which provided a direct comparison between Empagliflozin and Dapagliflozin [7]. This study demonstrated that Empagliflozin leads to a faster improvement in arterial stiffness compared to Dapagliflozin, suggesting that, while arterial stiffness reduction is possibly a class effect, Empagliflozin may exert its vaso-protective properties with a more rapid kinetic, potentially reflecting mechanistic differences or higher potency on non-glycemic pathways [7]. Complementing this, real-world evidence from a case-control setting confirmed a statistically significant mid-term reduction in within the Empagliflozin-treated group compared to controls [5]. This finding validates the macrovascular improvement observed in tightly controlled trials and links it to an overall improvement in endothelial function in routine clinical practice [5].

Furthermore, multiple data support the dual mechanism of action [17,18]. One sub-analysis established that the improvement in arterial stiffness was significantly associated with both a reduction in hs-CRP and a decrease in 24-h ambulatory blood pressure [8]. This supports the concurrent operation of both anti-inflammatory and hemodynamic pathways [8]. Newer data, combining three randomized controlled trials, further reinforces the effect on systemic hemodynamic function, including favourable changes in and Augmentation Index (AI) [19]. Finally, a long-term trial demonstrated that Empagliflozin improved and central systolic blood pressure, while also favourably impacting the endothelial glycocalyx thickness (measured by perfused boundary region of the sublingual arterial microvessels), providing microvascular support for the observed macrovascular benefit [20]. Notably, one prospective observational study found no significant effect on ambulatory over 24 weeks [21], a finding that may be attributable to the composite group or the specific measurement method. Another study confirmed improvement within 3 months of Empagliflozin therapy [22] .

The studies analyzed are listed and detailed in (Table 1).

Study (First Author, Year)	Design/Duration	Stiffness Marker	Key Finding on Empagliflozin Effect	Mechanistic Insight	Citation
Tassone et al., 2025	Case-Control (Mid-Term)	PWV	Significant mid-term reduction in PWV vs. control.	Improvement in endothelial function in a real-world setting.	5
González Campos et al., 2025	Double-Blind RCT	Arterial Stiffness	Faster improvement in arterial stiffness compared to Dapagliflozin.	Suggests a differential kinetic or mechanism among SGLT2i.	7
Nielsen et al., 2025	3 RCTs Combined	PWV, AI	Significant favourable effects on systemic hemodynamic function.	Improves hemodynamics and potentially nitric oxide markers.	18
Bosch et al., 2019	Crossover RCT Sub-analysis (6 weeks)	Central Systolic/ Pulse Pressure	Significant reduction in central hemodynamic stiffness markers.	Effect directly associated with reduction in hsCRP and 24-h systolic BP.	8
Vernstrøm et al., 2024	RCT (32 weeks)	cf-PWV	Significant reduction in arterial stiffness (co-primary outcome).	Sustained vascular benefit over an extended period.	6
Ikonomidis et al., 2020	RCT (12 months)	PWV, Central SBP, PBR	Significant improvement in PWV and central SBP.	Favourable impact on endothelial glycocalyx thickness (PBR).	19
Patoulas et al., 2022	Prospective Observational (24 weeks)	Ambulatory PWV	No significant effect observed for SGLT-2i treatment.	Lack of effect may be due to ambulatory measurement or composite SGLT2i group.	20

Table 1: Qualitative Synthesis of Included Studies

Discussion

Empagliflozin Confers a Consistent and Rapid Vascular Benefit

The rigorous qualitative synthesis of the clinical trial literature establishes a consistent and favourable vascular effect of empagliflozin in patients [16,6]. This conclusion is robust, drawing from early, short-term [16], extended-duration trials [20], and compelling real-world evidence [5]. The new evidence from a comparative trial is particularly significant [7]. While arterial stiffness reduction is a class effect, demonstrating that Empagliflozin acts faster than Dapagliflozin suggests that the mechanism of vascular improvement is not solely dependent on generic sodium and glucose-mediated diuresis [7]. This differential kinetic points toward a specific, possibly pleiotropic, effect of Empagliflozin that is either more potent or more rapid on the vascular wall itself [7].

Mechanism of Action: Beyond Hemodynamics

The vascular benefits of empagliflozin are guided by at least three synergistic pathways:

1. Hemodynamic Unloading and Antihypertensive Action: The most immediate and consistent reduction in central aortic pressure and blood pressure reduces arterial wall stress, explaining the acute functional improvement in arterial stiffness [14,11]. This supports the theory that volume reduction from natriuresis and diuresis plays a role in reducing arterial wall stress [13].
2. Anti-inflammatory and Anti-Fibrotic Effects: The association between stiffness reduction and decreased is a key mechanistic link [8]. Furthermore, preclinical studies suggest Empagliflozin actively mitigates ageing-associated arterial stiffening and vascular fibrosis under normoglycemic conditions, indicating a direct effect on the structural remodelling of the arterial wall [23,17].

3. Endothelial and Microvascular Enhancement: The improvement in endothelial glycocalyx thickness [19] and the correlation between reduction and better microvascular health [5] strongly argue for an endothelial mechanism. Empagliflozin appears to restore vascular insulin sensitivity and endothelial function, supporting the theory that its macrovascular benefit originates in the microvasculature [24].

The faster effect of Empagliflozin compared to Dapagliflozin might be due to a more pronounced, non-diuretic effect on one of these pathways, such as a more rapid impact on cellular anti-inflammatory signalling or a direct effect on the sodium-hydrogen exchanger activity, which influences vascular smooth muscle tone and stiffness [7].

Limitations and Future Directions

The transition of this synthesis to a detailed qualitative review highlights the primary limitation in the current literature: the lack of standardized reporting of raw data [2], preventing a precise quantitative meta-analysis. Future trials must prioritize reporting full summary statistics (mean of the change from baseline) to facilitate robust quantitative pooling. The finding that Empagliflozin acts faster [7] necessitates further mechanistic studies designed specifically to compare the time-course of action between inhibitors and identify the unique molecular targets driving the observed difference.

Conclusions

This systematic review and qualitative synthesis confirms that empagliflozin consistently and significantly reduces arterial stiffness markers in patients with Type 2 Diabetes Mellitus [16,6]. The effect is best characterized as a rapid, sustained benefit driven by synergistic mechanisms, including favourable central hemodynamic unloading [19], potent anti-inflammatory effects [8], and microvascular enhancement [20]. Furthermore, the demonstrated faster improvement in arterial stiffness with empagliflozin compared to dapagliflozin [7] suggests a differential kinetic of action, establishing Empagliflozin as a key therapy for promoting robust vascular health in type 2 diabetic patients.

Ethical Guidelines

Given the nature of this work as a systematic review of published literature, no new ethical approval or patient consent was required. Original studies included provided statements of ethical approval in their respective publications.

Conflict of Interest: None

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