ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2023 May 26; 15(5): 205-283

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

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Monthly Volume 15 Number 5 May 26, 2023

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Monthly Volume 15 Number 5 May 26, 2023

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INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJC* as 0.35. The *WJC*'s CiteScore for 2021 is 0.9, and Scopus CiteScore rank 2021: Cardiology and Cardiovascular Medicine is 260/336.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Hua-Ge Yu*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Yun-Xiaojiao Wu*.

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Ramdas G Pai, Dimitrios Tousoulis, Marco Matteo Ciccone, Pal Pacher

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

PUBLICATION DATE
May 26, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/gerinfo/242

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World Journal of Cardiology

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World J Cardiol 2023 May 26; 15(5): 205-216

DOI: 10.4330/wjc.v15.i5.205

ISSN 1949-8462 (online)

MINIREVIEWS

Extracorporeal veno-venous ultrafiltration in congestive heart failure: What's the state of the art? A mini-review

Andrea Urbani, Filippo Pensotti, Andrea Provera, Andrea Galassi, Marco Guazzi, Diego Castini

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Charach L, Israel; Sangani V, United States

Received: December 27, 2022
Peer-review started: December 27, 2022
First decision: January 9, 2023
Revised: January 19, 2023
Accepted: April 24, 2023
Article in press: April 24, 2023
Published online: May 26, 2023

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Abstract

Hospitalizations for heart failure exceed 1 million per year in both the United States and Europe and more than 90% are due to symptoms and signs of fluid overload. Rates of rehospitalizations or emergency department visit at 60 days are remarkable regardless of whether loop diuretics were administered at low *vs* high doses or by bolus injection *vs* continuous infusion. Ultrafiltration (UF) has been considered a promising alternative to stepped diuretic therapy and it consists in the mechanical, adjustable removal of iso-tonic plasma water across a semipermeable membrane with the application of hydrostatic pressure gradient generated by a pump. Fluid removal with ultrafiltration presents several advantages such as elimination of higher amount of sodium with less neurohormonal activation. However, the conflicting results from UF studies highlight that patient selection and fluid removal targets are not completely understood. The best way to assess fluid status and therefore establish the fluid removal target is also still a matter of debate. Herein, we provide an up-to-date systematic review about the role of ultrafiltration among patients with fluid overload and its gaps in daily practice.

Key Words: Fluid overload; Ultrafiltration; Diuretics; Heart failure

Core Tip: This mini review aimed to evaluate the role of ultrafiltration in congestive heart failure and to compare this approach to standard therapy essentially based on diuretics. Evidences are still controversial and matter of debate, however it is clear that the use of ultrafiltration has beneficial effects on outcomes such as rehospitalization for heart failure and symptoms attenuation. This review of the literature also highlighted the pivotal role of a non-invasive multiparametric assessment of fluid overload to guide physicians through tailoring patient's decongestion.

Citation: Urbani A, Pensotti F, Provera A, Galassi A, Guazzi M, Castini D. Extracorporeal veno-venous ultrafiltration in congestive heart failure: What's the state of the art? A mini-review. *World J Cardiol* 2023; 15(5): 205-216
URL: https://www.wjgnet.com/1949-8462/full/v15/i5/205.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i5.205

INTRODUCTION

Hospitalizations for heart failure (HF) exceed 1 million per year in both the United States and Europe and more than 90% are due to symptoms and signs of fluid overload. In addition, up to 1 in 4 patients (24%) is readmitted within 30 d and 50% of patients are readmitted within 6 mo[1,2]. Recurrent fluid overload in HF has uniformly been associated with worse outcomes independently of age and renal function[3]. Data from the Diuretic Optimization Strategies Evaluation trial show that 42% of patients with acutely decompensated HF reached the composite end point of death, rehospitalizations or emergency department visit at 60 d regardless of whether loop diuretics were administered at low *vs* high doses or by bolus injection *vs* continuous infusion[4]. Therefore, the need for adjunctive treatment strategies to standard stepped diuretic therapy in patients presenting with fluid overload in the context of decompensated HF is critical. One promising therapy is extracorporeal veno-venous ultrafiltration (UF). Ultrafiltration consists in the mechanical, adjustable removal of iso-tonic plasma water across a semipermeable membrane with the application of hydrostatic pressure gradient generated by a pump [5].

The fluid removed from the intravascular compartment is constantly replaced by fluid from the third space configurating the so called "intra-vascular refill" phenomenon, thus allowing gradual and controlled fluid overload resolution[6]. Despite fluid removal with UF presents several advantages such as elimination of higher amount of sodium with less neurohormonal activation, results from clinical studies regarding efficacy and safety have been variable.

Herein, we provide an up-to-date systematic review about the role of UF among patients with fluid overload and its gaps in daily practice.

PATHOPHYSIOLOGY AND CONSEQUENCES OF FLUID OVERLOAD

The initial trigger of fluid overload is a reduced cardiac output that results from failing myocardium. This process causes an arterial hypovolemia which triggers a cascade of events designed to increase intra-arterial blood volume. The main mechanism involved is a neurohumoral activation of the renin-angiotensin-aldosterone (RAAS) axis that increases renal and sodium avidity, thereby resulting in an increase of effective blood volume. In a setting of HF, proximal sodium and water retention are so elevated that distal nephron chronically undergoes low sodium delivery, maintaining persistent RAAS activation[7]. Also, increased sympathetic tone leads to splanchnic arterial and venous constriction resulting in blood redistribution from the splanchnic capacitance vasculature to the circulatory volume. This expands the effective circulating volume by redistribution in a setting where volume expansion is already ongoing[8]. At the beginning, these changes occur as compensatory mechanisms to maintain effective circulating blood volume, over time they become harmful with the development of pathological inappropriate blood volume and interstitial fluid expansion contributing to fluid overload and organ congestion. An excessive effective circulating blood volume leads to hemodynamic congestion with increased central filling pressures[9]. Deranged hemodynamics and neurohormonal activation leading to excessive tubular reabsorption produce long-standing venous congestion. Elevation of central venous pressure is rapidly transmitted to the renal veins, causing increased interstitial and tubular hydrostatic pressure that decrease net glomerular filtration[10]. Hence, in this context, venous congestion of the kidneys rather than arterial underfilling is associated with decreased renal blood flow and an increase in creatinine[6,11]. Moreover, congestion within peripheral vascular tissues can produce endothelial activation followed by up-regulation of inflammatory cytokines, which promotes additional fluid retention[12,13]. Therefore, reducing congestion should be the foremost goal in patients with HF and fluid congestion[6].

DETECTING FLUID OVERLOAD IN HF

Historically, the gold standard to evaluate fluid overload has been pulmonary artery catheterization (PAC) that allows a direct measurement of right atrial pressure and pulmonary capillary wedge pressure (PCWP)[14]. For several years it has been widely used but then, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial showed that the use of PAC to guide diuretic therapy in comparison with serial clinical assessment did not improve mortality[15]. Currently, due to its invasive nature and the lack of evidence, the use of Swan Ganz catheterization is restricted to a selected group of critically ill patients in tertiary hospitals with high level of user competence.

For what concern the non-invasive assessments of congestion, a multiparametric point of care ultrasound (POCUS) can play a key role. In the Figure 1, we make a comprehensive list of all the most used POCUS parameters.

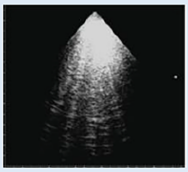
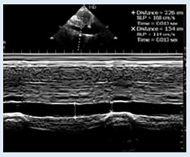
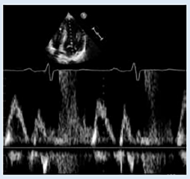
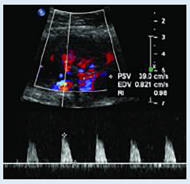
Lung ultrasound (LUS) can be used to assess interstitial oedema and pleural effusion in patients with known or suspected HF and detects the so-called B-lines that originates from the extravascular fluid[16,17]. B-lines are hyperechoic artefacts which appear as vertical lines originating from the pleural surface [18]. More than three B-lines in more than two intercostal spaces bilaterally are considered diagnostic of interstitial and alveolar oedema in acute HF[8,19]. In comparison to chest X-ray, lung ultrasound is more accurate for the diagnosis of interstitial oedema and HF, although B-lines can occur in other condition such as interstitial lung disease and non-cardiogenic pulmonary oedema[16,20,21]. Echocardiography can, also, be used to non-invasively and quickly estimate right and left-sided filling pressure. An appraisal of the right atrial pressure can be performed by evaluating the collapsibility and width of the inferior vena cava (IVC)[22]. Any variation in right atrial pressure is transferred backward, and modifies IVC size, in fact a significant increase in right atrial pressure, as seen in HF, would eventually result in IVC distention. Pulsed doppler and tissue Doppler are useful tools in estimating left-sided filling pressure. The E/e' ratio > 14 has high specificity for increased filling pressures, especially if E-wave deceleration time is short and A-wave velocities are low[23,24]. Furthermore, congestion and high central venous pressure lead to increased renal interstitial pressures that affects primarily renal venous flow which can be evaluated with Doppler ultrasound. Specifically, the presence of an intermittent renal venous flow rather than continuous as in healthy subjects has been strongly related with an increased central venous pressure measured invasively and has been associated with a worse prognosis in both acutely decompensated HF and among stable patients with chronic HF[25,26]. Despite diagnosis of congestion is currently made with the combination of signs and symptoms, a suggestive X-ray and the measurement of elevated natriuretic peptides (NPs), these additional non-invasive POCUS-guided approach can increase the accuracy of the diagnosis and, more importantly, can be helpful in tailoring patient's decongestion during the hospitalization (Table 1).

USE OF DIURETICS IN ACUTE HF AND DIURETIC RESISTANCE

Diuretic agents, especially loop diuretics, have been for decades the backbone of the therapy for fluid overload[30,31]. Guidelines recommend the use of intravenous loop diuretic rather than oral as first line therapy and an early as possible administration because of its association with reduced in-hospital mortality[32]. The initial diuretic regimen depends on whether the patient is diuretic naïve or not. In fact, diuretic naïve patients should receive an initial dose of at least 20-40 mg of intravenous furosemide, whereas patients already on an ambulatory diuretic regimen should receive 1-2 times the 24-h home dose intravenously. A spot urine sodium content of > 50-70 mEq/L and an hourly urine output of > 100-150 mL during the first 6 h usually identifies patients with an initial acceptable diuretic response[33,34]. If these targets are not reached, a prompt doubling of loop diuretic dose is usually required and should be repeated until maximal dose of loop diuretics is administered; as maximal dose of loop diuretic is given, an addition of another diuretic agent should be considered as increasing the loop diuretic dose does not improve natriuresis any further. Despite diuretics are highly effective in the early stages of acute HF, in a significant subset of patients loop diuretics become increasingly ineffective with disease progression due to the onset of diuretic resistance[35]. A recent definition of diuretic resistance has been proposed which implies a failure to increase fluid and sodium (Na+) output sufficiently to relieve volume overload, edema, or congestion, despite escalating doses of a loop diuretic to a ceiling level (80 mg of furosemide once or twice daily or greater in those with reduced glomerular filtration rate or HF)[36]. Diuretic resistance is the result of several factors such as impaired absorption, decreased renal blood flow, hypoalbuminemia and proteinuria, all leading to a reduced levels of active diuretics in the tubular lumen[35,37]. Unfortunately, clinical signs and symptoms are often unreliable to detect diuretic resistance. A poor diuretic response predicts mortality rate after discharge, subsequent rehospitalization, or renal complications from congestive HF[36]. Therefore, finding more effective treatments for fluid removal is an unmet need.

Table 1 Differences between ultrafiltration and diuretics

Loop diuretics	Isolated ultrafiltration
Hypotonic urine	Isotonic plasma water
Direct neurohormonal activation	No direct neurohormonal activation
Unpredictable elimination of sodium and water	Precise control of rate and amount of fluid removal
Diuretic resistance	Restoration of diuretic responsiveness
Hypokalemia and hypomagnesemia	No effect on plasma concentration of potassium and magnesium
No need for anticoagulation	Need for anticoagulation
No extracorporeal circuit	Need for extracorporeal circuit

Parameters assessed by POCUS indicative of fluid overload	Echographic windows and transducer positions	Pathological reference values	Clinical and prognostic significance	Ref.
B-Lines 	8 chest zones measured with phased-array or curvilinear transducer placed in the intercostal spaces	A cut off-value of ≥ 3 B-lines in at least two intercostal spaces per hemithorax	Indicates interstitial oedema and identifies acute HF in patients with dyspnea with high sensitivity (94%-97%) and specificity (96%-97%)	[27]
IVC size 	Subcostal view with curvilinear or phased-array transducer at 1.0 to 2.0 cm from the junction with the right atrium	An IVC smaller than 21 mm that collapses more than 50% is considered normal	It might detect increasing intravascular volume even prior to any change in symptoms or body weight	[28]
Doppler left sided filling pressure (E/e' ratio) 	Apical 4-chamber view with Doppler imaging and tissue doppler	E/e' ratio > 14	It indicates rising filling pressure especially if E deceleration time is short and A-wave velocities are low	[23]
Doppler Intermittent renal venous flow 	Left lateral decubitus position using a convex or sector transducer aligned with the lowest intercostal space offering a longitudinal view of the right kidney	When central venous pressure increases, renal venous flow becomes firstly pulsatile and then biphasic	It is an earlier marker of development of congestion and suggests a poor prognosis	[29]

DOI: 10.4330/wjc.v15.i5.205

Figure 1 Direct and indirect non-invasive estimation of fluid overload with point of care ultrasound. IVC: Inferior vena cava; POCUS: Point-of-care ultrasound; HF: Heart failure.

HOW DOES VENO-VENOUS UF WORK?

As briefly described in the introduction, the mechanism of action of UF is based on the use of a transmembrane pressure gradient generated by a pump, which through a semi-permeable membrane causes the removal of plasma water from whole blood. The net effect at the end of the process is the achievement of an isotonic concentration between the ultrafiltrate and the plasma water removed from the circulation[10].

UF requires a venous access to fulfill the filtration process through the hemofilter and the subsequent reintroduction of the ultrafiltered plasma into the systemic circulation[38].

Optimal anticoagulant therapy by continuous infusion of heparin is also required to preserve the function of the filter during the whole process.

The Figure 2 schematically shows the UF process; the blood, after being extracted from the patient by venous access, is transferred to the extracorporeal circuit of the UF and then reintroduced into the bloodstream.

Newer devices allow, *via* a double-lumen venous catheter placed in the jugular or basilic vein, a blood draw with minimal recirculation.

There are various methods by which the UF process can be achieved: isolated UF, hemofiltration and UF in combination with dialysis.

Isolated UF is only a method of fluid control, whereas all the others can simultaneously achieve a certain degree of blood purification with different mechanisms. For example hemodialysis accomplishes blood purification with solutes moving from high concentration to low concentration along the electrochemical gradient whether UF, as stated above, the substances travel due to a pressure gradient.

According to a duration-based classification, UF techniques can be classified as acute or isolated, intermittent or continuous (< 24 h) and slow continuous (> 24 h)[39].

With pure UF, an extracorporeal blood pump, either by suction applied to the ultrafiltrate compartment (negative pressure) or by resistance induced in the venous line (positive pressure) transfers the blood through the filter where the UF process is achieved.

Advantages of pure UF include the avoidance of arterial puncture, short exposure to systemic anticoagulation and, furthermore, it does not require specialized dialysis personnel[40].

Using an appropriate UF rate allows the extracellular fluid to gradually fill the removed intravascular space, thus keeping the volume constant; this effect differs UF from diuretics which remove intravascular volume without causing adequate filling from the extravascular space, the main site of congestion in patients with HF.

On the other hand, if the UF rate is too high, the rate by which the intravascular volume is removed exceeds the reabsorption of fluid from the interstitium into the vascular space, thus losing the real benefit of using UF.

Therefore, to obtain a real benefit from UF, the challenge is to find the correct rate of decongestion while maintaining an adequate circulating blood volume[41].

PROS AND CONS OF DIURETIC THERAPY *VS* UF

With the usage of loop diuretics, the reduction of net body water is achieved through the removal of hypotonic urine whereas UF determines the production of an iso osmotic and isonatremic diuresis. Thus, for any amount of fluid withdrawn, the net quantity of sodium removed is greater with UF than with diuretic agents.

The use of loop diuretics, moreover, causes also an inhibition of sodium chloride uptake in the macula densa thus enhancing the RAAS system activation.

On the other hand, UF through iso-osmotic and isonatremic diuresis maintains the same uptake of sodium chloride from the macula densa, avoiding RAAS system activation.

Thereby, the prolonged use of loop diuretics increases water and sodium retention in the proximal tubule with subsequent reduction of net sodium delivering in the loop of Henle decreasing the efficacy of loop diuretics to relieve the congestion.

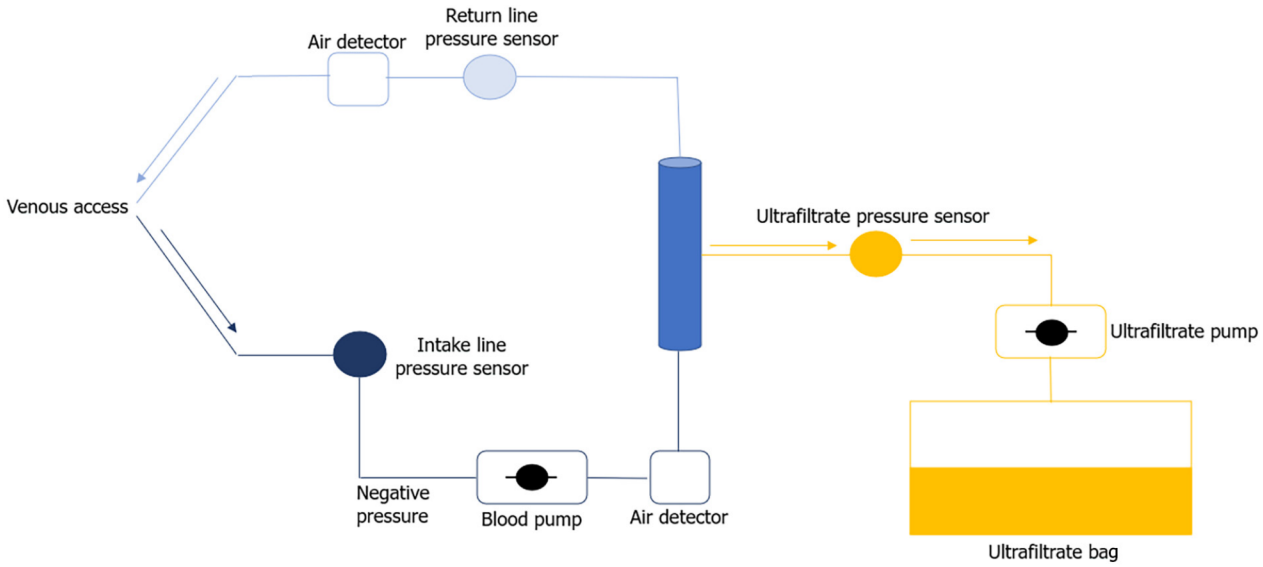
The final goal of the ultrafiltrative process determines an euvolemic state which is obtained by withdrawing intravascular volume which is equal in size to that reabsorbed from the extracellular space [41].

Compared with standard intravenous diuretic therapy UF, by reduction of neurohormonal pathways, also improve functional capacity in patients with HF.

As explained in the study of Agostoni *et al*[42], UF unequivocally improved the functional performance of patients with HF. Cardiopulmonary exercise test obtained after 4 d shows higher values of peak VO2 and better VD/VT ratio in UF patients compared with standard diuretic therapy. The authors suggest that favorable influences of UF on the functional capacity are related to the protective role of vasopressin and atrial peptides during and after UF that allows a more “physiological" fluid metabolism and lung decongestion in patient with HF. The study also demonstrated that UF was a more powerful stimulus than loop diuretics on the release of norepinephrine, with much less effect on the RAAS system[42]. In Table 1 we highlighted main differences of using UF or diuretics.

EVIDENCES ABOUT THE USE OF UF IN HF FROM RCTS

The first two randomized clinical trial (RCT) in which an UF-based decongestion was compared to a diuretic-based approach have been the Relief for Acutely Fluid-Overloaded Patients With



DOI: 10.4330/wjc.v15.i5.205

Figure 2 A schematic representation of the ultrafiltrative process.

Decompensated Congestive Heart Failure (RAPID-CHF) and the Use of Nitroprusside in Left Ventricular Dysfunction and Obstructive Aortic Valve Disease (UNLOAD) trial[43,44].

In the RAPID-CHF, authors demonstrated the feasibility and the potential beneficial effects of UF (with Aquadex system) *vs* usual care among patients admitted to the hospital for an acute decompensation of congestive HF (20 UF, 20 usual care). These patients received a single, 8-h course of UF with fluid removal rates determined by the attending physician (to a maximum of 500 cc/h), whereas usual care patients were treated with diuretics according to the guidelines. Weight loss after 24 h from enrollment, used as primary end-point, was greater in the UF group although did not reach a statistical significance. This trial also highlighted that at 1-d and 30-d follow-up patients had a sustained and more significant symptoms relief (dyspnea) compared to the usual care. Furthermore, there were no differences between groups in terms of hemodynamic parameters (*e.g.*, blood pressure, heart rate) and adverse events.

However, the authors concluded that the small sample size (n = 40) reduced the significance of this study and did not allow to draw definitive conclusions about the potential beneficial role of UF in this subset of patients.

The investigators of the UNLOAD trial compared early UF strategy (at 24 h from hospitalization) *vs* diuretics in a population of 100 patients admitted with acutely decompensated HF in a prospective, randomized, multicenter trial. In the UF group, fluid was removed at an average fixed rate of 241 mL/h for 12 h. In the standard-care group, average daily diuretic dose of intravenous furosemide or equivalent was 181 mg during the 48 h after randomization. The study demonstrated a clear trend of each outcome in favor of UF; weight loss (primary endpoint), dyspnea improvement and net fluid loss assessed at 48 h from enrollment resulted statistically significant (P = 0.001) in the UF arm of the study as compared to diuretics arm. Furthermore, the UF group had fewer patients re-hospitalized for HF at 90 d [16 of 89 (18%) *vs* 28 of 87 (32%), P = 0.037].

One of the main limits of both the RAPID-CHF and UNLOAD trial was to not include a comprehensive assessment of hemodynamic parameters during the study.

Giglioli *et al*[45], in their ULTRADISCO trial performed a standardized evaluation of hemodynamic status obtained using Pressure Recording Analytical Method monitoring system by radial artery cannulation. Stroke volume indexed, cardiac index, cardiac power output, systemic vascular resistance was measured during hospitalization, at discharge, and at 1 and 3-mo follow-up among patients with acute decompensated HF (ADHF) treated with UF (using PRISMA system) *vs* conventional diuretics strategy. As a result, authors demonstrated that UF benefits can go beyond the net fluid loss and clinical improvement by significantly ameliorating hemodynamic status[45].

A different kind of population was target of the CARRESS-HF trial. In this study Bart *et al*[46] compared UF with a diuretic-based stepped pharmacologic therapy in patients hospitalized with ADHF with signs of congestion and worsening renal function (defined as an increase in the serum creatinine level of at least 0.3 mg per deciliter between 12 wk before and 10 d after the index admission for HF.) Ultrafiltration was performed at a fixed fluid-removal rate of 200 mL per hour. Both the primary endpoints (weight loss and serum creatinine variation) and secondary endpoints (clinical and laboratoristic) resulted statistically not significant. This trial also showed more adverse events in the UF arm such as bleeding, catheter thrombosis and advanced kidney failure. The reasons of these results remain

still unclear although it is possible that the patients involved are not the subpopulation in which UF achieve its potential beneficial effect[46].

In the CUORE trial, investigators randomized highly selected patients with severe systolic congestive HF to UF (using Dedyca system) or standard therapy. Those patients randomized to UF had a significantly lower frequency of rehospitalization for congestive HF than control subjects and this result was maintained for up to 1 year. Furthermore, the overall reduction in rehospitalizations was linked to more significant maintenance of a body weight, renal function and lower diuretic dose in the first 6 mo after discharge[47].

The AVOID-HF trial, in contrast with the CARRESS-HF trial, remains faithful to the findings of other studies mentioned above in which UF is beneficial when applied early during the episode of HF decompensation. The AVOID-HF has the largest sample size with a total of 224 patients randomized to UF arm (using Aquadex system) or standard diuretic therapy and has a predefined decongestion dose adjustment protocol. The trial was interrupted prematurely for slow enrollment rate. Despite only one third of the sample size was achieved from the investigators, this trial showed a trend toward reduction in rehospitalization for HF in the first 90-d of discharge[48].

Lastly, Hu *et al*[49], in their single center experience trial has demonstrated that early UF effectively and safely reduces volume overload in patients with ADHF. Patient were enrolled in the first 24 h of admission randomlyassigned into early UF (n = 40) or torasemide plus tolvaptan (n = 60) groups. Criteria of inclusion were acutely decompensated HF patients of age more than 18 years old and who had 1 or more sign of congestion (lung rales on auscultation, chest X ray documenting pulmonary congestion, congestive hepatomegaly and/or ascites, jugular venous pulse > 10 cm; lower limb edema, B-type NP > 400 pg/mL). Primary and secondary efficacy endpoint were increase in urine output, weight loss, reduction of dyspnea and brain natriuretic peptide; each endpoint reached statistical significance[49].

In conclusion, Table 2 summarize the different RCTs designs and outcomes.

PATIENT SELECTION CRITERIA ACCORDING TO THE LITERATURE

Given current data, it has not been yet clearly defined which subpopulation of patients suffering from acute HF refractory to diuretic therapy can benefit from UF. The conflicting results from UF studies highlight that patient selection and fluid removal targets are not completely understood.

Heterogeneity of HF patients (*e.g.*, baseline clinical characteristics, hemodynamic profile, severity of renal functional impairment), the timing and the UF protocols used in the trials contributed to these inconsistent results.

As mentioned, guidelines recommend this therapeutic option in patients with a lack of hemodynamic and laboratory response despite maximal diuretic therapy[30,31]. Unfortunately, data regarding which patients may benefit the most from this strategy are scarce.

However, despite the conflicting results of the RCTs, we can still assume some broad indications from them. According to CARRESS-HF, UF may not be useful among patients with ADHF and worsening renal function[46]. Furthermore, in contrast with all other trials, the median time from the index hospital admission (the admission qualifying the patient for enrollment in the study) to randomization was 34 h. This data reinforce the belief that a more effective UF process could be related to an earlier beginning of treatment.

From some of the trials that demonstrated an effectiveness of UF, we can suggest how continuous, or at least frequent, assessment of hemodynamic stability and fluid overload are essential prerogatives before and during the treatment[45,48].

Baseline clinical characteristics of the patient and protocol used in these trials suggest in which clinical setting UF may be used.

KNOWLEDGE GAPS, FUTURE DIRECTIONS AND ONGOING CLINICAL RESEARCH

Ultrafiltration has been principally used in decompensated HF patients as an escalation after diuretic failure or in the presence of cardiorenal syndrome. Earlier utilization of UF can expedite and maintain the compensation of acute HF by simultaneously reducing volume overload without causing intravascular volume depletion and re-establishing acid base and electrolyte balance. Despite the crucial need of alternatives to diuretics-based decongestive strategy there are still several gaps of knowledge about the correct use of UF. What clearly emerges from the literature is the lack of strong evidences able to support the routine use of UF as first and early step of treatment whereas the overall potential and beneficial effect remains clear.

To draw definitive conclusions, we need more data comings from new RCTs. At the moment, REVERSE-HF, a multicenter randomized controlled trial, is ongoing across the United States.

Table 2 Overview of most relevant randomized controlled trials on ultrafiltration-based decongestive therapy

RCTs	Target population	UF device	Primary and secondary endpoint	Results
RAPID-CHF (2005)	ADHF, *n* = 40	Aquadex system, 8-h course	Weight loss at 24 h of treatment (Primary endpoint); Volume removal after 24 h	Weight reduction resulted not statistically significant (P = 0.24); Volume removal was significantly more in UF arm (P < 0.001)
UNLOAD (2007)	ADHF, *n* = 200	Aquadex System, Mean fluid removal rate 241 mL/h	Weight loss at 48 h; Dyspnea score at 48 h	Weight loss resulted significantly increased in UF arm (P < 0.001), whereas there were no differences between groups in Dyspnea score (P = 0.588)
ULTRADISCO (2011)	ADHF, *n* = 30	PRISMA, treatment duration 46 h	Changes in hemodynamics assessed using PRAM: SVi, CI, CPO, SVR were measured during hospitalization, at discharge, and at 1 and 3-mo follow-up	UF arm as compare to standard care had a significant improvement of global hemodynamic status
CARRESS-HF (2012)	ADHF, *n* = 188; Recent increase in serum creatinin >/= 0.3 mg/dL	Aquadex System at a fixed rate of 200 mL/h	Bivariate changes in sCr and change in weight 96 h after randomization	
CUORE (2014)	ADHF, LVEF </=40%, *n* = 56	Dedyca system	HF rehospitalization at 1 yr	UF arm has a significant lower endpoint incidence (P = 0.002)
AVOID-HF (2016)	ADHF, *n* = 224	Aquadex system at an ajdusted rate on a per protocol established basis	Time to first HF event (HF rehospitalization or unscheduled outpatient or emergency treatment with intravenous loop diuretic agents or UF) within 90 days of hospital discharge	30-d HF rehospitalizations: 11 of 2876 (UF arm) *vs* 24 of 2882 (diuretics arm), P = 0.06
Hu *et al*[49], 2021	ADHF, *n* = 100	FQ-16 type HF ultrafiltration dehydration device (Beijing Hartcare Medical Technology Co., Ltd)	Weight loss and an increase in urine output on days 4 and 8 of treatment; Secondary outcome evaluated: BNP, NYHA class, IVC collapse index, JVP	Early ultrafiltration group had a significantly greater weight loss (P < 0.001) than the torasemide + tolvaptan group and urine increase (P < 0.001); Secondary outcomes that were followed up demonstated a clear trend towards benefits of UF as compared to diuretics arm

ADHF: Acutely decompensated heart failure; BNP: Brain natriuretic peptide; CI: Cardiac index; CPO: Cardiac power output; IVC: Inferior vena cava; JVP: Jugular venous pressure; HF: Heart failure; NYHA: New York Heart association; PRAM: Pressure Recording Analytical Method; sCr: Serum creatinine; SVi: Stroke volume indexed; SVR: Systemic vascular resistance; UF: Ultrafiltration; RCT: Randomized clinical trial.

An important target of decongestive therapies to achieve is the so-called dry weight; however, the best way to assess fluid status and dry weight is still a matter of debate.

POCUS can, potentially, be a helpful tool for a quick and objective fluid status assessment. There are several echographic markers of the high pressures associated with congestive process, as described above, which have been proposed[50].

However, there is still a paucity of combined POCUS scoring systems able to predict adverse outcomes of patients with clinical and laboratoristic signs of congestion. One of the proposed scoring systems is Venous Excess Ultrasound grading system of the severity of venous congestion[51].

Bioelectrical impedance (BIA) is, also, an attractive non-invasive method for assessing the total body water. Measurements of bioimpedance vector require 2 pairs of electrodes to be placed on the wrist and ankles. This method, potentially, could help the physician to guide the reduction of patient's fluid overload as showed in some trials[52].

Several authors have investigated if an objective tool such as BIA is better than clinical findings for guiding UF in hemodialysis patients. As a result of several RCTs, BIA-based interventions in hemodialysis patients for correction of overhydration have little to no effect on all-cause mortality, whereas BIA improved systolic blood pressure control. These results should be interpreted with caution as the size and power of the studies are low. Further studies, larger or with a longer follow-up period, should be performed to better describe the effect of BIA-based strategies on survival[53].

In a study by Hanna *et al*[54], they proposed that a protocol driven-UF with invasive PCWP as hemodynamic parameter can guide the physician for a safe and effective interruption of ultrafiltrative system, reaching the goal of sustained value </= 18 mmHg for more than 4 h.

The use of biomarkers able to show acute kidney injury can help physician to assess fluid status and guide decongestion. At the state of art, serum creatinine is the sole biomarker used in daily practice to guide fluid removal. However, serum creatinine can be elevated also in the context of volume depletion without acute tubular damage. Conversely, this parameter can be normal in documented tubular injury due to the delayed achievement of detectable changes of this analyte. It is therefore evident that we need to undercover new useful biomarkers able to be more specific for kidney damage. Neutrophil gelatinase-associated lipocalin (NGAL) attracts as a newly more specific biomarker of acute kidney

injury; NGAL is not elevated in case of volume depletion as serum creatinine. In vitro studies found other genes expressed only after brief dose of ischemia as kidney injury molecule-1, tissue inhibitor of metalloproteinase-1, and clusterin, although none of these genes were expressed after volume depletion, despite the rise in serum creatinine in both models[55].

CONCLUSION

In conclusion, ultrafiltration represents an attractive alternative to pharmacologic therapy. More long-term data about safety, incidence of rehospitalization for HF and cost-effectiveness are crucial to definitely allocate this treatment also as a main option. Furthermore, we need more comprehensive and non-invasive tools to guide physicians in the fluid status management of congested patients.

FOOTNOTES

Author contributions: All authors have made contributions to conception and design of this review, engaged in preparing the article or revising it analytically for essential intellectual content, gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Conflict-of-interest statement: The authors declare no conflict of interest regarding this article.

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S-Editor: Wang JL
L-Editor: A
P-Editor: Yu HG

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2023 May 26; 15(5): 217-228

DOI: 10.4330/wjc.v15.i5.217

ISSN 1949-8462 (online)

MINIREVIEWS

Acute heart failure as an adverse event of tumor necrosis factor inhibitor therapy in inflammatory bowel disease: A review of the literature

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Wang LH, China; Wen XL, China; Wu SC, China

Received: January 16, 2023
Peer-review started: January 16, 2023
First decision: January 30, 2023
Revised: February 9, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: May 26, 2023

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Abstract

Tumor necrosis factor inhibitors (anti-TNFs) are widely used therapies for the treatment of inflammatory bowel diseases (IBD); however, their administration is not risk-free. Heart failure (HF), although rare, is a potential adverse event related to administration of these medications. However, the exact mechanism of development of HF remains obscure. TNFα is found in both healthy and damaged hearts. Its effects are concentration- and receptor-dependent, promoting either cardio-protection or cardiomyocyte apoptosis. Experimental rat models with TNF α receptor knockout showed increased survival rates, less reactive oxygen species formation, and improved diastolic left ventricle pressure. However, clinical trials employing anti-TNF therapy to treat HF had disappointing results, suggesting abolishment of the cardioprotective properties of TNFα, making cardiomyocytes susceptible to apoptosis and oxidation. Thus, patients with IBD who have risk factors should be screened for HF before initiating anti-TNF therapy. This review aims to discuss adverse events associated with the administration of anti-TNF therapy, with a focus on HF, and propose some approaches to avoid cardiac adverse events in patients with IBD.

Key Words: Tumor necrosis factor inhibitors; Inflammatory bowel disease; Heart failure; Adverse event; TNFα receptor

Core Tip: Tumor necrosis factor inhibitors (anti-TNFs) are widely used for the treatment of inflammatory bowel diseases (IBD). However, heart failure, although rare, is an adverse event associated with the use of anti-TNFs in these patients. This review discusses the adverse events, especially heart failure, associated with the administration of anti-TNF therapy. We believe that our study makes a significant contribution to the literature because it discusses the current understanding in the field and proposes approaches to avoid the occurrence of adverse events due to anti-TNFs in patients with IBD.

Citation: Grillo TG, Silveira CFDSMP, Quaglio AEV, Dutra RM, Baima JP, Bazan SGZ, Sassaki LY. Acute heart failure as an adverse event of tumor necrosis factor inhibitor therapy in inflammatory bowel disease: A review of the literature. *World J Cardiol* 2023; 15(5): 217-228
URL: https://www.wjgnet.com/1949-8462/full/v15/i5/217.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i5.217

INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), presents with chronic and progressive intestinal inflammation with periods of remission and activity, affecting mainly young people, with a peak of incidence between the third and fourth decades of life[1]. The etiopathology of IBD is poorly established, but it is believed to be related to an inappropriate inflammatory response to gut microbes in predisposed individuals[2]. There is still no curative therapy for IBD. Thus, treatment aims to alleviate symptoms, restore quality of life, and delay the progression and development of complications[3]. The choice of therapy depends on the location, activity, and severity of the disease, along with previous response to therapy and presence of complications. Evaluation of individual patient characteristics and the cost/benefit ratio of medications are also considered[4]. The therapeutic arsenal currently includes aminosalicylates (mesalazine and sulfasalazine); local and systemic corticosteroids (budesonide, prednisone, methylprednisolone, and hydrocortisone); immunosuppressants (azathioprine and 6-mercaptopurine); JAK inhibitors (tofacitinib); and biological therapies such as tumor necrosis factor inhibitors (anti-TNFs; infliximab, adalimumab, certolizumab pegol, and golimumab), anti-integrin antibody (vedolizumab), and anti-IL-12/23 antibody (ustekinumab)[4]. As anti-TNFs are widely used therapies, their adverse effects should be recognized in a timely manner to avoid patient morbidity and mortality. They are administered for the induction and maintenance of therapy in patients who fail to respond to conventional therapy. Infliximab, adalimumab, and certolizumab pegol are approved for use in CD. and infliximab, adalimumab, and golimumab, in UC[4]. Contraindications to their use include active infection, demyelinating disease, cancer, and heart failure (HF) [absolute in the New York Heart Association (NYHA) functional classification III–IV][5]. This review aims to discuss adverse events due to the use of anti-TNF therapy, with a focus on HF. Additionally, we performed a literature review on cases of HF secondary to the use of anti-TNFs in patients with IBD.

ADVERSE EVENTS WITH USE OF ANTI-TNF THERAPY

Infliximab is a human–mouse chimeric monoclonal antibody administered intravenously. Adalimumab and golimumab are fully humanized monoclonal antibodies that are injected subcutaneously. Certolizumab pegol is a conjugated Fab antibody fragment administered subcutaneously. In CD, anti-TNFs (infliximab, adalimumab, and certolizumab pegol) are indicated for inducing remission in moderate-to-severe disease with inadequate response or intolerance to conventional therapy (steroids and/or thiopurines). They are effective in patients who are biological therapy-naive and biological therapy-refractive. Patients who achieved remission with anti-TNF agents need to continue the maintenance treatment. The effects of suspending anti-TNF therapy after long-term remission are not established; therefore, the decision must be individualized. In cases of complex perianal fistulas, the use of infliximab or adalimumab is recommended for induction and maintenance[4]. In UC, anti-TNFs are recommended in cases of moderate-to-severe active colitis, along with adalimumab, golimumab, or infliximab for inducing remission[6]. These drugs are recommended as maintenance therapy with or without thiopurines in patients who attained remission. In severe acute colitis refractory to intravenous steroids, infliximab may be a therapeutic rescue therapy[6,7]. Hypersensitivity reactions are among the most common adverse events with administration of anti-TNFs; they are either acute (during or within 24 h of the infusion) or delayed (24 h to 14 d after the infusion)[8]. The acute reactions are rapid in approximately 2% of the reactions, but < 1% lead to a severe reaction[9]. The presence of antibodies against infliximab increases the risk of infusion reactions[10], and case studies suggest that hypersensitivity to adalimumab is also due to the presence of anti-drug antibodies[11].

Neutropenia, thrombocytopenia, and anemia are also observed. Neutropenia may occur due to a blockade of TNFα (regulates proinflammatory factors involved in the differentiation and maturation of hematopoietic progenitor cells) that may mediate marrow failure due to inhibition of stem cell differentiation[12,13]. Isolated thrombocytopenia after administration of anti-TNF therapy has been reported by Salar *et al*[14] in 2007 and Casanova *et al*[15] in 2012, respectively; however, the cause/effect mechanism remains unclear. It may be related to autoimmune platelet destruction secondary to antiplatelet antibodies, immune complexes, or an idiosyncratic reaction. Anemia related to the use of anti-TNF remains debatable. Some studies have reported aplastic anemia due to administration of infliximab in rheumatoid arthritis[16] and infliximab-induced autoimmune hemolytic anemia[17].

Further, dermatological manifestations, such as eczema, psoriasis, infections, acne, dermatitis, and other erythema, are also reported. Psoriasis is a common adverse effect of anti-TNF therapy, occurring in approximately 1.5%–5% of the patients, mostly women, within an average of 2–6 mo after starting the therapy[18,19]. Autoimmune disorders, such as lupus-like syndrome, vasculitis, antiphospholipid syndrome, sarcoidosis, interstitial lung disease, optic neuritis, inflammatory eye disease, central nervous system demyelination, and peripheral neuropathies, are also reported[20]. Demyelination may occur, but it is unclear whether there is a causal relationship[21]. As anti-TNFs are immunosuppressive agents, they can increase the risk of infections of bacterial, viral, or fungal origin. Uncommon infections, such as listeriosis, have also been linked to the administration of anti-TNF therapy, with a higher risk in the first year of therapy[22,23]. Anti-TNFs can reactivate latent tuberculosis in immunocompromised individuals, emphasizing the importance of screening with clinical history, chest X-rays, and tuberculin tests before initiation of the therapy[24,25]. A high risk of infection with varicella zoster virus is observed in patients with IBD, and those receiving anti-TNF have a high risk of herpes zoster[26]. However, screening for a herpes virus infection is not required before the initiation of therapy[25]. Hepatitis B virus reactivation can also occur during anti-TNF therapy or after its withdrawal[27]. In the case of hepatitis C, biological agents do not present with a contraindication during concomitant infection and have a good safety profile; however, they are contraindicated in acute infections[28]. In patients with human immunodeficiency virus (HIV) infection, the risk/benefit of administering anti-TNFs should be weighed due to the increased risk of opportunistic infections[29]. Screening for hepatitis B and C viruses and HIV with serological tests is also recommended[25]. The possibility of cytomegalovirus infection recurrence by reactivation of latent infection is low after the use of biological therapy in most cases[8]. Screening before therapy is not required[25]. Fungal infections related to anti-TNF use are also reported, particularly in those with risk factors, such as opioid use, leukopenia, advanced age, and more severe disease[30]. The blocking of TNFα possibly alters the cytotoxic immune response to fungal infections[31]. Warris *et al*[32] reported a case of pulmonary aspergillosis in a patient with CD receiving infliximab. Histoplasmosis was also reported in a case series by Lee *et al*[33] after infliximab infusions in immunocompromised patients.

Malignancies (mainly non-melanoma skin cancer, melanoma, and lymphomas) are reported in patients with IBD due to chronic intestinal inflammation and the carcinogenic effects of immunosuppressive drugs[8,34,35]. TNF can trigger apoptosis by activating caspases, and its inhibition can lead to growth and/or metastases and tumor recurrence[36]. However, whether the use of anti-TNF monotherapy increases the overall risk of cancer in patients with IBD remains unclear[37]. Studies conducted by Biancone *et al*[38,39], Caspersen *et al*[40], and Fidder *et al*[41] failed to observe an increased risk of lymphoma, leukemia, or other hematologic malignancies with the use of anti-TNF monotherapy. Cardiovascular effects have also been reported, including HF, as discussed below.

HEART FAILURE

HF is a clinical syndrome secondary to the inability of the heart to pump sufficient blood to supply peripheral metabolic demands or to do so under increased filling pressures. Acute HF (AHF) has been increasingly described as a condition with unique pathophysiology, distinct from that of chronic heart failure, and is among the most common causes of hospitalization in the elderly[42]. The patients can be categorized into new-onset (*de novo)* HF and worsening chronic HF. The latter accounts for the greater number of hospitalizations. Patients with *de novo* HF may have no prior risk factors, such as in myocarditis, but more commonly have preexisting conditions that favor the development of HF, or present with structural heart diseases without overt symptoms. Those with chronic HF may have precipitating factors for decompensation, including infections, poor adherence to treatment, and medications for other comorbidities[42,43]. Data on pathophysiology of AHF suggests that, apart from the architectural changes in the left ventricle due to increasing filling pressure and activation of the renin–angiotensin–aldosterone system, the inflammatory activation plays a pathogenic role in the progression of HF due to association with increasing stiffness of the vessels that leads to HF decompensation[42-48]. Several conditions may be classified as risk factors for HF, including ischemic heart disease, hypertension, hyperlipidemia, diabetes, smoking, hypertensive heart disease, valvular heart disease, Chagas disease, congenital heart disease, and deposit diseases[49].

HF is diagnosed after thorough anamnesis, investigation of personal risk factors, family history, and current symptoms, such as dyspnea, edema of the lower extremities, orthopnea, paroxysmal night dyspnea, and palpitations[42]. The general clinical examination may indicate an increase in the respiratory rate and a decrease in oxygenation levels, edema, cachexia, and signs of poor perfusion, such as altered mental status. A detailed examination may indicate an increased jugular pulse, reflecting the increased left ventricle filling pressure, auscultation of the S3 and S4, along with mitral regurgitation murmur due to dilation of the left ventricle. The signs of pulmonary congestion include crackling sound on inspiration and dullness of the lung bases on percussion due to pleural effusion. The abdominal examination may show hepatomegaly due to an increase in central venous pressure, along with ascites due to right HF[50-52]. Patients should also be assessed using complementary tests, including renal function, levels of N-terminal-pro hormone B-type natriuretic peptide (NT-pro BNP), and electrolytes. The imaging examinations include electrocardiogram, chest radiography, and echocardiogram[53-56]. The treatment for AHF depends on whether the patient presents with congestion, low output, or both. Four hemodynamical profiles have been postulated for better organization of the medications employed in the early management of AHF, as demonstrated below and summarized in Figure 1[57,58].

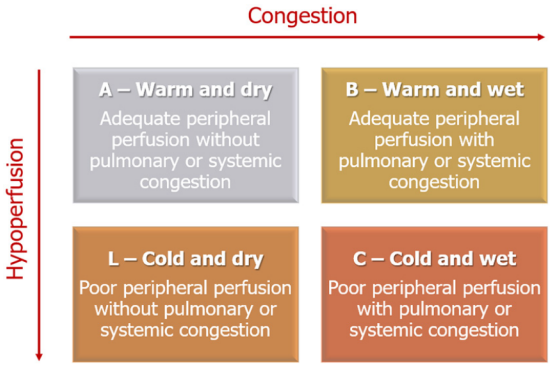
It is also important to assess patient's prognosis on admission to determine the requirement of advanced HF therapy, such as implantable cardiac devices or heart transplant[59]. Patients are considered to have worst prognosis if they are aged > 65 years; have a history of multiple hospitalizations; fail to adhere to treatment; present with functional classification NYHA III or IV; and have cachexia, syncope, sleep apnea, type II diabetes, or depression. Other factors include having had a reversed cardiac arrest; having pulmonary disease or cognitive dysfunction; having poor perfusion, congestion, tachycardia, persistent hypotension or low tolerance to exercise; having altered electrolyte levels, such as sodium < 130; having elevated BNP, troponin, or cytokines; having hemoglobin < 11 g/dL, creatine > 2.75 mg/dL, or urea 92 mg/dL; and showing atrial fibrillation in electrocardiogram, complete left bundle block, alternating T wave, long QT, low heart rate variability, progressive left ventricle dilatation, ejection fraction < 30%, right ventricle dysfunction, mitral or tricuspid regurgitation, restrictive pattern or decreased cardiac output, increase in pulmonary pressures, and peripheral vascular resistance[59].

HEART FAILURE AS AN ADVERSE EVENT OF ANTI-TNF USE

TNFα is found in both healthy and damaged hearts. Thus, it is challenging to understand its mechanisms of action. It binds to two different receptors: TNFα receptor-1 (TNFR1) and -2 (TNFR2) that are generally expressed on the heart cells[60,61]. In HF, TNFα induces β-adrenergic receptor uncoupling, increases oxidation and formation of nitric oxide, increases levels of inflammatory cytokines, and downregulates levels of contractile proteins, thus contributing to myocardial dysfunction. Long-term TNFα signaling leads to alterations in the heart geometry due to hypertrophy, apoptosis, and fibrosis [62]. The role of TNFα in HF pathophysiology is complex. Its effects are concentration-dependent and function *via* two different pathways: Survivor activating factor enhancement (SAFE) pathway functioning under low TNFα concentrations, and death-promoting pathway functioning in high TNFα concentrations. The SAFE pathway involves stimulation of other cytokines, such as cardiotrophin-1, that act on glycoprotein 130 receptor, leading to eccentric hypertrophy due to sarcomere organization in series. This pathway is observed in athletes with left ventricle hypertrophy[63-65]. In addition to the concentration of TNFα, its repercussion on the cardiac muscle depends on the receptor that it binds to as binding to TNFR1 may be cardio-damaging and binding to TNFR2 may be cardioprotective[60,66,67]. The mechanisms of HF caused by the use of anti-TNF are summarized in Figure 2.

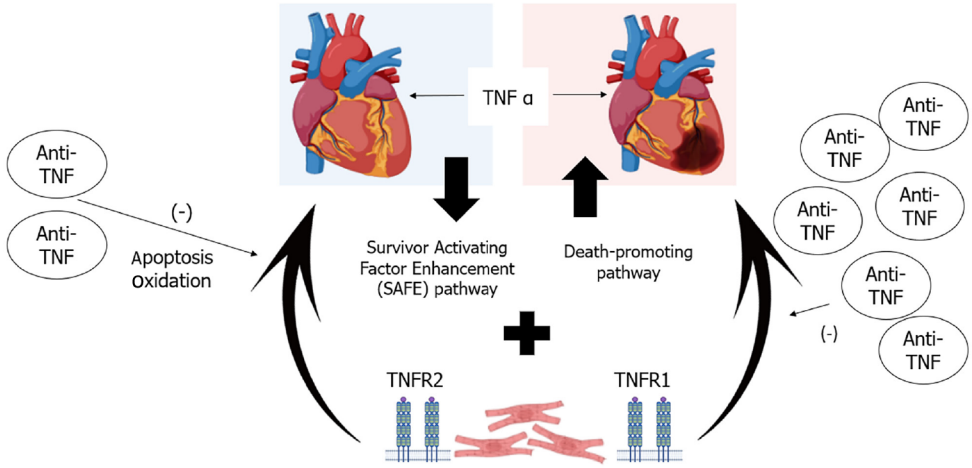
Studies with animal models have suggested that TNFR1 Levels are upregulated after myocardial infarction without change in TNFR2 Levels. Other studies showed an absence of cardio-protection in acute ischemic models of TNFR1- and TNFR2-knockout rats, suggesting the involvement of both the receptors for maintaining a healthy heart[68,69]. In another knockout model study, Hamid *et al*[70] explored the left ventricle remodeling after myocardial infarction; the study indicated that TNFR1 knockout improved the left ventricle ejection fraction, reduced left ventricle dilatation through cardiomyocyte hypertrophy and apoptosis, and also decreased fibrosis and inflammation. In contrast, knockout of TNFR2 reversed the effects, suggesting a strong protective role of TNFR2. However, knockout of both the receptors increased survival rates, reduced reactive oxygen species formation, and improved diastolic left ventricle pressure; thus, this indicated the ambivalence of role of TNFRs on the heart health[68-70]. Further, Cacciapaglia *et al*[5] developed an *in vitro* model for TNFα preconditioning, exposing the cardiac cells to a lower dose of TNFα. The results suggested that the cells developed more resistance to subsequent TNFα toxic dose exposure and conferred more protection against oxidation and apoptosis.

From animal models to human randomized control trials, the concept of cardiac detrimental effects of TNFRs inspired the studies ATTACH, RECOVER, and RENAISSANCE (the last two are combined as RENEWAL) that were designed to understand the effects of infliximab and etanercept on HF with optimized clinical treatment. The ATTACH study failed to observe improvement and, surprisingly,



DOI: 10.4330/wjc.v15.i5.217

Figure 1 Clinical profiles of acute heart failure. Patients with acute heart failure present differently at admission depending on the degree of congestion and hypoperfusion of the tissues. Such profile differentiation provides guided treatment with better outcomes.



DOI: 10.4330/wjc.v15.i5.217

Figure 2 Mechanisms of heart failure caused by the use of anti-tumor necrosis factor agents. Tumor necrosis factor (TNF)-α is found in both healthy and damaged hearts and its effects are concentration dependent *via* two pathways: The survivor activating factor enhancement pathway working at low concentrations and the death-promoting pathway working at high concentrations. In addition to the concentration, its repercussion in the muscle depends on the receptor to which TNFα-1 (TNFR1) and -2 (TNFR2) binds, with the latter being cardioprotective. Thus, it is suggested that the development/worsening of heart failure in patients using anti-TNF is due to a suppression of the cardioprotective concentration of TNFα, making cardiomyocytes susceptible to apoptosis and oxidation or also to selective cytotoxicity.

indicated worsening of HF after therapy discontinuation. The RENAISSANCE study also showed an increased hazard ratio for the worsening of HF in the treatment group than that in the control group [71]. The disappointing clinical results, along with evidence from experimental models, suggest that the current rationale for the worsening of HF while administering anti-TNFα is that the dose employed in the randomized controlled trials abolishes the cardioprotective concentration of TNFα, therefore making the cardiomyocytes susceptible to apoptosis and oxidation[5]. A consensus is lacking on whether TNFα functions as a parallel phenomenon to, and not the cause for, HF, along with a possible selective cytotoxicity of anti-TNFα on cardiomyocytes in HF[62]. A study by Chung *et al*[72] evaluated the safety of infliximab in patients (n = 150) with moderate-to-severe HF (NYHA III or IV). The patients randomly received placebo, infliximab 5 mg/kg, and infliximab 10 mg/kg at 0, 2 and 6 wk and were followed for 28 wk. There was no improvement in the clinical status of patients who received infliximab at 14 wk, and after 28 wk, there were more hospitalizations in the infliximab 10 mg/kg group (n = 20) due to worsening of the HF condition, along with adverse clinical events persisting for up to 5 mo after discontinuation of therapy. Abedin *et al*[73] reported a case of acute coronary syndrome after infliximab infusion in a patient without previous heart disease. The patient was a 49-year-old Hispanic woman with rheumatoid arthritis and previously well-controlled hypertension. She presented to the emergency department 10 min after the start of infliximab infusion (20 mg had been infused). The patient had no other risk factors and no family history of coronary artery disease.

Kwon *et al*[74] followed patients with rheumatoid arthritis, psoriatic arthritis, and CD who were treated with an anti-TNF agent (etanercept or infliximab). A total of 47 patients developed HF; of these, 81% had no previous symptoms and 19% had worsening of preexisting symptoms. Among those who

developed HF, 50% had no risk factors. The median interval between the first infusion of anti-TNF and diagnosis of HF was 3.5 mo (24 h to 24 mo). Keating *et al*[75] reported a case of anti-TNF-induced AHF. The 32-year-old patient had hypothyroidism and a bicuspid aortic valve and presented with Turner syndrome and CD. Biological therapy with adalimumab was initiated due to no response to budesonide. Examination indicated a transthoracic echocardiogram with normal ejection classification (> 55%). Eighteen weeks after administering adalimumab, the patient was admitted to the emergency department with edema and dyspnea. Further, we reported a case of AHF 6 mo after administering infliximab in a 50-year-old woman with CD and diabetes and a previous history of arterial hypertension. The patient presented with cardiac symptoms after optimization of the infliximab dose (10 mg/kg)[76]. The standard treatment is administered after diagnosis of HF due to anti-TNFα therapy. The current guidelines show evidence of the best prognosis for therapy for HF with low ejection fraction, while specific treatment for preserved ejection HF is unavailable. Treatment for low ejection fraction HF includes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitor, beta-blockers, aldosterone inhibitor, and, more recently, sodium–glucose cotransporter-2 inhibitors. Symptomatic medication includes diuretics, vasodilators, and digoxin. AHF may require intravenous administration of inotropes and vasopressors[77]. Studies have suggested that the use of anti-TNFs should be discontinued, and a new class of medication should be selected for treatment of the primary disease; these studies also highlighted a lack of specific guidelines for the management of cardiovascular disease in patients with IBD[8,78,79]. Some therapeutic options for the treatment of IBD in case of adverse reactions to anti-TNFs include Janus kinase (JAK) inhibitors (tofacitinib), anti-IL-12/23 antibody (ustekinumab), and anti-integrin antibody (vedolizumab).

Tofacitinib can be used in patients with moderate-to-severe UC who are intolerant or refractory to treatment with anti-TNFs. Despite its ease of rapid onset of action, oral administration, and low immunogenicity, it is also having risks such as venous thromboembolism and hyperlipidemia[80]. However, long-term data on adverse cardiovascular events with tofacitinib are lacking in patients with IBD, and it remains unclear whether the risk of venous thromboembolism is disease- or drug-related [79]. Ustekinumab, a monoclonal antibody, is an option in patients with CD and with moderate-to-severe UC intolerant or refractory to anti-TNFs. In IBD, the relationship of cardiovascular events in these patients is unclear[81,82]. Vedolizumab, a humanized monoclonal antibody, is also an option in patients with CD and with moderate-to-severe UC refractory or intolerant to anti-TNFs, with better outcomes in patients not treated with anti-TNFs[83,84]. Randomized and observational studies have not reported an increase in cardiovascular events in patients with IBD[85-88]; however, an increase in cerebrovascular events, such as stroke and cerebral hemorrhage, is reported[79]. The selection of the most appropriate medication in this scenario is challenging. The clinicians should carefully analyze the different medication classes available, with their safety and efficacy profiles, to define a personalized treatment strategy for each patient, considering risk factors inherent to the patient and the proposed medication, while aiming for the best outcome.

CONCLUSION

The recommendations for HF screening prior to IBD treatment with anti-TNFα drugs are lacking. Some guidelines suggest screening, while others only mention avoidance of biological drugs when a patient presents with class III/IV HF. The European Crohn's and Colitis Organization (ECCO) reports that patients with IBD have a modest increase in the risk of ischemic heart disease, especially in women; however, they have not mentioned requirement of screening tests for cardiovascular diseases before administration of biological therapy[1,4,7,89,90]. The guidelines of the American College of Gastroenterology and the Brazilian Consensus on Inflammatory Bowel Diseases have also not provided recommendations for screening these patients[6,91,92]. The guidelines of the British Society of Gastroenterology recommend that the use of anti-TNFs be contraindicated in cases of congestive HF and that screening be performed before starting treatment; however, they have no suggestions on the best strategies for screening[93]. Considering the indication of anti-TNFα drugs for other immune mediated diseases, although with a very low certainty, guidelines on rheumatoid arthritis recommend the following strategies: Inclusion of a non-TNF inhibitor in place of a TNF inhibitor for patients with NYHA class III or IV HF and also switching to a non-TNF inhibitor instead of a TNF inhibitor for patients who develop HF[94]. The stratification of patients with HF should not be challenging as a simple clinical examination is sufficient to identify patients with NYHA classes III and IV disease. However, issues arise when the patients present with severe HF and are oligosymptomatic, especially if they are not accustomed to exerting themselves on a regular basis. As patients may develop HF after pregnancy, viral infections, or alcohol abuse, yet not present with any symptoms consistent with NYHA III or IV, this makes them susceptible to underdiagnosis. Taken together, in the absence of evidence supporting heart disease screening prior to initiating anti-TNFα drugs, and considering the current availability of a low-cost, radiation-free test that can easily assess the patient's heart function, such as echocardiogram, we recommend that an initial cardiac evaluation be a part of the patients' routine care. We suggest increasing employment of an echocardiogram for diagnosing HF prior to initiating

treatment. This strategy may prevent the incidence of adverse events in patients receiving this treatment. We hope that this review highlights this topic and would encourage future studies to clarify the benefits of using HF screening tools in patients with IBD prior to the use of anti-TNF medications to control inflammatory processes and restore quality of life, without causing further damage to the patients. It is reinforced that anti-TNF therapy has changed the course of treatment for IBD and other immune-mediated diseases in recent decades, altering its progressive and disabling course. Due to the more frequent use of these therapies, concerns about safety arise, and this article reinforces the importance of studying the subject in greater depth, including investigating the role of cardiac receptors and their relationship with the appearance of adverse events in these patients. Another point worth mentioning is the need for new algorithms and protocols, especially for populations at risk, in order to avoid the unwanted effects of the prescribed therapy.

FOOTNOTES

Author contributions: Grillo TG, Silveira CFDSMP, Quaglio AEV, Dutra RM, Baima JP, and Bazan SGZ undertook the majority of the writing; Sassaki LY designed the outline and coordinated the writing of the paper; all authors revised the manuscript for important intellectual content and approved the final version.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Country/Territory of origin: Brazil

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S-Editor: Xing YX
L-Editor: Wang TQ
P-Editor: Yu HG

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World Journal of Cardiology

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World J Cardiol 2023 May 26; 15(5): 229-243

DOI: 10.4330/wjc.v15.i5.229

ISSN 1949-8462 (online)

MINIREVIEWS

Atrial fibrillation and coronary artery disease: An integrative review focusing on therapeutic implications of this relationship

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Berezin AE, Ukraine; Patoulias D, Greece

Received: February 4, 2023
Peer-review started: February 4, 2023
First decision: February 20, 2023
Revised: March 5, 2023
Accepted: May 6, 2023
Article in press: May 6, 2023
Published online: May 26, 2023

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Abstract

The incidence of both atrial fibrillation (AF) and coronary artery disease (CAD) increases with advancing age. They share common risk factors and very often coexist. Evidence points to an intricate relationship between atrial tissue excitability and neuronal remodeling with ischemia at the microcirculatory level. In this review, we delineated this complex relationship, identified a common theme between the two, and discussed how the knowledge of this relationship translates into a positive and meaningful impact in patient management. Recent research indicates a high prevalence of CAD among AF patients undergoing coronary angiography. Further, the incidence of AF is much higher in those suffering from CAD compared to age-matched adults without CAD underlying this reciprocal relationship. CAD adversely affects AF by promoting progression *via* re-entry and increasing excitability of atrial tissue as a result of ischemia and electrical inhomogeneity. AF in turn accelerates atherosclerosis *via* endothelial dysfunctional and inflammation and together with enhanced thrombogenicity and hypercoagulability contribute to micro and macrothrombi throughout cardiovascular system. In a nutshell, the two form a vicious cycle wherein one disease promotes the other. Most AF recommendations focuses on rate/rhythm control and prevention of thromboembolism. Very few studies have discussed the importance of unmasking coexistent CAD and how the treatment of underlying ischemia will impact the burden of AF in these patients. Inflammation and endothelial dysfunction remain central to both disease processes and form a handsome therapeutic target in the management of the two diseases. The

relationship between AF and CAD is complex and much more than mere coincidence. The two diseases share common risk factor and pathophysiology. Hence, it is impractical to treat them in isolation. Accordingly, we share the implications of managing underlying ischemia and inflammation to positively impact and improve quality of life among AF patients.

Key Words: Atrial fibrillation; Coronary artery disease; Antithrombotic therapy; Ischemia; Early rhythm control; Endothelial dysfunction

Core Tip: Evidence points to an intricate relationship between atrial tissue excitability and neuronal remodeling with ischemia at the microcirculatory level. In this review, we delineated this complex relationship, identified a common theme between the two, and discussed how the knowledge of this relationship translates into a positive and meaningful impact on patient management.

Citation: Batta A, Hatwal J, Batta A, Verma S, Sharma YP. Atrial fibrillation and coronary artery disease: An integrative review focusing on therapeutic implications of this relationship. *World J Cardiol* 2023; 15(5): 229-243
URL: https://www.wjgnet.com/1949-8462/full/v15/i5/229.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i5.229

INTRODUCTION

Cardiovascular diseases including coronary artery disease (CAD) and atrial fibrillation (AF) along with other cardiovascular diseases remain the leading cause of morbidity and mortality worldwide[1]. The prevalence of both CAD and AF increases with advancing age and they often coexist[2-5]. However, this relationship is not a mere coincidence and recent evidence points to the intricate relationship between the two. Dedicated studies have demonstrated a high prevalence of CAD among nonvalvular AF patients, with majority of AF (> 50%) patients having underlying CAD as identified by invasive or computed tomography coronary angiography[5-7]. This is significantly higher than the prevalence of CAD in the general population, which is estimated to be about 12%-14%. Furthermore, there is abundant evidence that AF is an independent risk factor for CAD and incident acute coronary syndromes[4,8,9]. The interrelationship of the two is further highlighted by the fact that the people with coexistent AF and CAD have a more severe CAD and higher SYNTAX scores compared to those without AF[8,10]. Also, the morbidity and mortality is significantly higher when CAD is associated with paroxysmal or persistent AF with increased odds for developing heart failure, ventricular arrythmias, and major adverse cardio-cerebro vascular events (MACCEs)[4,8-10]. However, despite the obvious association, this relationship is also influenced by a number of confounding risk factors such as diabetes, hypertension, age, and obesity which are common to both CAD and AF. Hence, this leads to confusion in establishing causality and reverse causality solely based on the results from registries and observational studies.

A recent mendelian randomization study by Yan *et al*[4] shed important light on this relationship and concluded beyond doubt that CAD is an independent risk factor for AF after removing all bias. Furthermore, they made an argument that treatment and prevention of AF is crucial to prevent MACCE among CAD patients[4]. Hence, the two might be more closely related than thought, and logically the therapeutic strategies are expected to be similar as well.

PATHOPHYSIOLOGICAL BASIS OF THE RELATIONSHIP

The basic pathology in CAD is the formation and progression of atherosclerotic plaques in coronary arteries leading to narrowing and resultant myocardial ischemia. Indeed, this process is identical in other vascular beds involved by atherosclerotic process and manifests as variable clinical presentation depending on the vasculature involved. In the heart, the same can manifest as acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) depending upon the progression and stability of the atherosclerotic plaques. The major pathophysiological pathways involved in initiation and progression of AF include re-entry and focal ectopic activity. The re-entry is in turn promoted by the short refractoriness, slowed conduction, and atrial remodeling as a result of atrial dilatation. The enhanced automaticity of the atrial tissue stems from the enhanced early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs)[9,11].

Common risk factors

The two diseases share identical risk factors, which trigger varied pathophysiological responses culminating in either or both of the two diseases. Diabetes mellitus (DM), hypertension, advancing age, dyslipidemia, obesity, smoking, and decreased physical activity are the major risk factors for CAD as per abundant evidence in the scientific literature. Indeed, these very same risk factors remain the most commonly implicated factors responsible for the initiation and progression of AF[8,9,11,12]. The interplay of the various risk factors and their role in the pathogenesis of AF and CAD have been demonstrated in Figure 1.

DM particularly in the setting of poorly controlled blood sugars is a major risk factor for initiation of AF. Research has shown a consistent positive correlation between increasing hemoglobin A1C and AF burden. The most popular hypothesis for this association is the structural alteration and fibrosis in atrial myocardium as a result of inflammation, endothelial dysfunction, formation of reactive oxygen intermediates, and deposition of advanced glycation end products[13,14]. All of these to a large extent result in microvascular dysfunction and atrial tissue hypoxemia. Prolonged action potential duration secondary to ischemia pave the way for EADs and DADs. Often there is coexistent autonomic neuropathy and dysfunction in DM, which together with altered calcium (Ca^{2+}) and I_{na} homeostasis contributes to the progression of AF[15].

Hypertension remains the most common risk factor for both AF and CAD. It increases the risk of development of AF by more than 30% for any given age[16]. Left ventricular hypertrophy and subsequent diastolic dysfunction in longstanding hypertension contributes to atrial dilatation and dysfunction. Furthermore, alterations in the renin angiotensin aldosterone system along with the increased expression of pro-inflammatory cytokines induce atrial fibrosis[17,18]. The net result of these pathogenic mechanisms is the development of focal aberrant ectopic firing due to altered Ca^{2+} homeostasis and the development of re-entry circuits along clinical or subclinical fibrosis in atrial myocardium[19].

Obesity is often associated with other cardiovascular comorbidities, which contribute to enhanced overall MACCE risk. In addition, many advocate that obesity is an inflammatory disease process characterized by increased expression of various pro-inflammatory cytokines and resultant endothelial dysfunction. This often correlates with increased left atrial volume and fibrosis, which have a pathogenic role in the development of AF[20]. According to certain estimates, the risk of AF increases in a linear fashion with increasing body mass index (BMI) and roughly a 1 kg/m^2 increase in BMI confers a 4% increased risk of developing AF[9,21].

Positive feedback cycle

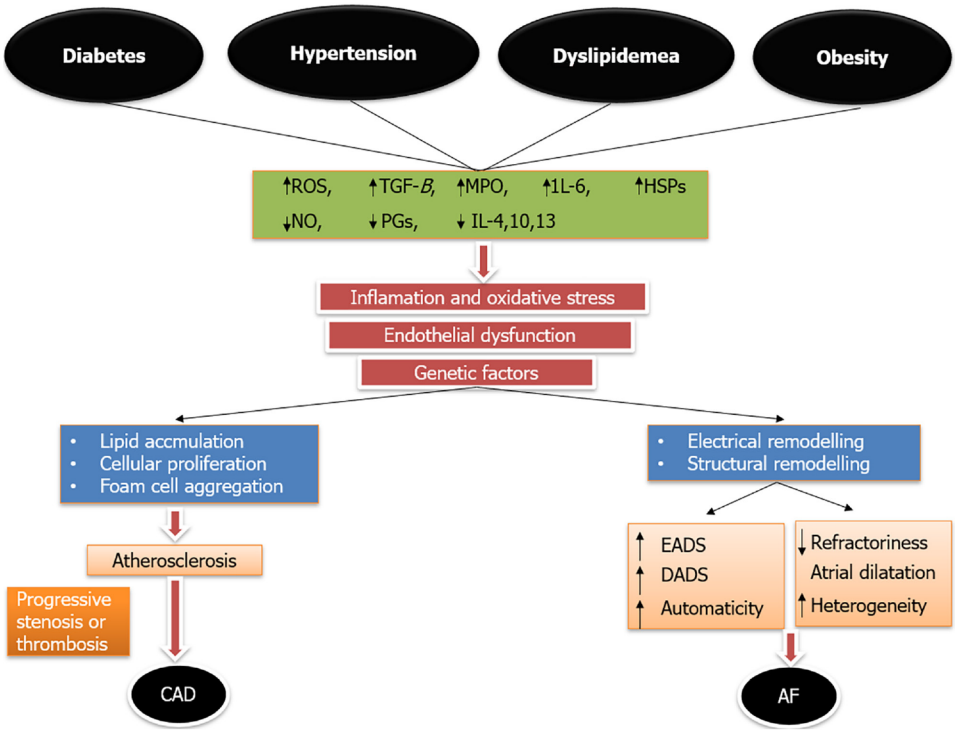
Besides sharing common risk factors, CAD and AF by themselves have a direct relationship with each other. A positive feedback mechanism between the two, culminates in a vicious cycle resulting in increased the burden of the two diseases. CAD comprising both macrovascular and microvascular disease leads to ischemia of the atrial tissue which precedes local inflammation and culminates in fibrosis and prolonged conduction times, all of which trigger the three principle mechanisms involved in the pathogenesis of AF which are focal ectopy, re-entry and neural alteration. In addition, there is heterogeneity in the electrical conduction, altered Ca^{2+} and sodium currents, and autonomic system dysregulation, all of which promote the progression and persistence of AF[4,8,9,11,12,22,23] (Figure 2).

On the other end, AF by itself can induce the two key pathogenic mechanisms involved in CAD, namely endothelial dysfunction and inflammation. Decreased release of nitric oxide coupled with increased expression of von Willebrand factor is the key pathogenic process in endothelial dysfunction [9,11,17]. AF also triggers systemic and myocardial inflammation by virtue of enhancing expression of protease-activated receptors and inflammatory cytokines, which not only initiate atherosclerotic process but also contribute to plaque instability and resultant ACS. Besides this, the beat-beat variability resulting in inefficient contractility and reduced cardiac output also contribute to reduced coronary blood flow and resultant ischemia independent of atherosclerotic CAD. Coagulation system activation coupled with enhanced platelet activity due to increased expression of p-selectin and cluster of differentiation 63 (CD63) on endothelial cells leads to micro and macro thrombi, which not only increases the risk of cerebrovascular accident but also ACS[24-26] (Figure 3).

The two more often than not coexist and together they confer worse outcomes than when the two occur in isolation. When AF complicates pre-existing CCS or ACS, it leads on to higher MACCE events including stroke, heart failure, and cardiogenic shock and also doubles overall cardiovascular mortality [8,9,11,27]. Further, it complicates clinical decision making and predisposes an individual to not only increased thrombotic events but also to major bleeding events secondary to aggressive antithrombotic therapy, which is often indicated. As a result, there is a need for a comprehensive assessment and management of the two diseases in conjunction and not as separate disease entities. The two diseases more often than not are linked in their etiopathogenesis and warrant kindred treatment to break the links which propagate the two diseases.

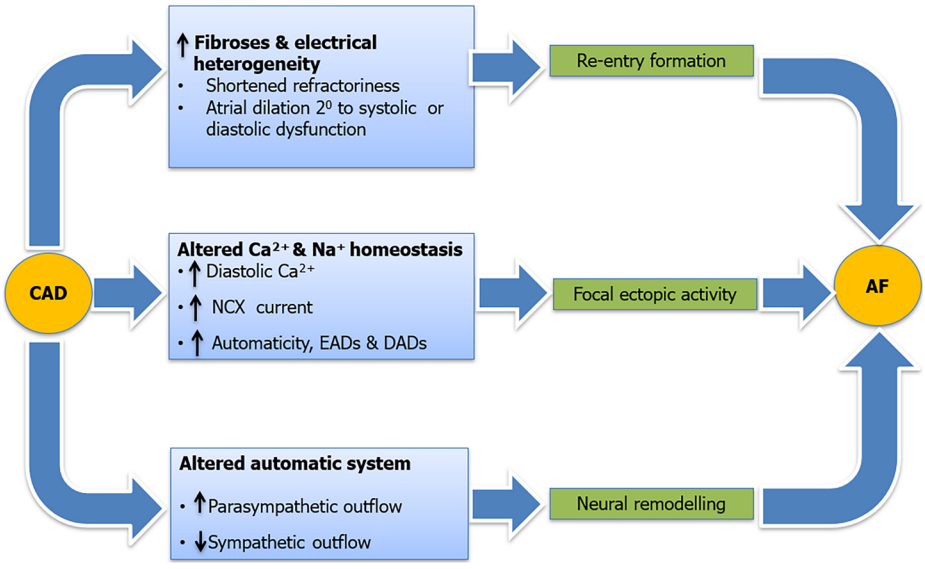
Differences in pathogenesis of AF in CAD patients compared to those without CAD

The vast majority of patients suffering from AF (> 85%) have underlying CAD or cardiovascular risk



DOI: 10.4330/wjc.v15.i5.229

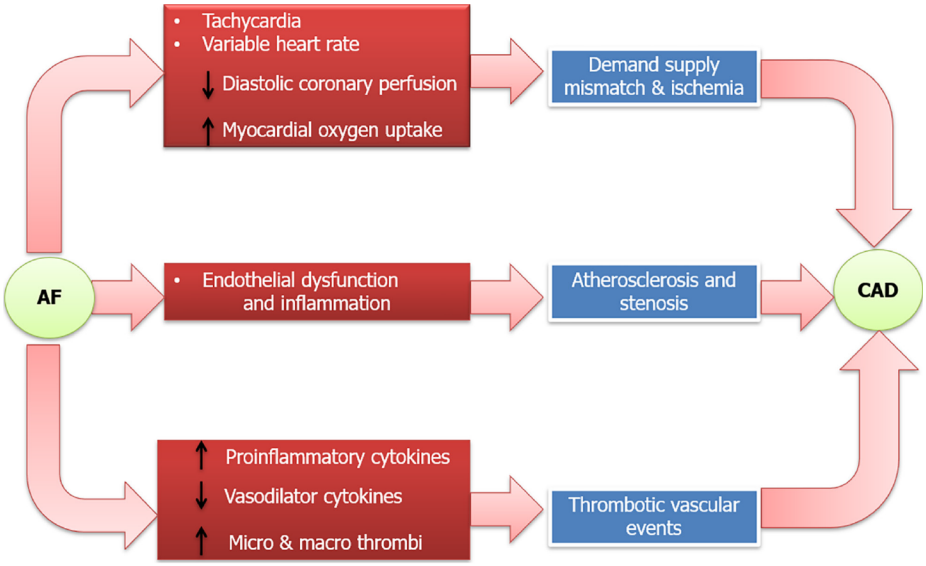
Figure 1 Interplay of various common risk factors in the pathogenesis of coronary artery disease and atrial fibrillation. Variable genetic expression manifests as varied clinical phenotype in the form of either or both atrial fibrillation and coronary artery disease in an individual. AF: Atrial fibrillation; CAD: Coronary artery disease; EAD: Early after depolarization; DAD: Delayed after depolarization; HSPs: Heat shock proteins; IL: Interleukin; MPO: Myeloperoxidase; NO: Nitric oxide; PGs: Prostaglandins; ROS: Reactive oxygen species; TGF-β: Transforming growth factor beta.



DOI: 10.4330/wjc.v15.i5.229

Figure 2 Pathogenic mechanism that predisposes an individual suffering from coronary artery disease to develop atrial fibrillation. AF: Atrial fibrillation; CAD: Coronary artery disease; NCX: Na^+/Ca^{2+} exchanger; EAD: Early after depolarization; DAD: Delayed after depolarization.

factors including hypertension, diabetes, obesity, and dyslipidemia. In less than 15% of all AF patients, none of these risk factors are present[28,29]. Most of them are relatively younger and commonly labeled as lone AF. Familial AF also contributes to a fraction of lone AF patients with well-defined chromosomal abnormalities most notably 10q22-q24[9,29]. The basic difference in the pathophysiology of AF in individuals having underlying cardiovascular risk factors and CAD predominantly is that they have structural alterations in the atrial tissue, which predispose them to develop electrical remodeling or directly lead to re-entry and ectopy culminating in AF. On the other hand, AF occurring in younger individuals without any risk factors is often attributable to the electrical remodeling as a result of



DOI: 10.4330/wjc.v15.i5.229

Figure 3 Pathogenic mechanisms that predispose an individual suffering from atrial fibrillation to develop coronary artery disease. AF: Atrial fibrillation; CAD: Coronary artery disease; NCX: Na^+/Ca^{2+} exchanger.

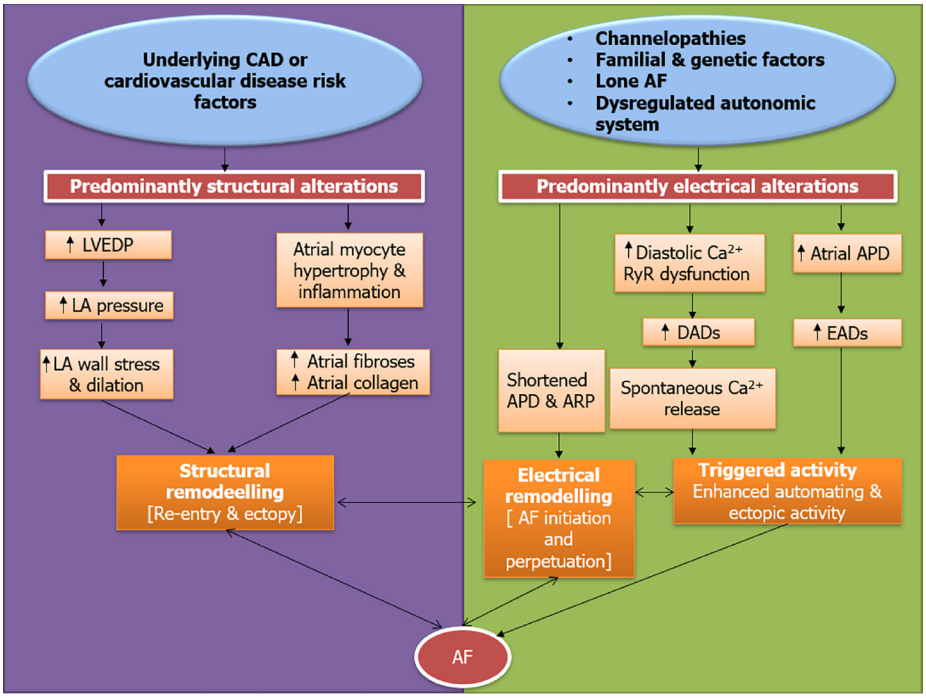
abnormal Ca^{2+} homeostasis, dysregulated ryanodine receptors, altered action potential durations, and reduced atrial refractory period. All of these culminate in changes in ion channel function, enhanced automaticity and atrial ectopy, which is a precursor to AF[28-30]. Whatever may be the initial insult, the pathways soon converge and either of the structural or the electrical remodeling ultimately aggravates the other resulting in a vicious cycle of AF initiation and progression (Figure 4). Another important difference is in the clinical presentation and outcomes. Patients with underlying cardiovascular risk factors and CAD have less symptoms related to AF, but rather commonly present with complications related to AF including heart failure or stroke. By contrast, the risk of thromboembolism is relatively lesser in the lone AF/familial AF patients, who very often present to outpatient clinics with symptoms related to AF such as recurrent palpitations or dyspnea[28,30]. Given the aggressive disease course with accelerated atherosclerosis and thromboembolism in those with underlying cardiovascular risk factors, there is a need for the aggressive control of risk factors and institution of effective antithrombotic therapies to prevent complications.

IMPLICATION ON CHA_2DS_2VASC SCORE AND STROKE RISK

A consistent pool of evidence points towards the increased burden of AF in those having coexistent CAD compared to those without CAD[8,11,27]. Furthermore, this increased duration and burden of AF translates into increased MACCE events in patients with coexistent CAD compared to those without CAD. Therefore, it makes sense that people with AF and coexistent CAD need better risk factor modification, pharmacological therapy for CAD, and more aggressive antithrombotic therapy to prevent adverse outcomes[6,31].

Among the components of the CHA_2DS_2VASc score, the symbol 'V' stands for vascular disease. The widely accepted determinants of this vascular disease as per the guidelines are prior myocardial infarction, peripheral artery disease, or the presence of an aortic plaque. Most of the current guidelines and online medical calculators thus do not account for CAD as a determinant of 'V' while calculating the CHA_2DS_2VASc score[32,33]. Therefore, this gives an impression that underlying CAD status (excluding past myocardial infarction) has no bearing on stroke risk as determined by the CHA_2DS_2VASc score.

However, in a recent, large, prospective study by Steensig *et al*[6], underlying CAD not only was very frequent among AF patients, but more importantly CAD was strongly associated with elevated thromboembolic risk beyond the usual components of the CHA_2DS_2VASc score[6]. Hence, the study made a strong case for inclusion of significant angiographically proven CAD in the 'V' component of the CHA_2DS_2VASc score to more comprehensively account for the thromboembolic risk in a given individual with AF. Indeed, this made a turning point in the approach to managing AF patients and the same was reflected in the European Society of Cardiology 2020 AF guidelines. For the first time, angiographically proven CAD was included as a determinant of in the 'V' in the CHA_2DS_2VASc score [34]. Since then, the inclusion of significant CAD has gained acceptance among practicing cardiologists as evidenced by a recent survey by the European Heart Rhythm Association, wherein 79% of the



DOI: 10.4330/wjc.v15.i5.229

Figure 4 Key differences in the pathogenesis of atrial fibrillation in patients with underlying coronary artery disease or risk factors compared to those without underlying cardiovascular risk factors. AF: Atrial fibrillation; APD: Action potential duration; ARP: Absolute refractory period; CAD: Coronary artery disease; DAD: Delayed after depolarization; EAD: Early after depolarization; LA: Left atrium; LVEDP: Left ventricular end-diastolic pressure; RyR: Ryanodine receptor.

respondents were aware of the inclusion of significant CAD and employed the same in their practice [35].

A recent study by Shi *et al*[36] shed new insights into the stroke risk in AF patients. They concluded that among AF patients with coexistent CAD, the stroke risk was not dependent on AF but on the atherosclerotic risk factors and the presence of CAD. They made a strong case for aggressive risk factor modification in particularly underlying CAD for stroke reduction in AF patients[36].

CLINICAL IMPACT OF UNDERLYING CAD ON AF

Recent evidence supports the close association of AF and CAD. Not only does underlying CAD increase the odds of developing AF but it also has significant therapeutic and clinical implications. Consistent literature points towards increased MACCE in AF patients, who have underlying CAD compared to those without underlying CAD. Furthermore, complexity in administering appropriate antithrombotic regimen is a challenge and it predisposes an individual to increased minor and major bleeding events. Hence, given the significant therapeutic and prognostic implications of CAD on AF, a more holistic and balanced approach is needed while managing the two diseases, as it is impractical to treat either one in isolation. Table 1 highlights the prominent studies over the last three decades, which have analyzed the clinical impact of underlying CAD in AF patients[6,36-44]. Consistently, underlying CAD in AF patients has been shown to correlate positively with worse overall outcomes.

"COMBINED APPROACH" TO REDUCING THE BURDEN OF THE TWO DISEASES

A recent article by Fanaroff *et al*[27] and the accompanying editorial nicely summarize the impact of coexistent AF and CAD on various clinical endpoints[27,45]. The main theme of the paper was the heightened thrombogenicity when the two occur together and authors concluded that the downstream risk of recurrent ACS and percutaneous coronary intervention (PCI) was extremely high in these group of patients compared to when they occurred in isolation. While they focused on only one and a very important aspect of this relationship, others have gone beyond the antithrombotic therapy. Another very relevant aspect is the enhanced atherogenicity throughout the systemic vasculature, which has been well documented in literature and elaborated upon in this review. The coexistence of the two sets in motion a vicious cycle that culminates in accelerated atherosclerosis and its various clinical manifest-

Table 1 Prominent studies over the last three decades highlighting the clinical impact of underlying coronary artery disease in patients suffering from atrial fibrillation

Ref.	Year	Type of study	Number of patients	Principal findings and comment
Petersen *et al*[37]	1990	Double blind RCT	516	Active angina was the only independent predictor of stroke on multivariate analysis [OR of 3.3 (95%CI: 1.3-8.9, P = 0.02)]
Ezekowitz *et al*[38]	1995	RCT	516	Active angina was an independent predictor of silent brain infarctions (15% *vs* 5% in those without angina; P = 0.02)
Van Walraven *et al*[39]	2003	Metanalysis of 6 RCTs	2501	Observed rate of stroke or TIAs was 3-fold higher in group with history of angina (5.6 *vs* 1.4 events/100 patient years; P = 0.002)
Goto *et al*[40]	2008	Observational cohort study	63589	MACCE events were consistently higher at 12 mo in AF patients with concomitant CAD compared to those without CAD (19.70 *vs* 14.52; P < 0.05)
Olesen *et al*[41]	2012	Registry based cohort study	87202	Stroke risk significantly higher in AF patients who had underlying CAD or past history of MI [HR of 1.14 (1.03-1.27)]
Rasmussen *et al*[42]	2011	Observational cohort study	3315	Risk of stroke or death significantly higher among those with underlying CAD [HR of 1.99 (1.46-2.72)]
Anandasundaram *et al*[43]	2013	Systematic review of 19 observational studies	6465	Atherosclerotic vascular disease was a significant independent predictor of stroke, thromboembolism and mortality in AF patients (P < 0.05)
Steensig *et al*[44]	2018	Prospective cohort study	12690	CAD was independently associated with increased risk of ischemic stroke in AF patients. Concomitant CAD increased stroke risk by 29% compared to AF patients without CAD [crude IRR of 1.62; (1.41-1.87)]
Steensig *et al*[6]	2018	Observational cohort study	96430	CAD was an independent predictor of composite endpoints [adjusted IRR, 1.25; (1.06-1.47)] over and above the usual components of vascular disease in CHA_2DS_2 VASC score
Shi *et al*[36]	2021	Observational cohort study	2335	Risk of stroke was more dependent on underlying atherosclerotic risk factors than AF per say (P < 0.001)

AF: Atrial fibrillation; CAD: Coronary artery disease; CI: Confidence interval; HR: Hazard ratio; IRR: Incidence rate ratio; MACCE: Major adverse cardio-cerebro vascular event; MI: Myocardial infarction; OR: Odds ratio; RCT: Randomized control trial; TIA: Transient ischemic attack.

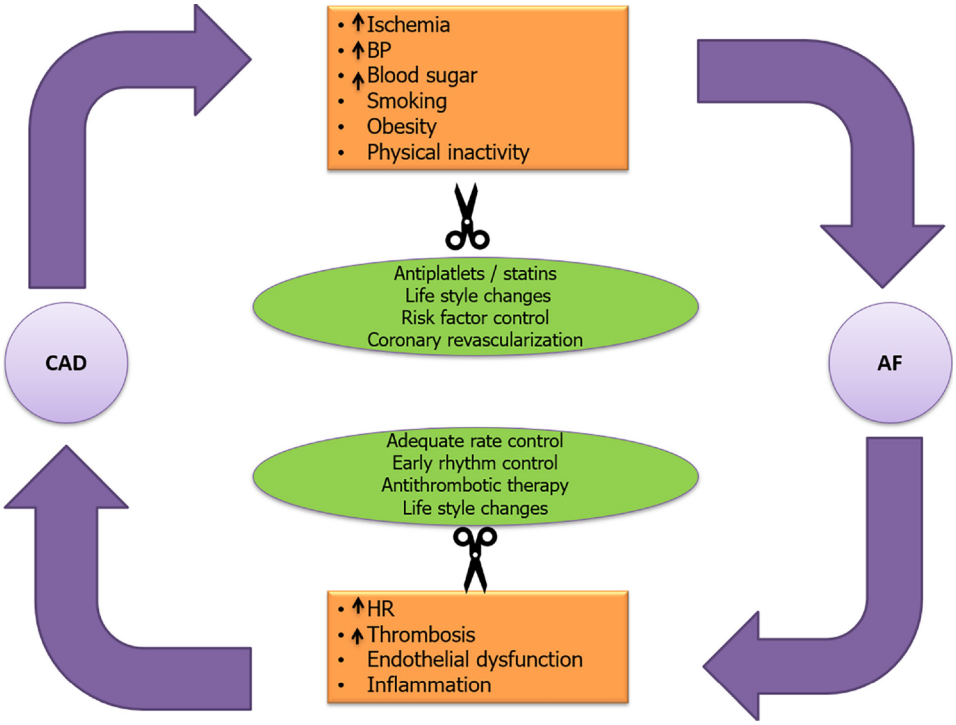
ations[9,28,30]. Besides the increased thrombogenicity and atherogenicity conferred as a result of the coexistence of the two diseases, there is a direct relationship of one with the other disease. Such that, one disease can directly lead to the other and vice versa (Figures 2 and 3). Hence, targeting and breaking the common links between the two makes sense and should be considered in any individual suffering from either of the two diseases (Figure 5).

THERAPEUTIC STRATEGIES FOR DISRUPTING THE VICIOUS CYCLE

Similar to all cardiovascular diseases, the prevention starts with risk factor control and modification right at the primary care level. Controlling the most commonly implicated risk factors including physical activity, obesity, dietary modifications with reduced intake of sweetened foods and salt, smoking cessation, blood pressure control, and management of dyslipidemia and blood sugars when altered leads to a reduction of both CAD and AF[9,11]. The optimal control of these risk factors markedly reduces ones odds of developing CAD and AF by inhibiting common initiating pathways and weakening the links between them two (Figure 5).

When one of the two diseases is diagnosed in a given individual, every attempt should be made to unmask the other disease as very often the two are associated. Coexistent CAD has been reported in more than half of AF patients in various studies[5-7,46]. Thus, diagnosing the concomitant CAD by invasive or noninvasive seems logical. This translates into optimal management of not only the masked CAD and in reducing the burden of AF but also predicts an individual's thromboembolic risk and guides optimal antithrombotic regimen[6,27]. Similarly, in those with CAD and other risk factors, the occurrence of MACCE events including stroke and heart failure should be followed by active surveillance for paroxysmal or persistent AF by appropriate rhythm monitoring tools. Unmasking paroxysmal AF guides institution of oral anticoagulants which leads to significant reduction of not only thromboembolic risk but also myocardial infarction among CAD patients.

Besides primary prevention, in those with established CAD and/or AF, the key to improve outcomes is simultaneous and optimal control of both the disease. Accordingly, given the intricate relationship between the two, it is impractical to treat the two in isolation. Most therapies that reduce the burden of either of these diseases, invariably also modifies and reduces the burden of the other disease. For



DOI: 10.4330/wjc.v15.i5.229

Figure 5 Vicious cycle between coronary artery disease and atrial fibrillation that culminates in a positive feedback as a result of the connections as highlighted in the orange boxes. Strategies to break this cycle are also depicted in the green ovals. AF: Atrial fibrillation; BP: Blood pressure; CAD: Coronary artery disease; HR: Heart rate.

example, statins that are used in CAD, have been shown to reduce the incidence and burden of AF[47]. Also, therapies aimed at reducing the burden of CAD including PCI or bypass graft surgery, have shown to significantly reduce the burden of concomitant AF and improve morbidity and mortality. Likewise, therapies such as rate control in AF patients using beta blockers or calcium channel blockers also significantly reduce coronary ischemia and myocardial oxygen uptake[48].

SPECIFIC THERAPIES

Antithrombotic agents

Antithrombotic agents encompass both antiplatelet and oral anticoagulants. Both CAD and AF are characterized by heightened thrombogenicity in the blood and resultant ischemic events. This is logarithmical increase in this thrombogenicity when the two coexist. To further complicate clinical decision making, there is an increased risk of bleeding as well attributable to these antithrombotic drugs. Balancing ischemic and bleeding risk in a given patient remains the top priority and necessitates adherence to clinical practicing guidelines.

The choice of antithrombotic agents in coexistent CAD and AF depends upon the clinical status of the underlying CAD. In patients suffering from CCS and AF, the consensus is towards the use of oral anticoagulants alone, preferably using the newer oral anticoagulants (NOACs). Recent research has shown that NOACs alone fair comparably to the combination of NOACs and aspirin but with the advantage of significantly lower risk of bleeding.

The decision making in AF patients with ACS and those undergoing PCI and stenting is however complex. In patients with ACS the recommendations are combining a $P2Y_{12}$ antiplatelet agent with an oral anticoagulant (preferably NOAC over vitamin K analogues) for at least 6-12 mo after ACS and then continuing only oral anticoagulant beyond 1 year. In those undergoing PCI, the guidelines recommend triple antithrombotic therapy including aspirin, $P2Y_{12}$ agent and a NOAC for the 1st month following PCI, followed by dual therapy with a $P2Y_{12}$ agent and NOAC for 6-12 mo and continuing only a NOAC in most patients beyond the 1st year. However, despite the evidence and clear guidelines only a minority of AF and CAD patients receive optimal antithrombotic therapy largely attributable to the gaps in knowledge, fear of bleeding or physician preference rendering these patients at high risk of recurrent ischemic events[27,49,50].

Statins

Statins have emerged as one of the most important and first-line therapy for prevention and treatment of CAD. Besides its lipid-lowering effects, it has pleiotropic effects on the form of reduction in inflammation in the atherosclerotic plaques and improving plaque stability. Recent studies have shown that the early initiation of statin therapy in ACS patients help in reducing the incidence of atrial and ventricular arrythmias[47,51]. These beneficial actions are in part attributable to the improved autonomic control and improved myocardial stability. A large recent metanalysis has shown that prior statin use markedly reduced the incidence of new-onset AF after admission for ACS[47]. Hence, early statin use and adequate lipid control are essential for reducing AF burden among CAD patients.

Rate controlling and antianginal agents

Tachycardia in AF predisposes patients with underlying CAD to recurrent myocardial ischemia due to increased myocardial oxygen consumption and reduced diastolic coronary perfusion at higher heart rates. This not only translates into worse symptoms but roughly doubles the risk of ACS in this population. Hence, rate control is the initial and most crucial step in managing people with both CAD and AF. Beta blockers and nondihydropyridine calcium channel blockers are the preferred agents in this regard and the resting target heart rate is less than 110/min[9,48]. Ivabradine is ineffective in controlling heart rates in AF patients and on the contrary may even aggravate AF as was seen in the SIGNIFY trial and a recent meta-analysis[52,53]. Hence, it should be avoided in AF. Digoxin, although an effective drug in controlling the heart rates in AF patients especially those with left ventricular dysfunction, is best avoided in patients with CAD for the fear of predisposition to arrythmias and worsening myocardial ischemia due to increased myocardial oxygen consumption[48].

Among the choice of antianginal agents in patients symptomatic despite adequate rate control, ranolazine is preferred among the second-line drugs, as it prevents the automaticity in atrial tissue by suppressing diastolic depolarization and atrial tissue excitability in addition to suppressing the early and delayed after depolarizations. All of this results in the increased initiation and progression of AF. Moreover ranolazine use is tied to better rhythm control in AF patients in a recent meta-analysis[54,55]. Trimetazidine is a second-line antianginal used especially in those with underlying left ventricular dysfunction. It largely has a neutral effect on underlying AF and can be used as an add-on therapy in those with ischemic cardiomyopathy and AF. Limited data have suggested that favorable effects on P-wave duration and dispersion may help reduce the incidence of AF in these subgroup of patients[56]. The use of nitrate and nicorandil in AF should be avoided as these have been tied with increased incidence and aggravation of underlying AF in CAD patients[48].

Early rhythm control strategy

Early rhythm control strategy preferably with catheter ablation has been increasingly realized as an effective means of reducing the overall MACCE events in patients suffering from AF[57-59]. The benefit is most in those with high comorbidly burden and in those with a recent diagnosis of AF. There has been a clear trend in the superiority of rhythm control compared to rate control in recent years largely attributable to the incremental benefit of early rhythm over rate control alone in terms of improved overall symptoms and quality of life scores and reduced heart failure hospitalizations, stroke, dementia, and overall cardiovascular death[57,58]. This has reflected in increasing recommendations for catheter ablations in multiple subsets of patients including those with underlying CAD. Since AF is common in patients with underlying CAD and high comorbidity burden, all attempts should be made to diagnose it early and accordingly if symptoms are not controlled despite initial medical therapy and rate control, catheter ablation should be considered.

Targeting endothelial dysfunction

Robust evidence points towards the central role of endothelial dysfunction in CAD initiation and progression. Further, endothelial dysfunction now is increasingly realized as an important mediator in AF pathogenesis as well[60]. Often it coexists with other cardiovascular comorbidity such as diabetes, hypertension, dyslipidemia, and obesity. Decreased expression of nitric oxide, inflammation, increased oxidate stress, increased apoptosis, and vascular remodeling all contribute to endothelial dysfunction at the cellular level. Endothelial dysfunction as diagnosed by flow-mediated vasodilation often correlates with increased systemic vascular complications and poor outcomes[61]. Endothelial dysfunction is a dynamic thing and is reversible to large extent with appropriate intervention. At present, the only therapy to improve endothelial dysfunction includes aggressive risk factor modification including smoking cessation, appropriate blood pressure and blood glucose control, weight reduction, and exercise. Pharmacological therapies including antithrombotic therapies and statins also have shown incremental benefit in addition to lifestyle intervention. Other pharmacological agents including calcium channel blockers, angiotensin inhibitors, antioxidant agents, betablockers, phosphodiesterase inhibitors, nicorandil, ivabradine, and l-arginine have also shown some benefit in small studies but it is yet early stages to comment on the role of these agents in improving endothelial dysfunction in clinical practice[9,60,61].

Table 2 Impact of various antidiabetic agents on the burden of atrial fibrillation and coronary artery disease and their surrogate endpoints

Antidiabetic drug class	Impact on AF burden/ surrogate end points	Impact on CAD burden/ surrogate end points
Insulin[71]	Increased (↑)	Neutral or increased (-/↑)
Metformin[72]	Reduced (↓)	Reduced (↓)
Sulfonylureas[71]	Neutral (-/↑)	Increased (↑↑)
Thiazolidinediones[73]	Reduced or neutral (-/↓)	Increased (↑↑)
DPP-4 inhibitors[74]	Reduced (-/↓)	Reduced (↓)
GLP-1 receptor agonists[75]	Neutral or slightly increased (-/↑)	Reduced (↓↓)
SGLT-2 inhibitors[76]	Reduced (↓↓)	Reduced (↓↓↓)

AF: Atrial fibrillation; CAD: Coronary artery disease; DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide 1; SGLT-2: Sodium-glucose cotransporter-2.

Therapies targeting inflammation

Inflammation is implicated in pathogenesis of both CAD and AF. The testimony of the same lies in the fact that many antiinflammatory drugs have shown incremental benefit in reducing the incidence and burden of either of the two diseases. While evidence is more robust for its positive impact in CAD, data are emerging on its role in AF patients[62,63]. Two large randomized studies have already shown the positive impact of colchicine and canakinumab in reducing MACCE events in CAD patients attributable to decreased inflammation[64,65]. On the other hand emerging evidence shows that therapies targeting inflammation indeed prevent the occurrence or decrease the recurrences of AF in CAD patient. Recent studies have shown that colchicine or corticosteroids administration after catheter ablation can help reduce recurrence of AF[63].

Effect of diabetes and antidiabetics drugs on AF and CAD

Diabetes remains one of the largest independent risk factors for development of atherosclerosis. Approximately one-third of all patients suffering from diabetes have concomitant CAD, which remains the leading cause of morbidity and mortality in the diabetic population[66]. Recent evidence points to the excess prevalence of AF in diabetic population, independent of other cardiovascular risk factors[67,68]. Furthermore, patients with concomitant AF and diabetes have worse clinical outcomes including excess stroke, dementia, and heart failure compared to AF in the absence of diabetes[67,69]. Diabetes confers enhanced systemic vascular atherogenicity and thrombogenicity, which in part is driven by endothelial dysfunction and inflammation, a pathogenic process very similar to both AF and CAD. The major contributors to this pathogenesis include the direct glucose and free fatty acid toxicity at the cellular levels, which results in excess of reactive oxygen species, advanced glycation end-products, upregulation of the polyol, hexosamine, and protein kinase C pathways. This results in dysregulated cellular metabolism and mitochondrial function, which are essential for normal endothelial function and its antiinflammatory and antithrombotic properties[67,68]. As such, this relationship is very relevant while managing patients with AF and/or CAD. Naturally, there is a desire to use antidiabetic drugs, which help improve the burden of these diseases. Table 2 illustrates the prominent effects of various classes of antidiabetic drugs on AF and CAD. Expectedly, the antidiabetic drugs, which improve the clinical endpoints of either CAD or AF, are expected to confer a beneficial effect on the other disease as well. Overall, antidiabetic drugs that have consistently shown incremental benefit in reducing burden of either AF and CAD include sodium-glucose cotransporter-2 inhibitors, dipeptidyl peptidase-4 inhibitors, and metformin. Accordingly, we believe that these agents should preferentially be used during institution of antidiabetic therapy in these patients ahead of agents, which have neutral or harmful effects on either of the two diseases (sulfonylureas, thiazolidinediones)[68,70].

CONCLUSION

The relationship between AF and CAD is complex and the two are intricately related at the pathophysiological level. The two diseases share common risk factors and pathogenesis and often culminate in a vicious cycle. Hence, it is impractical to treat them in isolation. The worsening of one is invariably accompanied by accelerated progression of the other disease as well. Accordingly, we share the implications of this relationship in diagnoses and management of the two diseases. In this review, we discuss the key strategies to break the cycle and highlight the recent, evidence-based therapeutic

options to break the common links between the two and reduce morbidity and mortality.

FOOTNOTES

Author contributions: Batta A and Sharma YP contributed to the conception and design; Batta A, Hatwal J, and Sharma YP contributed to the analysis and interpretation; Batta A, Batta Ak, and Verma S contributed to the data collection; Batta A and Hatwal J contributed to writing the article; Batta A and Sharma YP contributed to critical revision of the article; Batta A and Sharma YP contributed to final approval of the article; Batta Ak contributed to the statistical analyses; Batta A and Sharma YP will serve as guarantors for the overall accuracy of the manuscript.

Conflict-of-interest statement: All authors have no conflicts of interest to declare.

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S-Editor: Li L
L-Editor: Filipodia
P-Editor: Yu HG

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2023 May 26; 15(5): 244-252

DOI: 10.4330/wjc.v15.i5.244

ISSN 1949-8462 (online)

MINIREVIEWS

Current knowledge and contemporary management of non-A non-B aortic dissections

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Sef D, United Kingdom; Ueda H, Japan

Received: February 11, 2023
Peer-review started: February 11, 2023
First decision: March 28, 2023
Revised: April 10, 2023
Accepted: April 25, 2023
Article in press: April 25, 2023
Published online: May 26, 2023

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Abstract

Non-A non-B aortic dissection (AAD) is an infrequently documented condition, comprising of only a small proportion of all AADs. The unique anatomy of the aortic arch and the failure of the existing classifications to adequately define individuals with non-A non-B AAD, have led to an ongoing controversy around the topic. It seems that the clinical progression of acute non-A non-B AAD diverges from the typical type A and B dissections, frequently leading to serious complications and thus mandating early intervention. Currently, the available treatment methods in the surgical armamentarium are conventional open, endovascular techniques and combined hybrid methods. The optimum approach is tailored in every individual case and may be determined by the dissection's location, extent, the aortic diameter, the associated complications and the patient's status. The management of non-A non-B dissections still remains challenging and a unanimous consensus defining the gold standard treatment has yet to be reached. In an attempt to provide further insight into this perplexing entity, we performed a minireview of the literature, aiming to elucidate the epidemiology, clinical course and the optimal treatment modality.

Key Words: Aortic dissection; Aortic disease; Aortic surgery; Thoracic aorta disease; Aortic arch dissection

Core Tip: The available treatment options in the surgical armamentarium are conventional open surgery with standard aortic arch replacement or frozen elephant trunk (FET), interventional therapies such as the thoracic endovascular aortic repair (TEVAR) and hybrid techniques combining TEVAR with debranching of the supra-aortic vessels. In the case of a favorable arch anatomy, TEVAR is the preferable treatment option. Alternatively, when the entry tear is located in the proximal segment of the aortic arch, a hybrid arch repair, aortic arch replacement or even FET should be given thorough consideration.

Citation: Christodoulou KC, Karangelis D, Efenti GM, Sdrevanos P, Browning JR, Konstantinou F, Georgakarakos E, Mitropoulos FA, Mikroulis D. Current knowledge and contemporary management of non-A non-B aortic dissections. *World J Cardiol* 2023; 15(5): 244-252
URL: https://www.wjgnet.com/1949-8462/full/v15/i5/244.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i5.244

INTRODUCTION

As part of the cluster of the clinical entities related to acute aortic syndromes[1], acute aortic dissection (AAD) is a challenging and life-threatening cardiovascular emergency[2], with approximately 6 new cases per 100000 population per annum[3]. In an AAD, an intimal tear compromises the medial layer's structural integrity, separating the aortic wall layers. Subsequently, a "new" false lumen is formed, allowing blood to enter the tunica media[3]. If not addressed, it has a significant propensity for developing into a fatal disorder due to rupture, myocardial infarction, cardiac tamponade, aortic valve insufficiency[4], or even end-organ malperfusion[5]. Since the second half of the previous century, the Stanford and DeBakey classifications are the primary systems, which have consistently determined the patients' management. However, by default, they both fail to distinguish and address dissections confined or involving the aortic arch[5]. von Segesser *et al*[6] were the first to introduce the term "non-A non-B" when referring to intima tears sparing the ascending aorta.

Non-A non-B AAD can be defined as an entry intimal tear, located beyond the left subclavian artery (LSA), with the dissection extending retrogradely into the aortic arch (descending entry type), or as an entry tear located between the innominate and the LSA (arch entry type), with or without distal extension of the dissection[7]. It seems that there is scarcity of data regarding their natural history, clinical course and management[8]. Accordingly, we performed a minireview of the literature, to unveil the details of the topic with regards to epidemiology, contemporary classification systems as well as the available surgical armamentarium and possible treatment options.

EPIDEMIOLOGY, RISKS AND PREDISPOSING FACTORS

Non-A non-B AAD is an infrequently documented condition, comprising only a small proportion of all AADs. Its comparatively elevated mortality, hinders the ascertainment of its true incidence, since a considerable number of patients die prior to the diagnosis[2]. Regardless of the divergent results across different studies, a recent review exhibited that the incidence of non-A non-B AAD lies between the respective of type A and type B, varying from 2.8% to 16.5%[5]. The affected individuals tend to be 5 to 10 years younger in comparison to patients with other AADs[9], while some disagreement exists as to whether or not there is a prevailing type of location for the entry tear (arch or descending)[10,11].

There are several risk factors associated with non-A non-B AADs, with chronic and mainly poorly controlled hypertension being the most frequently reported. In the majority of the published cases, roughly 80% of the patients have a medical history of hypertension[5,8,10,12,13]. Tobacco addiction, hypercholesterolemia and diabetes mellitus were also found to pose a great risk for AAD. In addition, connective tissue disorders like Ehlers-Danlos and Marfan Syndromes, inflammatory vasculitis, pregnancy, trauma, previous heart surgery, the presence of bicuspid aortic valve, stimulant usage, infections and some very rare genetic disorders are among the predisposing medical conditions linked to AAD[2]. Additionally, a non-A non-B dissection can be attributed to an intramural hematoma and penetration aortic ulceration[1].

Furthermore, the role of other factors has also been investigated. Recent papers have exhibited a correlation between this specific type of AAD and anatomic characteristics of the aortic arch. Rylski *et al*

[12] demonstrated that arch types are distributed variably among different dissections. Type I in which the vertical distance between innominate artery and the top of the aortic arch is less than the diameter of the left common carotid artery (LCCA), was usually seen in type A AADs, while in non-A non-B AADs arch type II (vertical distance between innominate artery and aortic arch is equal or twice the diameter of the LCCA) prevailed (49%). In approximately 1/3 of the non-A non-B patients (28%), two instead of the three branches arise from the arch, since the innominate and the LCCA were found to share a common trunk and in 16% of the cases the left vertebral artery arose directly from the arch[10]. Irrespective of these variations, the aortic arch's curved shape and its branches, form two natural barriers, which can prevent a dissection from spreading further. The origin of the innominate artery serves as the proximal barrier, while the distal barrier is considered to be the LSA. As a result, these margins may be incriminated as the two very distinctive arch and descending entry dissection types[11].

CLINICAL PRESENTATION

In most cases of AAD, the most common symptom is sudden, acute chest pain and/or back discomfort [3]. Nevertheless, in rare cases a subtle or discrete type of AAD[3] has been reported, which is typically detected intraoperatively, despite being misdiagnosed during the patient's initial assessment[14]. Wang *et al*[15] in their retrospective study, stated that all non-A non-B patients reported an abrupt onset of severe chest pain for at least a six-hour duration. Notably, a recent meta-analysis showed that nearly 50% of the patients were admitted with or developed over time, signs of at least one organ malperfusion and that 6% were at risk of an impending rupture[8]. In the same paper, the authors highlighted the surprisingly large proportion of patients (88%), who had a complicated clinical course, as distinct from type B dissections. Hence, cardiogenic shock, cardiac arrest, cardiac tamponade, periaortic hematoma, acute renal failure, stroke/neurologic deficits or even aortic rupture are some of the baseline characteristics of non-A non-B dissection patients[13].

CLASSIFICATION SYSTEM

Over the years and with the exploitation of the emerging imaging modalities, several classification systems have been proposed and deployed to facilitate the triage and enhance the post-treatment clinical outcomes. The two traditional and widely known DeBakey and Stanford classifications were introduced in the 1950s and 1960s, respectively, and are based on the intimal tear's location and extension[16,17]. It is evident, that since the aforementioned systems focus primarily on the ascending and descending part of the aorta, they lack clarity regarding aortic arch involvement[4].

The European Society of Cardiology guidelines about aortic diseases fail to include the arch dissection as a distinct entity. The American Heart Association guidelines propose the term "proximal type B aortic dissection" for patients with entry tears in the arch, expanding antegradely to the descending aorta[18,19]. The 2019 consensus of the European Association for Cardio-Thoracic Surgery and the European Society for Vascular Surgery, referred to non-A non-B AAD, as an arch involvement either by the most proximal tear or by retrograde extension, but sparing the ascending aorta[20].

Since the introduction of the term non-A non-B AAD back in 1994[6], several studies have proposed the modification of the already existing classifications, by adding this type of dissection. Based on the entry tear's location, in 2017, non-A non-B AADs were divided into two distinct groups; arch and descending entry tear[10]. Recently, Qanadli *et al*[4] driven by the Stanford classification, proposed the incorporation of "type C" AAD, referring to the corresponding non-A non-B dissection suggested earlier by Rylski *et al*[10]. For the first time, they also mention, grades of malperfusion syndrome (MPS grade 0-3). More specifically, the absence of malperfusion is classified as grade 0, compression of the true lumen as grade 1, while the extension of the dissection to renal artery is categorized as grade 2. According to the authors grade 3 incorporates both the absence of malperfusion and the extension of the dissection to the renal artery. Therefore, the MPS grade dictates the need for additional therapy to maintain perfusion of vital organs.

Sievers *et al*[9] extended the Stanford classification by including all types of AAD, the location of primary aortic entry tear and the malperfusion status (TEM). According to their proposal, T refers to type A, type B or non-A non-B dissections, E includes E0: No visible entry site, E1: Entry tear in ascending aorta, E2: Tear in arch, E3: Tear in descending aorta and M includes M0, M1, M2, M3 when no malperfusion, coronary artery, subra-aortic arteries, renal/visceral ± lower extremity arteries were involved, respectively. They also mention the presence (+) and absence (-) of clinical symptoms of organ malperfusion offering a more complete picture of AADs in an attempt to achieve optimal therapeutic planning and outcome[9].

TREATMENT MODALITIES

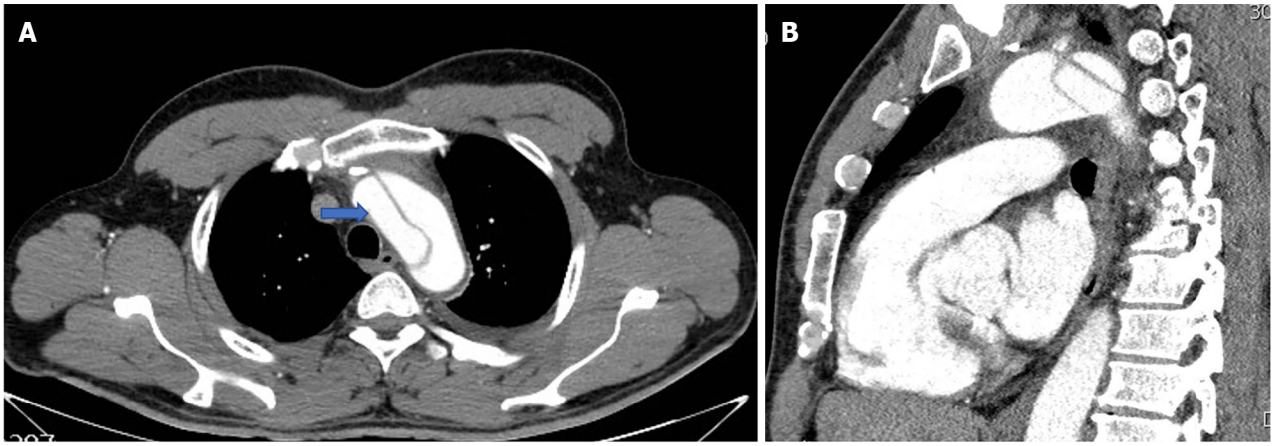
Decision on optimal medical treatment of AADs is determined based on the dissection's location, extent, the aortic diameter, the accompanying complications, the adjacent anatomy, the patient's status and comorbodities[21]. Stanford type A/DeBakey type I or II dissections, when left untreated, typically have a mortality rate exceeding 50% the first 48 h, so open surgery on emergency basis with replacement of the ascending aorta is highly recommended[3,19]. On the other hand, when the dissection involves solely the descending thoracic aorta (DTA) (Stanford type B/DeBakey type III dissections), the clinical course is usually uncomplicated. When that is the case, the 30-d mortality rate is approximately 10%, thus, conservative medical therapy or interventional, endovascular treatment (for complicated type B dissections) are the most common, yet not exclusive, treatment options[3,19]. However, aortic arch dissections have not been accurately classified, which leads to uncertainty and disagreement on treatment planning[4]. In addition, the contribution of the imaging modalities, towards an accurate diagnosis should not be omitted. The transthoracic echocardiography, although mostly employed in nonemergency cases, could potentially provide useful details regarding the proximal DTA, the aortic arch branches and detect some of the dissection's complications[19]. Yet, the valuable role of the preoperative computed tomography is constantly increasing, as it can sometimes detect the dissection and its extent, delineate the anatomy of the area, and even depict clinically significant incidental findings[22], enhancing the diagnostic accuracy and tailoring the treatment plan[19].

Aiming for the closure of the proximal entry tear, a great number of research papers have suggested the implementation of surgical treatment for non-A non-B AADs, explicitly exhibiting that conservative treatment is inferior to any type of intervention, presenting a 30-d mortality rate of 14% as compared to 3.6% for surgically or endovascularly treated patients[8]. According to recent data, it seems that the clinical manifestation and progression of acute non-A non-B AAD diverge from the typical type A and B dissections and especially from the acute type B AAD, which is confined to the DTA[23]. Valentine *et al*[24] noted that dissections including the arch had a worse outcome than those affecting only the DTA. Equally important results from an expert consensus state that the arch's involvement in the dissecting process has an immense impact on the patients' outcome, including but not limited to the prolonged hospital stay, the increased probability of cardiac and neurologic complications such as rupture, congestive heart failure, MPS, stroke, spinal cord injury (SCI) and the need for reintervention if not addressed betimes[20,25].

Because non-A non-B AADs are associated with an increased likelihood of a complicated course, the optimal management orders early intervention[5]. In spite of the fact that, during the past years, many therapeutic plans have been proposed, there remains a dearth of literature regarding pertinent studies comparing different modalities for the treatment of non-A, non-B AAD. Moreover, the existing studies have limited patient samples and lack long-term follow-up[21]. Therefore, a unanimous consensus defining the gold standard treatment has yet to be reached[5]. Currently, the available treatment options in the surgical armamentarium are conventional open surgery with standard aortic arch replacement or frozen elephant trunk (FET), interventional therapies such as the thoracic endovascular aortic repair (TEVAR) with extra-thoracic surgical transposition or chimney stent graft and hybrid techniques combining TEVAR with debranching of the supra-aortic vessels[8]. Lately, a new hybrid technique was launched by Wang *et al*[15] with satisfactory short-term outcomes, called the "inclusion aortic arch technique", as an alternative to the traditional hybrid surgery, so to avoid endoleaks and retrograde type A dissection, which may complicate the procedure.

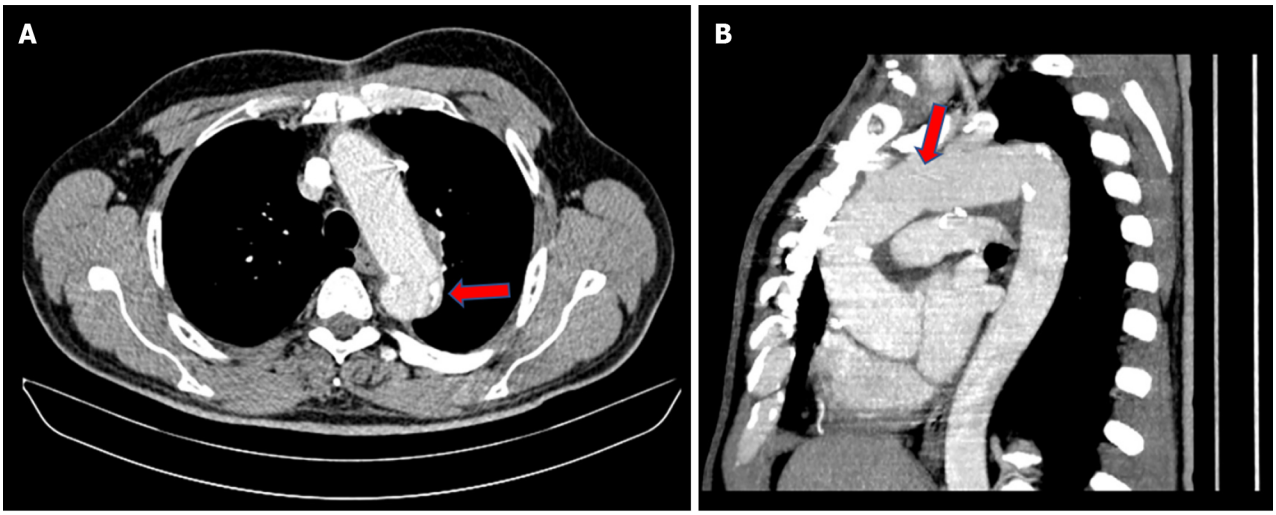
According to the International Registry of Acute Aortic Dissection study findings, arch entry and DTA entry type dissections differ from one another in terms of their course. More specifically, a DTA dissection, expanding retrogradely to the arch, has no impact on either early or late mortality or the management plan, with its clinical course resembling that of type B AAD. Whereas complicated arch entry dissections with antegrade expansion to the DTA, were found to have an elevated in-hospital mortality, requiring an even more urgent intervention[13,25]. Trimarchi *et al*[13] also presented data which argue that non-A non-B AAD should perhaps warrant a more aggressive approach. In their analysis, 14% of patients with an "uncomplicated" arch tear had progression of the dissection, which likely contributed to a 30% incidence of lethal stroke. In the same frame, Kosiorowska *et al*[7] stressed/pointed out the contemporary tendency towards an earlier intervention on the altar of a favorable aortic remodeling. In arch entry type patients, open aortic arch repair is preferable compared to endovascular techniques in term of survival and post-operative complications rate[7]. In these cases, there are several arch replacement grafts commercially available (Figures 1 and 2).

The arch entry dissections, can be managed with standard aortic arch replacement combined with FET, as the procedure is associated with low peri and post-operative mortality and complication rates [7]. Hybrid methods have been proposed as an effective alternative, which can prevent the need for cardiopulmonary bypass, hypothermic cardiac arrest and any related problems, but their efficacy has not yet been proven in the long run[26]. However, the study conducted by Tian *et al*[27], employing different hybrid methods (type I-III) to treat 46 patients, has demonstrated promising outcomes with respect to overall mortality and complication rates, in comparison to surgical or endovascular repair. Taking into account the lack of guidelines regarding postoperative thromboprophylaxis, caution must be exerted to avoid the graft's occlusion[28]. Irrespective of the entry type, evidence shows that TEVAR



DOI: 10.4330/wjc.v15.i5.244

Figure 1 Pre-operative computed tomography images of a non-A non-B aortic dissection case contained in the aortic arch, which was surgically managed in our department. A: Axial view, blue arrow shows the true lumen; B: Sagittal view.



DOI: 10.4330/wjc.v15.i5.244

Figure 2 The aortic arch was replaced with a graft (prefabricated aortic branched graft), which contained three pre-attached branches for all three great vessels. A: Axial view, red arrow demarcates distal anastomotic suture line; B: Sagittal view; red arrow the proximal suture line with the ascending aorta.

is a valid treatment option provided that the aortic arch has favorable anatomy[8]. Alternatively, when the entry tear is located in zone 1, a hybrid arch repair, aortic arch replacement or even FET should be given thorough consideration[8]. This minireview focuses primarily on the FET and TEVAR techniques.

ET AND FET

Treatment of non-A non-B AAD can be performed with a two-stage surgical technique called "ET"[29]. The first stage of ET includes a sternotomy and a reconstruction of the ascending aorta and the aortic arch with a graft while in the second stage, the floating extension of the graft (ET) in the descending aorta is utilized in order to extend the repair of the DTA. The second stage *per se* includes a lateral thoracotomy to approach the descending aorta. The evolution of surgical and endovascular techniques has resulted in the development of a composite prosthesis, known as the "Frozen ET"[20]. The use of FET instead of the conventional ET has been increasing over the last years[20].

Combining the benefits of both open and interventional repair, FET is a viable solution in cases of a proximal entry tear as well as for patients with non-A non-B AAD or complicated chronic type B, who are not suitable for TEVAR[30,31]. This one-stage procedure allows a total aortic arch replacement with antegrade delivery of a descending aortic stent-graft[32]. The stent-graft may serve as a proximal landing zone to facilitate future endovascular intervention in the distal aorta[30]. The FET technique has

been extensively applied in cases of acute dissections to restore true lumen patency, seal intimal tears in the descending aorta and promote false lumen thrombosis, as well as repairing chronic degenerative arch aneurysms[19,32]. FET implantation has the potential to prevent secondary thoracic and abdominal aortic replacement by enlarging the true lumen and promoting favorable remodeling of the distal aorta [19,33,34]. Yet, if replacement of the thoracic and abdominal aorta is required, its additional suture margins at each side, facilitate anastomosis[5,30]. The two most common commercially available hybrid FET prostheses namely the Thoraflex hybrid and E-vita open are associated with comparable outcomes [20].

Carino *et al*[8] mention that 7% of the non-A non-B patients underwent the FET procedure, pointing out that it should be considered in complicated cases, since it alleviates the compressed true lumen and covers any newly formed entry tears in the proximal DTA, applying pressure to the false lumen. Zhao *et al*[35] reported the in-hospital mortality rate of their 24 non-A non-B AAD patients treated with FET, to be 4.1%, while the 5-year survival rate was approximately 92%. The authors concluded that, this surgical technique represents a feasible option with acceptable short and long-term outcomes. Another study cohort, whilst exhibiting similar early results, stresses the importance of the continuous monitoring and follow-up, due to the potential need for aortic reintervention[31]; results in accordance with Tian *et al* [27] paper.

Although the technique is more invasive than TEVAR, it minimizes the risk of type Ia endoleaks and retrograde type A dissection[30]. On the other hand, FET's primary disadvantage is the increased risk of surgical trauma brought on by the necessity for extended periods of extracorporeal circulation, circulatory arrest, myocardial ischemia, stroke and SCI, due to the extensive coverage of the descending aorta with the occlusion of intercostal arteries[8]. Additionally, aortic valve insufficiency, bovine aortic arch, the dissection of the LCCA and preoperative cardiopulmonary resuscitation have all been linked to an increased risk for postoperative stroke[36,37]. Notably, in many studies, including a meta-analysis with 3000 "aortic surgical" patients, SCI was documented in 4% of the cases. By diminishing the circulatory arrest time and FET maneuvers above the 8th thoracic vertebra, SCIs could be substantially reduced[38]. Cerebrospinal fluid drainage and neuromonitoring should also be carried out for high-risk patients[39].

TEVAR

TEVAR, given its minimal invasive character, has recently been shown to be the most widely used technique to treat non-A non-B dissections, comprising 55% of the treatment[8]. The aim of the stent-graft's deployment in the thoracic aorta is the successful closure of the primary entry tear. As a result, the false lumen is excluded from the systemic circulation, thrombosed and shrank, thus it no more compresses the true lumen and organ perfusion is maintained. According to the location of the primary entry tear, different TEVAR sealing zones exist (zone 0, 1, 2, 3). Zone 3 TEVAR refers to entry tears located in the DTA with retrograde extension, with the stent-graft deployed distal to the LSA. For more proximal entry tears, zone 2 TEVAR is employed, which includes a sealing zone between the origin of the LCCA and the LSA. TEVAR zone 1 refers to graft apposition between the innominate artery and LCCA, while TEVAR zone 0 includes a sealing zone proximal to the innominate artery[3,5,10,20].

In order to establish a disease-free sealing zone, the sacrifice of important aortic arch branches can be, in some cases, unavoidable. Nonetheless, there are several techniques to maintain perfusion; supra-aortic branch bypass (hybrid technique), apposition of extra stent-grafts (chimney technique) or both [40]. TEVAR zone 2 can be accompanied with carotid-subclavian (CS) bypass/transposition or with chimney graft to the LSA. Similarly, TEVAR zone 1 can be followed by two chimney grafts to the LCCA and LSA, but more frequently, a single chimney graft to the LCCA and a CS bypass/transposition are used. Finally, TEVAR zone 0 can entail two chimney grafts to the innominate artery and LCCA followed by a left CS bypass, or alternatively a chimney graft to the innominate artery, right to left carotid bypass and CS bypass[20]. Compared to more distal landing zones, zone 0 is more likely to be associated with retrograde type A dissection, especially when accompanied by excessive oversizing of the stent-graft [41]. Yet, it has also been demonstrated that the use of chimney grafts in the aortic arch, increases the risk of post-operative complications[40].

Liu *et al*[21] studied 215 patients with a non-A non-B AAD, treated with TEVAR, open surgical techniques or conservatively. TEVAR was used in 127 patients (59.1%) with a success rate of 85.9%. The 30-d mortality rate was 1.6%, compared to 7.1% in patients treated with open techniques. However, during the follow up, 9 deaths occurred in the endovascular group, 5 of which were related to the dissection, while no deaths occurred in the surgical group. Supplementary, following TEVAR, patients had a worse clinical outcome in terms of aortic rupture, retrograde type A dissection, distal stent graft induced new entry, major stroke and the need for reintervention. Likewise, a study published in 2022, observed that 67% of the initial TEVAR cases (10/15), demanded reintervention, with eventually 4 patients deceasing during the first 30 d[7].

CONCLUSION

Management of non-A non-B dissections remains challenging. The paucity of relevant studies reflects the fact that non-A non-B AADs account for a relatively modest percentage of all AADs. Although little is known about their natural history and course of treatment, it has been explicitly shown that surgical intervention surpasses medical treatment in the case of a non-A non-B dissection[5,8,42]. Current data advocate that this clinical entity does not behave like an uncomplicated type B AAD, and perhaps a more aggressive approach is warranted. Open repair is mostly employed in arch entry, while TEVAR with hybrid procedures in descending entry dissections both of which are thought to be preferable as opposed to conservative treatment. Secondary analysis with long-term follow up of the existing studies as well as large prospective clinical trials will enlighten the field around non-A non-B AAD which still remains an obscure and perplexing variation of acute AAD. Future research is anticipated to determine the most optimal surgical method as well as the time to intervene, ultimately helping surgeons to navigate through these uncharted waters.

FOOTNOTES

Author contributions: Christodoulou KC wrote the manuscript; Karangelis D contributed to manuscript review and supervised the entire project; Efenti GM, Sdrevanos P, and Georgakarakos E contributed with bibliographic research and proofread the manuscript; Browning JR was responsible for the English language editing of the manuscript; Konstantinou F provided the accompanying figures; Mitropoulos FA and Mikroulis D designed the outline and coordinated the writing of the paper; and all authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Yu HG

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2023 May 26; 15(5): 253-261

DOI: 10.4330/wjc.v15.i5.253

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Importance of concomitant functional mitral regurgitation on survival in severe aortic stenosis patients undergoing aortic valve replacement

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ong H, Malaysia; Yang L, United States

Received: December 20, 2022
Peer-review started: December 20, 2022
First decision: February 20, 2023
Revised: March 20, 2023
Accepted: April 25, 2023
Article in press: April 25, 2023
Published online: May 26, 2023

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Abstract

BACKGROUND

Mitral regurgitation (MR) is commonly seen in patients with severe aortic stenosis (AS) undergoing aortic valve replacement (AVR). But the long-term implications of MR in AS are unknown.

AIM

To investigate MR's impact on survival of patients undergoing surgical AVR for severe AS.

METHODS

Of the 740 consecutive patients with severe AS evaluated between 1993 and 2003, 287 underwent AVR forming the study cohort. They were followed up to death or till the end of 2019. Chart reviews were performed for clinical, echocardiographic, and therapeutic data. MR was graded on a 1-4 scale. Mortality data was obtained from chart review and the Social Security Death Index. Survival was analyzed as a function of degree of MR.

RESULTS

The mean age of the severe AS patients who had AVR (n = 287) was 72 ± 13 years, 46% women. Over up to 26 years of follow up, there were 201 (70%) deaths, giving deep insights into the determinants of survival of severe AS who had AVR. The 5, 10 and 20 years survival rates were 75%, 45% and 25% respectively. Presence of MR was associated with higher mortality in a graded fashion (P = 0.0003). MR was significantly associated with lower left ventricular (LV) ejection

fraction and larger LV size. Impact of MR on mortality was partially mediated through lower LV ejection fraction and larger LV size. By Cox regression, MR, lower ejection fraction (EF) and larger LV end-systolic dimension were independent predictors of higher mortality (χ^2 = 33.2).

CONCLUSION

Presence of greater than 2+ MR in patients with severe AS is independently associated with reduced survival in surgically managed patients, an effect incremental to reduced EF and larger LV size. We suggest that aortic valve intervention should be considered in severe AS patients when > 2+ MR occurs irrespective of EF or symptoms.

Key Words: Aortic stenosis; Mitral regurgitation; Aortic valve replacement; Long term survival

Core Tip: This study is unique in several aspects: (1) Shows that mitral regurgitation negatively impacts survival in an independent fashion, an effect incremental to left ventricular size and ejection fraction; (2) Perhaps the longest follow up of severe aortic stenosis (AS) patients undergoing aortic valve replacement (AVR) (till death or 16-26 year follow up in survivors); (3) Gives insights into potential mitral regurgitation (MR) mechanisms; and (4) Validates echocardiographic MR severity against survival in patients with severe AS undergoing AVR.

Citation: Pai RG, Varadarajan P. Importance of concomitant functional mitral regurgitation on survival in severe aortic stenosis patients undergoing aortic valve replacement. *World J Cardiol* 2023; 15(5): 253-261
URL: https://www.wjgnet.com/1949-8462/full/v15/i5/253.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i5.253

INTRODUCTION

Significant mitral regurgitation (MR) is seen in about 20% of patients with severe aortic stenosis (AS) undergoing aortic valve replacement (AVR) or transcatheter aortic valve replacement (TAVR)[1-3]. Presence of MR is associated with worse symptoms, higher pulmonary artery pressures and higher short-term mortality in TAVR patients[1-5]. However, its impact on long term survival after AVR is not well characterized, especially in those with moderate or severe MR. The recent American College of Cardiology/American Heart Association (ACC/AHA) valve guidelines do not include presence of MR as an indication for AVR or TAVR[6]. We investigated the impact of different grades of MR on long term survival (to death or up to 26 years) in a cohort of patients undergoing surgical AVR for severe AS in period 1993-2003.

MATERIALS AND METHODS

The research project was approved by the institutional review board of Loma Linda University, Loma Linda, California. A need for an informed consent was waived because of its retrospective, observational study design without any intervention.

The data underlying this article will be shared on reasonable request to the corresponding author. This was a retrospective observational study conducted in a large university medical center. The study was approved by the institutional review board, which waived the need for patient consent. Some of the other results of this observational study have been published previously[7,8]. This report includes 15 additional years of follow up. The echocardiographic database was searched for patients with severe AS during the period from 1993 to 2003. Severe AS was diagnosed based on the generally accepted criteria prevalent at that time[9]. The criteria used included aortic valve area ≤ 0.8 cm^2 or a mean transvalvular gradient of ≥ 40 mmHg or peak gradient of ≥ 64 mmHg. This yielded a total of 740 patients. Complete clinical, echocardiographic, and pharmacological data were compiled on these patients from comprehensive chart review. Of these 287 underwent AVR and formed the study cohort.

Clinical variables

Various clinical comorbidities were defined as follows: Hypertension was defined as a blood pressure > 130/90 mmHg, being on any antihypertensive medication, or a documented history of hypertension. Diabetes mellitus (DM) was defined as a fasting blood sugar of > 126 mg/dL or being on treatment for

diabetes. Renal insufficiency was defined as a creatinine value of ≥ 2 mg/dL. Coronary artery disease (CAD) was defined as angiographic evidence of CAD with lesions > 50% as all had coronary angiograms before AVR.

All patients had standard 2-dimensional echocardiographic examinations. The left ventricular (LV) ejection fraction (EF) was assessed visually by a Level 3-trained echocardiographer and entered into a database at the time of the examination. This has been proven to be reliable and has been validated against contrast and radionuclide LV angiography[10,11]. Anatomic and Doppler examinations and measurements were performed according to the recommendations of the American Society of Echocardiography prevalent at that time and MR was graded 0-4[12,13].

Pharmacotherapy around the time of initial echo was recorded and placed into broad categories of beta blockers, calcium-channel blockers, digoxin and angiotensin receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI). Most of the patients continued on the medications for the length of the recorded clinical observation. Patients were on beta blockers, ACEI/ARB only if they had a concomitant indication for their use like hypertension or CAD. Beta blockers and ACEI/ARB are not recommended as primary treatment for severe AS. Hence the low treatment rate with beta blockers and ACEI/ARB.

The end point of the study was all-cause mortality. Mortality data were obtained from clinical records or the Social Security Death Index till the end of 2019.

Statistics analysis

Stat View version 5.01 (SAS Institute, Cary, North Carolina) program was used for statistical analysis. Kaplan-Meier survival curves were computed for patients with severe AS with and without MR and were compared using the log-rank statistic. Characteristics of patients with and without MR were compared using the Student *t* test for continuous variables and the χ^2 test for categorical variables, the largest *P* value for differences between the groups was taken. Cox proportional hazards models was employed to adjust for clinical comorbidities and covariate imbalances. Baron and Kenny method was employed for mediation analysis[14]. $P < 0.05$ was considered significant.

RESULTS

Patient characteristics

The baseline characteristics of the severe AS patients who had AVR were: mean age 72 ± 13 years, 46% women, mean LVEF 57 ± 19%, and DM in 22%, hypertension in 55%, and CAD in 55%. The mean aortic valve area was 0.70 ± 0.17 cm^2, transvalvular mean systolic gradient 44 ± 16 mmHg and peak gradient 72 ± 24 mmHg. Of the 287 patients, 42% had concomitant coronary artery bypass grafting (CABG) with AVR; 169 (59%) had no or mild (0 or1+) MR, 63 (22%) had moderate (2+) MR and 55 (19%) had moderate to severe or severe (3 or 4+) MR. Of the 55 patients with 3 or 4+ MR, 18 had mitral valve repair ($n = 11$) or replacement ($n = 7$).

Survival as function of degree of MR

As the survival curves were similar for MR grades 0 and 1+ and very close to 2+ MR, hence these groups were combined. As shown in (Figure 1), there was a graded decrease in survival with increase in MR ($P = 0.003$). The 5, 10 and 20 year survivals for those with 0/1+ MR were 78%, 50% and 33% respectively compared to 78%, 43% and 14% for 2+ MR and 64%, 30% and 15% for 3 or 4+ MR respectively. Comparison between grade 0-1 and 3-4+ MR showed significant difference with $P < 0.0001$. Similarly, comparison between grade 2 and 3-4 +MR showed difference with $P < 0.0001$. Comparison between grades 0-1 and grade 2 showed slight difference with $P = 0.03$.

Correlates of MR

Table 1 shows the comparison of patients with different degrees of MR. As it can be seen from the table, higher degrees of MR correlated strongly with larger LV end-diastolic and end-systolic dimensions ($P < 0.0001$), lower LVEF ($P < 0.0001$) and lower LV relative wall thickness ($P = 0.0002$). There was no relationship with age, gender, hypertension, diabetes, CAD, renal failure or severity of AS. As expected, those with MR had higher mitral E/A velocity ratio ($P < 0.0001$) and shorter E wave deceleration time ($P < 0.0001$) indicating higher left atrial pressure, higher pulmonary artery pressure ($P < 0.0001$) and higher prevalence of heart failure ($P = 0.0015$). It is notable that 38% of patients with 3 or 4+ MR had no dyspnea or heart failure.

Though MR was strongly related to lower EF, 47% of patients with 3 or 4+ MR had an LVEF ≥ 50% (ACC/AHA guidelines use an EF threshold of < 50% as a class I indication for AVR or TAVR in patients with severe AS).

Mediation analysis and Cox regression analysis

In view of strong correlations between MR grade, EF and LV size and as all these were predictive of

Table 1 Characteristics of aortic stenosis patients with different grades of mitral regurgitation

	0 or 1+ MR	2+ MR	3 or 4+ MR	*P* value
Age (yr)	70 ± 12	74 ± 9	72 ± 13	< 0.05
Women (%)	44	48	51	0.4
Syncope (%)	3	4	4	0.85
Angina (%)	38	49	47	0.12
Dyspnea (%)	39	38	62	0.002
Atrial fibrillation (%)	24	32	33	0.18
Hypertension (%)	58	57	44	0.06
Diabetes mellitus (%)	24	22	18	0.4
Coronary artery disease (%)	53	60	58	0.3
Renal insufficiency (%)	10	8	13	0.39
LV end-diastolic diameter (mm)	48 ± 7	48 ± 4	56 +10	< 0.0001
LV end-diastolic dimeter index (mm/m^2)	26 ± 4	27 ± 4	23 + 6	< 0.0001
Left ventricular end-systolic diameter (mm)	31 ± 9	33 ± 9	41 + 13	< 0.0001
LV end-systolic dimeter index (mm/m^2)	16 ± 4	18 ± 4	41 + 13	< 0.0001
Ventricular septum (mm)	14 ± 2	14 ± 3	14 + 3	0.2
Posterior wall (mm)	13 ± 2	13 ± 2	12 ± 2	0.13
Relative wall thickness	0.57 + 0.15	0.57 + 0.13	0.48 + 0.13	0.0006
LV ejection fraction (%)	62 ± 16	54 ± 17	45 ± 21	< 0.0001
Left atrial dimension (mm)	41 ± 9	43 ± 8	48 ± 6	< 0.0001
Aortic valve area (cm^2)	0.72 + 0.16	0.68 + 0.16	0.70 + 0.20	0.18
Aortic valve peak gradient (mmHg)	73 ± 23	71 ± 26	67 +22	0.09
Aortic valve mean gradient (mmHg)	45 ± 15	43 ± 17	41 +15	0.08
Aortic regurgitation grade	0.65+0.83	1.16+0.91	1.00+1.00	< 0.0001
Mitral E/A velocity ratio	1.00 + 0.53	1.09 + 0.64	1.60 + 0.67	< 0.0001
Mitral E wave deceleration time (ms)	270 ± 105	278 ± 112	194 +89	0.0001
Pulmonary artery systolic pressure (mmHg)	40 ± 13	45 ± 20	53 +14	< 0.0001
Beta-blocker use (%)	46	46	27	0.02
ACEI or ARB use (%)	25	33	36	0.12
Digoxin use (%)	35	32	38	0.47
Statin use (%)	31	21	35	0.09
Coronary artery bypass grafting (%)	38	49	47	0.12
Mitral valve repair (%)	3	2	20	< 0.0001
Mitral valve replacement (%)	2	10	13	0.06

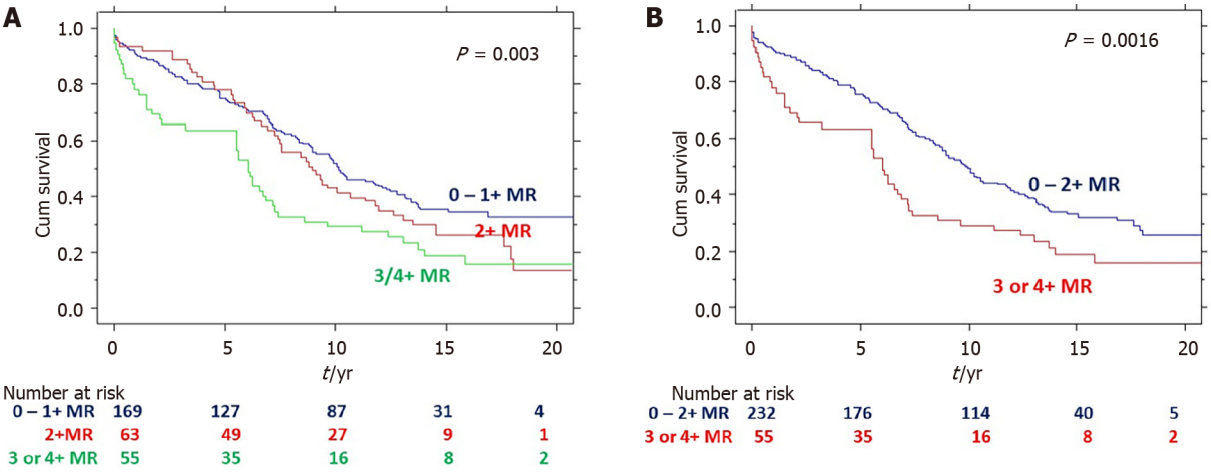
AS: Aortic stenosis; MR: Mitral regurgitation; LV: Left ventricular; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker.

survival, we performed mediation analysis described by Baron and Kenny by sequentially adding EF and LV end-systolic dimension to the Cox regression model that included MR severity[14]. Adding EF and LV end diastolic dimension, significantly reduced the χ^2 associated with MR, but MR still remained significant (P values for MR, EF and LV end –diastolic dimension: 0.0049, < 0.0001 and 0.0013 respectively and global χ^2 = 34.3). Addition of pulmonary artery pressure to the model did not improve its predictive value. This indicates that not all negative effects of MR were through increase in LV size and reduction in EF, but MR independently was related to survival as well. The results of Cox regression analysis are shown on Table 2.

Table 2 Results of Cox regression analysis on the effect of mitral regurgitation on survival

Variable	χ^2 value	*P* value
LV end-diastolic dimension	10.4	< 0.01
LV ejection fraction	23.3	< 0.0001
Mitral regurgitation	7.9	< 0.01

Global χ^2 = 34.3; LV: Left ventricular.



DOI: 10.4330/wjc.v15.i5.253

Figure 1 Survival in severe aortic stenosis patients undergoing aortic valve replacement as a function of preoperative severity of mitral regurgitation. A: MR severity split into 3 groups; B: MR severity split into 2 groups. MR: Mitral regurgitation.

Effect of MR on survival stratified by CABG status

Of the 287 patients with severe AS undergoing AVR, 121 had CABG and 166 did not have CABG. As shown in Figure 2, the deleterious effect of MR was seen in both groups of these patients (*P* = 0.007 and *P* = 0.05, respectively).

Mitral valve surgery in 3 or 4+ MR

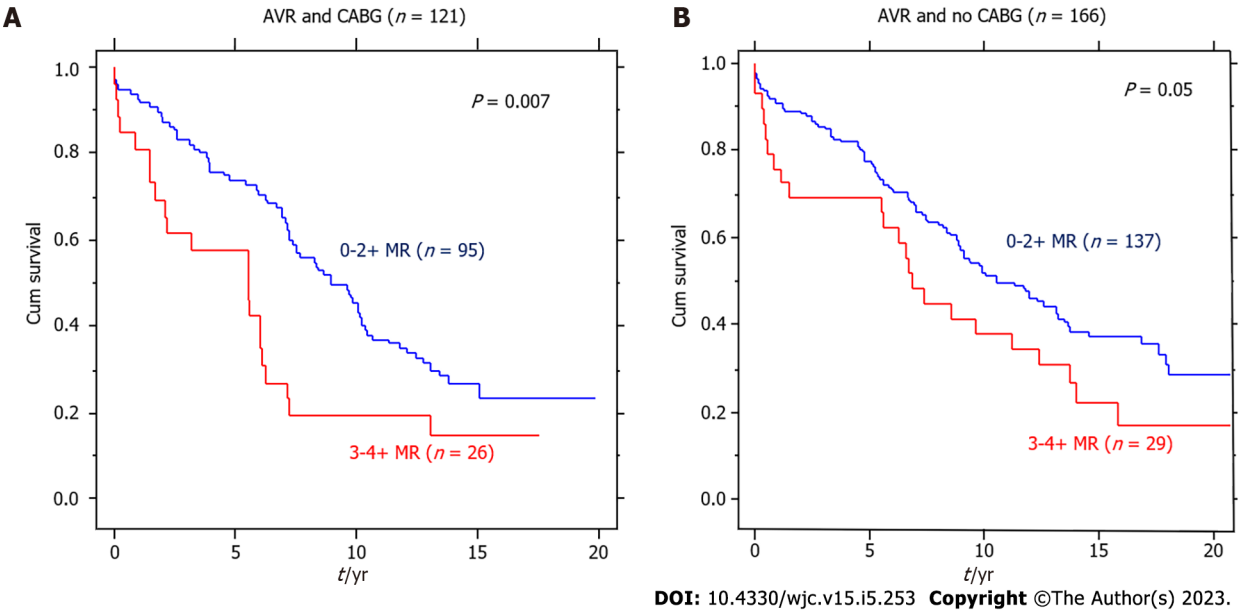
Mitral valve surgery was performed in 18 of the 55 patients with 3 or 4+ MR at the time of AVR. Of these 12 patients also underwent CABG at the time of mitral valve surgery. was a trend towards better survival with mitral valve surgery with 10- and 20-year survivals being 45% and 37% respectively in those with mitral valve surgery compared to 22% and 8% respectively for those without (*P* = 0.08, Figure 3).

DISCUSSION

Our observational study with very long-term data suggests harm produced by MR in patients with severe AS undergoing AVR. According to ACC/AHA guidelines, MR is not considered an indication for AVR in severe AS patients in the absence of symptoms or EF < 50% or a need for concomitant cardiac surgery. About 1/3 of our patients even with 3 or 4+ MR had no symptoms and one half of them had an EF ≥ 50% without a traditional indication for AVR. These findings are novel and have major clinical implications in the management of these patients. The other strength of our study is length of follow up – to death or 16-26 years in the long-term survivors.

Presence of MR was also associated with higher left atrial and pulmonary artery pressures and some degree of LV enlargement indicative of adverse LV remodeling and functional impairment. Data from patients undergoing TAVR or AVR for severe AS indicates that MR may regress by one grade in about half the patients, but not full regression in all the patients leaving the patients with significant MR which may have negative impacts in terms of symptoms, heart failure and reduced survival or a need for another procedure to eliminate MR[4,15].

The mechanism of MR seems to be mostly functional because of an increase in LV size leading to mitral leaflet tethering in contemporary series with calcific AS, though older series included rheumatic



DOI: 10.4330/wjc.v15.i5.253

Figure 2 Effect of preoperative mitral regurgitation severity on survival in aortic valve replacement patients stratified by concomitant coronary artery bypass grafting status. A: Patients who had AVR and CABG; B: Patients who had AVR only and no CABG. MR: Mitral regurgitation; AVR: Aortic valve replacement; CABG: Concomitant coronary artery bypass grafting.

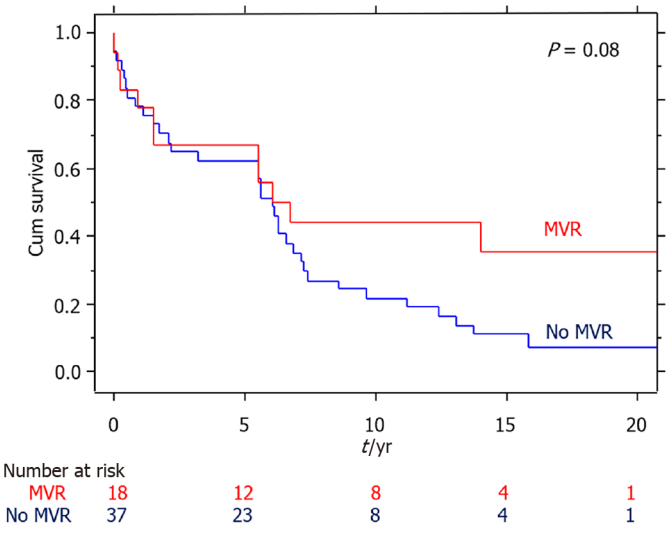


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Figure 3 Survival in patients with pre-aortic valve replacement 3 or 4+ mitral regurgitation as a function of mitral valve repair or replacement during aortic valve replacement surgery. MVR: Mitral valve repair or replacement.

valve disease as well[16]. There could also be an atrial mechanism due to atrial enlargement due to LV diastolic dysfunction or atrial fibrillation leading to secondary mitral annular dilatation[17]. Hence, monitoring asymptomatic severe AS patients for increases in LV or left atrial size or onset of atrial fibrillation may be important, besides evaluating for presence, degree and mechanism of MR. Performance of AVR or TAVR will reduce LV systolic pressure that drives MR. In addition, reverse remodeling of the LV and left atrium may occur as well and this will help in MR regression. One should also consider restoration of sinus rhythm to reduce the risk of genesis or progression of MR as atrial fibrillation may produce MR and even tricuspid regurgitation through atrial and annular dilation. Patients undergoing TAVR may introduce another issue of production of left bundle branch block or complete heart block needing a pacemaker. Both of these electrical disturbances may impair LV function and produce or worsen MR. These mechanistic factors should be kept in mind in patients with severe AS.

There are some limitations to this retrospective observational study. We do not have follow up echocardiographic data as the images are generally archived only for 7 years and many patients had these studies outside our healthcare system. Also, surgery for MR was at the discretion of the operating

surgeon.

CONCLUSION

In summary, 3 or 4+ MR is present in about 20% of patients undergoing AVR for severe AS and negatively impacts hemodynamics, symptoms and survival. We suggest that one should be vigilant for any MR in patients with severe AS and also the potential mechanisms that may lead to MR such as progressive LV or left atrial dilation or onset of atrial fibrillation. We also suggest that presence of ≥ 3+ MR in patients severe AS should be considered as a potential indication for AVR or TAVR as appropriate.

ARTICLE HIGHLIGHTS

Research background

Severe aortic stenosis (AR) and concomitant mitral regurgitation (MR) are common. But the impact of MR in those with severe AS on outcomes and management are unknown.

Research motivation

To study the impact of concomitant MR on outcomes in severe AS.

Research objectives

Does MR affect prognosis and decision making in severe AS patients.

Research methods

Of the 740 consecutive patients with severe AS evaluated between 1993 and 2003, 287 underwent AVR forming the study cohort. They were followed up to death or till the end of 2019. Chart reviews were performed for clinical, echocardiographic, and therapeutic data. MR was graded on a 1-4 scale. Mortality data was obtained from chart review and the Social Security Death Index. Survival was analyzed as a function of degree of MR.

Research results

Presence of MR was associated with higher mortality in a graded fashion. MR was significantly associated with lower left ventricular (LV) ejection fraction and larger LV size. Impact of MR on mortality was partially mediated through lower LV ejection fraction and larger LV size. By Cox regression, MR, lower ejection fraction (EF) and larger LV end-systolic dimension were independent predictors of higher mortality.

Research conclusions

Presence of greater than 2+ MR in patients with severe AS is independently associated with reduced survival in surgically managed patients, an effect incremental to reduced EF and larger LV size. We suggest that aortic valve intervention should be considered in severe AS patients when > 2+ MR occurs irrespective of EF or symptoms.

Research perspectives

More studies are needed to study the mechanisms of MR and its prevention in severe AS patients.

FOOTNOTES

Author contributions: Pai RG and Varadarajan P designed the study, analyzed the data, wrote the manuscript and revised the final form.

Institutional review board statement: The research project was approved by the institutional review board of Loma Linda University, Loma Linda, California.

Informed consent statement: A need for an informed consent was waived because of its retrospective, observational study design without any intervention.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

Country/Territory of origin: United States

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S-Editor: Liu XF
L-Editor: A
P-Editor: Yu HG

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2023 May 26; 15(5): 262-272

DOI: 10.4330/wjc.v15.i5.262

ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Observational Study

Pharmacoepidemiologic study of association between apparent treatment resistant hypertension, cardiovascular disease and interaction effect by sex and age

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Awad AK, Egypt; Jain S, India

Received: December 18, 2022
Peer-review started: December 18, 2022
First decision: March 1, 2023
Revised: March 31, 2023
Accepted: April 18, 2023
Article in press: April 18, 2023
Published online: May 26, 2023

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Abstract

BACKGROUND

A limited number of studies have been conducted to test the magnitudes of the association between apparent treatment resistant hypertension (aTRH) and risk of cardiovascular disease (CVD).

AIM

To investigate the association between aTRH and risk of CVD and examine whether sex and age modify this association.

METHODS

We applied an observational analysis study design using data from the United States Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT recruited participants (n = 25516) from 625 primary care settings throughout the United States, Canada, Puerto Rico, and United States Virgin Islands, aged 55 and older with hypertension and at least one additional risk factor for heart disease. aTRH was assessed from the year 2 visit. CVD event was defined as one of the following from the year 2 follow-up visit: Fatal or non-fatal myocardial infarction, coronary revascularization, angina, stroke, heart failure, or peripheral artery disease. Cox proportional hazards regression was used to examine the effect of aTRH on CVD risk. Potential modifications of sex and age on this association were examined on the multiplicative scale by interaction term and additive scale by joint effects and relative excess risk for interaction.

RESULTS

Of the total study participants (n = 25516), 5030 experienced a CVD event during a mean of 4.7 years follow-up. aTRH was associated with a 30% increase in risk of CVD compared to non-aTRH [hazards ratio (HR) = 1.3, 95%CI: 1.19-1.42]. Sex and

age modified this relationship on both multiplicative and additive scales independently. Stratified by sex, aTRH was associated with a 64% increase in risk of CVD (HR = 1.64, 95%CI: 1.43–1.88) in women, and a 13% increase in risk of CVD (HR = 1.13, 95%CI: 1.01–1.27) in men. Stratified by age, aTRH had a stronger impact on the risk of CVD in participants aged < 65 (HR = 1.53, 95%CI: 1.32–1.77) than it did in those aged ≥ 65 (HR = 1.18, 95%CI: 1.05–1.32). Significant two-way interactions of sex and aTRH, and age and aTRH on risk of CVD were observed (P < 0.05). The observed joint effect of aTRH and ages ≥ 65 years (HR = 1.85, 95%CI: 1.22–2.48) in males was less than what was expected for both additive and multiplicative models (HR = 4.10, 95%CI: 3.63–4.57 and 4.88, 95%CI: 3.66–6.31), although three-way interaction of sex, age, and aTRH on the risk of CVD and coronary heart disease did not reach a statistical significance (P > 0.05).

CONCLUSION

aTRH was significantly associated with an increased risk of CVD and this association was modified by both sex and age. Further studies are warranted to test these mechanisms.

Key Words: Apparent treatment resistant hypertension; Cardiovascular disease outcomes; Chronic kidney disease; Sex; Age

Core Tip: Apparent treatment resistant hypertension (aTRH) increased the risk of a cardiovascular event by 30%. This association varied by sex and age, with a stronger impact in women and in younger adults. These findings highlight the importance of controlling aTRH among those with excess risk of cardiovascular disease.

Citation: Nelson JT, Liu L. Pharmacoepidemiologic study of association between apparent treatment resistant hypertension, cardiovascular disease and interaction effect by sex and age. *World J Cardiol* 2023; 15(5): 262-272
URL: https://www.wjgnet.com/1949-8462/full/v15/i5/262.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i5.262

INTRODUCTION

Hypertension has long been a serious public health concern. Its impact on cardiovascular health and long-term outcomes has been well studied[1]. In the United States approximately 121.5 million (47.3%) adults suffer from hypertension leading to an added economic burden costing up to $51.1 billion per year[2]. One of the significant challenges in control of hypertension is the appearance of treatment resistant hypertension.

Treatment resistant hypertension is defined as having blood pressure (BP) that remains uncontrolled [systolic BP (SBP) ≥ 140 mmHg or diastolic BP (DBP) ≥ 90 mmHg] while a patient is on ≥ 3 different antihypertensive medications. Additionally, those who are on 4 or more different classes of antihypertensive medications, regardless of BP are also classified as treatment resistant hypertension. Individuals with diabetes or chronic kidney disease (CKD) have an altered definition, these patients with SBP/DBP ≥ 130/80 mmHg are classified as treatment resistant hypertension[3-5]. In addition to the number of antihypertensive medications and BP readings, ideally at least one of the medications should be a diuretic[6]. Apparent treatment resistant hypertension (aTRH) is used to define observed treatment resistant hypertension when factors relating to pseudoresistance (adherence to regimen, sufficient dose for therapy, *etc*.) are unknown[7].

It is estimated that 19.7% of patients on antihypertensive medication have aTRH, a 2% increase within the recent decade[3-5]. While it is known that treatment of hypertension can reduce the risk of cardiovascular events and mortality, little research has been done on outcomes of those with resistant hypertension[3,8]. Several cross-sectional studies have found relationships between aTRH and cardiovascular disease (CVD), however, longitudinal studies remain sparse[3,9]. What has been observed is that aTRH is associated with higher rates of cardiovascular and renal diseases, including: Coronary heart disease (CHD), peripheral artery disease (PAD), stroke, heart failure (HF), end-stage renal disease, and all-cause mortality. Of particular note is that aTRH increased the risk of CHD by 44% and the risk of death by 30% compared to non-aTRH[9,10].

Men and women experience differing rates of hypertension and CVD[11,12]. However, findings of sex-specific aTRH studies remain inconsistent[3,5,13-15]. Women experience an increase in risk of hypertension post-menopause indicating a possible impact of sex and age on the risk of aTRH and CVD

outcomes[12].

Of the many risk factors for CVD, age is one of the most important factors as age is an independent risk factor for the development of atherosclerosis[5,11,16,17]. However, the degree of this effect does not impact men and women in the same way neither in the risk of incident hypertension nor in the progress of hypertension in clinical treatment[11,18]. Several studies have observed that age is significantly and independently associated with risk of aTRH[3-5,14]. However, studies of the potential modification effects of sex and age on the association between aTRH and risk of CVD are limited. In this study, we hypothesized that sex and age play an important role both independently and together in the risk of aTRH for CVD outcomes. To test this hypothesis, we examined the independent and additive effects of sex and age on aTRH and risk of CVD, and whether sex and age modify the association between aTRH and CVD risk.

MATERIALS AND METHODS

Study sample

We analyzed data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). In ALLHAT, a total of 42418 participants aged 55 and older were recruited from 625 primary care settings throughout the United States, Canada, Puerto Rico, and United States Virgin Islands. Participants were randomly assigned into four groups and then received one of four antihypertensive treatment arms: Chlorthalidone, amlodipine, lisinopril, and doxazosin. Participants who received doxazosin are excluded in the analysis because this group was discontinued early. All participants had hypertension and at least one additional risk factor for CHD. Participants were followed for an average of 6 years[19-21]. The study design and process of ALLHAT have been published in detail elsewhere[21].

This study, using de-identified data from the National Heart, Lung, and Blood Institute, has been approved by Drexel University Institutional Review Board (# 1608004781).

Measures

Exposure (aTRH): In ALLHAT the recruited participants were initially randomized to one of 4 first-line antihypertensive drugs. Additional anti-hypertensive medications were added on to therapy over the course of follow-up visits, thus, aTRH was determined at the year 2 visit to allow time for additional medications to be added, consistent with follow-up studies[10,21]. aTRH was defined as BP ≥ 140/90 while on 3 antihypertensive medications, or being on 4 antihypertensive medications regardless of BP at the year 2 visit. For subjects with either type II diabetes or CKD (assessed by glomerular filtration rate, epidermal growth factor receptor (eGFR) < 60 mL/min), the cut-offs of SBP/DBP were set at ≥ 130/80 mmHg. Due to subjects being randomized to first-line anti-hypersensitive treatment, the condition that one medication be a diuretic for aTRH classification could not be applicable in the study.

Outcome (CVD): Subjects were classified as having had a CVD event if they experienced one of the following after the year 2 follow-up visit: Fatal or non-fatal myocardial infarction (MI), coronary revascularization, angina, stroke, HF, or PAD. These events were ascertained from follow-up visits and medical recording during the course of the trial[10].

Covariates: Covariates were selected based on their independent associations with both the exposure (aTRH) and outcome (CVD), existing literature, and use of a directed acyclic graph[10]. All covariates were measured at baseline of ALLHAT. They included: Race (white, African American, American Indian/Alaskan Native, Asian/Pacific Islander, other), ethnicity (Hispanic), geographic region (East, Midwest, South, West, Canada, Puerto Rico/Virgin Islands), measures of GFR, SBP and DBP at baseline, and history of CHD, history of MI or stroke, history of coronary revascularization, previous use of BP medication, smoking status (current, former, never), history of left ventricular hypertrophy, estrogen use (in women subgroup analysis only), aspirin use, and enrollment in concurrent lipid lowering trial.

Statistics

Univariate analysis was conducted to describe the baseline characteristics of participants by aTRH status. Student's *t* test was used to examine mean difference in continuous variables, and Chi-square tests to examine rate and proportion differences in categorical variables. We used Cox Proportional Hazards regression models to examine the association between aTRH and CVD risk with adjusting covariates. Assumptions of the proportional hazards in Cox model were tested graphically by log-log survival curves. To test potential modification effects of sex (men *vs* women) and age (< 65 *vs* ≥ 65) on the association between aTRH and CVD risk, we assessed potential multiplicative interaction (*e.g.*, aTRH*modifier) on CVD risk. We also assessed potential additive interaction effects on CVD risk by estimating the joint effects and calculating the relative excess risk for interaction (RERI)[22]. If the RERI ≠ 0 then there is evidence that the observed additive risk of our exposures is different (more or less depending on the direction of the RERI) than what was expected. The methods of the calculations and hypothesis tests for the RERI have been discussed and published in detail elsewhere[23]. To test the overall interaction effect of sex and age and aTRH on CVD risk, we tested three-way interaction through

a product interaction term (*e.g.*, aTRH*sex*age) in Cox models. Observed joint effects were compared to expected for both additive and multiplicative models to determine presence of effect modification and subgroup analyses were performed.

Sensitivity analyses: To avoid overfitting attributable to multiple control covariates, we applied a propensity score analysis technique[24]. A propensity score for the probability of aTRH was estimated utilizing all confounders and created using the boosted CART method in the "twang" package in R software[25-27]. Extreme weights were trimmed and inverse probability weighting was used to weight observations by the propensity score[24,28]. Second, in the ALLHAT study, missing data in BP measures occurred at year 2 visit. We conducted a sensitivity analysis using Markov Chain Monte Carlo method for multiple imputation based on the randomness of the missing values[29]. Third, because of the pathophysiologic differences between hemorrhagic and ischemic stroke, we conducted a subgroup of CVD analysis by strokes and CHD (fatal CHD or nonfatal MI, coronary revascularization, or hospitalized angina). Fourth, to control the effects attributable to the conclusion of patients who had uncontrolled hypertension (BP ≥ 140/90) but with < 3 medications (n = 11223), on the estimate of hazards ratio (HR) for CVD risk, we excluded this group of patients in the final sensitivity analysis.

Data analyses were conducted using SAS software (Version 9.4, SAS Institute Inc., Cary, NC, United States). Statistical significance as set up at a two-sided $P < 0.05$.

RESULTS

From the original sample of 42418 subjects in ALLHAT, those on the doxazosin treatment arm (9061) were removed early for safety reasons. After excluding subjects with CVD events or death prior to year 2, and those missing year 2 visit information we had an analytic study sample of 25516. During the follow-up (average 4.7 years), 5030 (19.7%) participants had a CVD event. Table 1 shows baseline characteristics of the participants.

Overall subjects were more likely male (53.3%), from the South (41.6%), white (60.3%), and previously treated for hypertension (90.3%). Over a third (35.2%) had type 2 diabetes (T2DM), and 40.7% were former smokers. While over 40% of subjects were obese, the average body mass index (BMI) was 29.7 (SD 5.92). The average age was 66 years, and average GFR 78 mL/min. The rate of aTRH was 9.1% (n = 2329) in the total sample, 9.8% in men, 8.4%% in women, and 9.1% in those aged 65 and older. Subjects with aTRH were predominantly more likely to be African American, male, BMI ≥ 30 kg/m^2, and T2DM than their corresponding counterparts.

Table 2 shows that after adjustment for covariates, aTRH remained significantly associated with risk of CVD (HR = 1.30, 95%CI: 1.19–1.42, $P < 0.0001$).

Sensitivity analyses of propensity score for adjusting multi-covariates and multiple imputation for estimates of missing values produced similar results as did the analysis involving exclusion of participants with uncontrolled BP on < 3 medications. When CHD was examined as the endpoint instead of CVD, the overall risk associated with aTRH was stronger (HR = 1.56, 95%CI: 1.29–1.89).

Table 3 shows individual and joint effects. Among women, aTRH was associated with a 64% increase in risk of CVD event (95%CI: 1.43–1.88), and a 13% increase in risk of CVD (95%CI: 1.01–1.27) among men. aTRH had a stronger impact on risk of CVD among younger subjects than it did among older (HR = 1.53, 95%CI: 1.32–1.77 In those aged < 65, and HR = 1.18, 95%CI: 1.05–1.32 in those aged 65 and older). All HRs were statistically significant and the two-way multiplicative interaction terms of sex*aTRH, and age*aTRH and RERIs on risk of CVD were statistically significant ($P < 0.05$).

Results stratified by aTRH, age, and sex can be found in Table 4 and Figure 1. Females aged 65 and older with aTRH had the highest risk of CVD (HR = 2.61, 95%CI 2.20–3.01), followed by men < 65 years with aTRH (HR = 2.17, 95%CI: 1.76–2.58). The observed joint effect (HR = 1.85, 95%CI: 1.22–2.48) was less than expected for both additive and multiplicative models (HR = 4.10, 95%CI: 3.63–4.57 and HR = 4.88, 95%CI: 3.66–6.31 respectively). However, the three-way interaction term for sex, age and aTRH was not significant for CVD ($P = 0.28$), and CHD ($P = 0.42$).

DISCUSSION

The overall findings of the present study indicate that there is a positive association between aTRH and risk of CVD. Based on statistically significant two-way interactions of sex with aTRH, and age with aTRH, heterogeneous strata results, statistically significant RERIs, and differing observed and expected joint effects, this study highlights that the association between aTRH and risk of CVD is modified independently by sex and age on both the additive and multiplicative scales.

Although it appeared there was a potential three-way interaction such that sex may modify the interaction of age and aTRH, and vice versa that age may modify the interaction of sex and aTRH on CVD risk, testing for these three-way interactions were not statistically significant. The results suggest that the interaction of sex and aTRH, or of age and aTRH did not depend on the third factor. This finding adds new insights into the body of the literature, that sex and age independently modify the

Table 1 Baseline characteristics overall and by apparent treatment resistant hypertension status, *n* (%)

	Overall	Resistant hypertension		
		Yes	No	*P* value
Total	25516	2329 (9.1)	23187 (90.9)	
Treatment group				< 0.001
Chlorthalidone	11808 (46.3)	853 (36.6)	10955 (47.3)	
Amlodipine	6955 (27.3)	554 (23.8)	6401 (27.6)	
Lisinopril	6753 (26.5)	922 (39.6)	5831 (25.2)	
Race				< 0.001
White	15397 (60.3)	1272 (54.6)	14125 (60.9)	
African American	8808 (34.5)	953 (40.9)	7855 (33.9)	
Am. Indian/Alaskan Native	58 (0.2)	3 (0.1)	55 (0.2)	
Asian/Pacific Islander	312 (1.2)	26 (1.1)	286 (1.2)	
Other	941 (3.7)	75 (3.2)	866 (3.7)	
Hispanic	4485 (17.6)	204 (8.8)	4281 (18.5)	< 0.001
Sex				< 0.001
Male	13597 (53.3)	1333 (57.2)	12264 (52.9)	
Female	11919 (46.7)	996 (42.8)	10923 (47.1)	
Geographic region				< 0.001
East	3917 (15.4)	337 (14.5)	3580 (15.4)	
Midwest	4736 (18.6)	449 (19.3)	4287 (18.5)	
South	10603 (41.6)	1165 (50.0)	9438 (40.7)	
West	2635 (10.3)	254 (10.9)	2381 (10.3)	
Canada	461 (1.8)	33 (1.4)	428 (1.9)	
PR/VI	3164 (12.4)	91 (3.9)	3073 (13.3)	
Preventive HTN treat	23033 (90.3)	2242 (96.3)	20791 (89.7)	< 0.001
Obese	10604 (41.6)	1085 (46.6)	9519 (41.1)	< 0.001
History of MI or stroke	5499 (21.6)	498 (21.4)	5001 (21.6)	0.84
History of coronary revascularization	3016 (11.8)	327 (14.0)	2689 (11.6)	< 0.001
Type 2 diabetes	8975 (35.2)	1061 (45.6)	7914 (34.1)	< 0.001
left ventricular hypertrophy	5110 (20.0)	551 (23.7)	4559 (19.7)	< 0.001
History of CHD	5981 (23.6)	534 (23.2)	5447 (23.7)	0.61
Smoking status				< 0.001
Current	5491 (21.5)	423 (18.2)	5068 (21.9)	
Past	10394 (40.7)	992 (42.6)	9402 (40.6)	
Never	9631 (37.7)	914 (39.2)	8717 (37.6)	
Aspirin use	9084 (35.6)	922 (39.6)	8162 (35.2)	< 0.001
Estrogen use (in women)	2230 (18.7)	182 (18.3)	2048 (18.8)	0.84
Age (years) (mean ± SD)	66.6 ± 7.5	67 ± 7.5	67 ± 7.5	0.78
BMI (kg/m^2) (mean ± SD)	29.7 ± 5.9	30 ± 5.9	30 ± 5.9	< 0.001
SBP (mm Hg) (mean ± SD)	146.0 ± 15.6	152 ± 15.1	145 ± 15.5	< 0.001
DBP (mm Hg) (mean ± SD)	84.0 ± 10.0	85 ± 10.6	84 ± 9.9	0.001
Cholesterol (mean ± SD)	215.7 ± 42.5	216 ± 44.8	216 ± 42.2	0.79

GFR	78.0 ± 19.3	75 ± 20.6	78 ± 19.2	< 0.001

HTN: Hypertension; MI: Myocardial infarction; CHD: Coronary heart disease; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; GFR: Growth factor receptor; PR: Puerto Rico; VI: United States Virgin Islands.

Table 2 Hazard ratios of apparent treatment resistant hypertension for cardiovascular disease risk and sensitivity analyses

	Model 1			Model 2			Model 3		
	HR	95%CI		HR	95%CI		HR	95%CI	
aTRH	1.51	1.39	1.64	1.49	1.37	1.62	1.3	1.19	1.42
Sensitivity analyses									
Propensity score							1.33	1.20	1.48
Multiple imputation sensitivity analysis							1.24	1.16	1.33
CHD							1.56	1.29	1.89
Without uncontrolled on < 3 drugs							1.3	1.18	1.44

aTRH: Apparent treatment resistant hypertension; HR: Hazards ratio; Model 1: Crude; Model 2: Adjusted for age and sex; Model 3: Adjusted for age, sex, region, race, body mass index, diabetes; GFR: Growth factor receptor, history of CHD, history of myocardial infarction (MI)/Stroke, history of coronary revascularization, baseline systolic blood pressure (BP), baseline diastolic BP, left ventricular hypertrophy, smoking status, baseline BP medication use, aspirin, lipid lowering trial. Propensity score weighting sensitivity analysis (model 3). Multiple imputation sensitivity analysis (model 3); CHD: Coronary heart disease-outcome CHD (fatal CHD or nonfatal MI, coronary revascularization, or hospitalized angina) (model 3).

Table 3 Joint effects for interaction of sex and apparent treatment resistant hypertension, and age and apparent treatment resistant hypertension on cardiovascular disease risk

		aTRH (No)		aTRH (Yes)		
		HR	(95%CI)	HR	(95%CI)	HR (95%CI) by sex
Sex	Female	Reference		1.67	(1.45, 1.91)	1.64 (1.43, 1.88)
	Male	1.25	(1.16, 1.34)	1.39	(1.12, 1.56)	1.13 (1.01, 1.27)
HR (95%CI) (M *vs* F)		1.25	(1.16, 1.35)	0.80	(0.66, 0.97)	
RERI (95%CI)		-0.52	(-0.75, 0.25)			
Interaction of sex and aTRH on CVD: $P < 0.0001$						
						HR (95%CI) by age
Age	< 65	Reference		1.56	(1.42, 1.71)	1.53 (1.32, 1.77)
	≥ 65	1.38	(1.31, 1.45)	1.61	(1.48, 1.73)	1.18 (1.05, 1.32)
	≥ 65 *vs* < 65	1.37	(1.28, 1.47)	1.05	(0.87, 1.27)	
RERI (95%CI)		-0.339	(-0.61, 0.06)			
Interaction of age and aTRH on CVD: $P = 0.0326$						

CVD: Cardiovascular disease; HR: Hazards ratio; aTRH: Apparent treatment resistant hypertension; F: Female; M: Male; RERI: Relative excess risk for interaction.

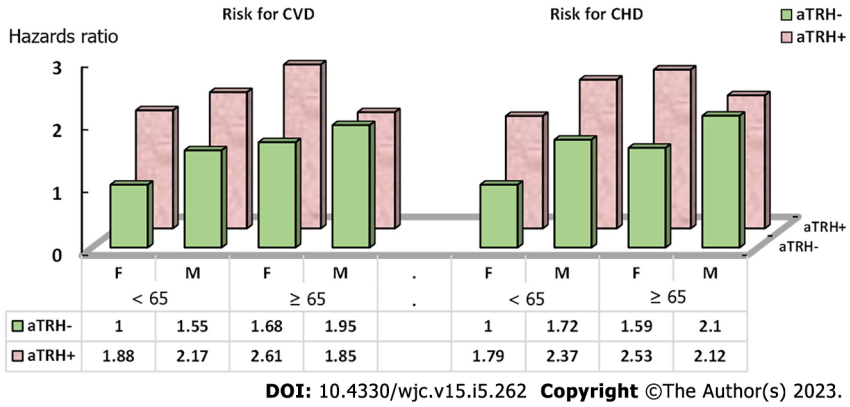
association between aTRH and CVD.

Treating BP becomes more difficult as a patient ages and is complicated by differing BP goals by age and a possible U-shaped relationship between BP and mortality among the elderly. Among this population also exists the risk of over-correcting and lowering BP too much which can cause other health concerns including dizziness and falls[2,30,31]. However, 2017 ACC/AHA changes to the guidelines no longer specify a different target BP for those ≥ 60 and the SPRINT study of older Americans indicated better health outcomes among those with more aggressive BP lowering targets (SBP 120 *vs* 140 mmHg)[32,33]. This area remains a topic of debate with more research needed on this

Table 4 Joint impact of age, sex, and apparent treatment resistant hypertension on cardiovascular disease and coronary heart disease risk

	Sex	Age	HR	(95%CI)
Risk for CVD				
aTRH				
No	Female	< 65	Reference	
No	Male	< 65	1.55	(1.43-1.67)
No	Female	65+	1.68	(1.56-1.79)
No	Male	65+	1.95	1.70-2.20)
Yes	Male	65+	1.85	(1.22-2.48)
Yes	Female	< 65	1.88	(1.64-2.11)
Yes	Male	< 65	2.17	(1.76-2.58)
Yes	Female	65+	2.61	(2.20-3.01)
Three-way interaction of sex, age, and aTRH on CVD, *P* = 0.2841				
Risk for CHD				
aTRH				
No	Female	< 65	Reference	
No	Male	< 65	1.72	(1.57-1.86)
No	Female	65+	1.59	(1.44-1.74)
No	Male	65+	2.1	(1.77-2.42)
Yes	Male	65+	2.12	(1.28-2.97)
Yes	Female	< 65	1.79	(1.47-2.11)
Yes	Male	< 65	2.37	(1.82-2.92)
Yes	Female	65+	2.53	(1.98-3.08)
Three-way interaction of sex, age, and aTRH on CHD, *P* = 0.4246				

CVD: Cardiovascular disease; HR: Hazards ratio; aTRH: Apparent treatment resistant hypertension; CHD: Coronary heart disease.



DOI: 10.4330/wjc.v15.i5.262

Figure 1 Joint effects of sex and age on the risk of cardiovascular disease and coronary heart disease by apparent treatment resistant hypertension status. CVD: Cardiovascular disease; CHD: Coronary heart disease; aTRH: Apparent treatment resistant hypertension; F: Female; M: Male.

unique population.

Research has shown that older women are more likely to adhere to medications and more likely to have their BP taken regularly, yet they appear to experience higher rates of uncontrolled hypertension [15]. Multiple mechanisms are believed to contribute to this increase in hypertension and uncontrolled hypertension in aging women including: Activation of the renin angiotensin system, obesity, activation

of sympathetic nervous system, and decline in estrogen levels[15,17,34]. Stress on the body due to hypertension is believed to be more severe in women than in men[35]. Coupled with gender biases in treatment and management of CVD symptoms and events, we can envision how uncontrolled hypertension and aTRH would lead to more adverse health outcomes in women than men, especially in an aging population[36,37]. The pathophysiology of aTRH is believed to be linked to blood volume and salt, and salt-sensitive hypertension increases in women post-menopause thus we would expect aTRH to be more prevalent among post-menopausal women[18,38,39].

Very few studies have examined potential effect modifiers on the relationship between aTRH and CVD. Our findings are consistent with existing research in that aTRH is positively associated with CVD and both sex and age independently can modify the association between aTRH and CVD[3-5,9,10]. However, these studies only examined relative measures of association. Our study both confirmed presence of two-way interaction on the multiplicative scale and also identified that this modification is present on the additive scale. Epidemiologists have noted that additive interaction is most important for public health as it indicates an absolute number of cases which would be prevented if the modifier were removed[22,40].

No study to date has examined potential three-way interaction with aTRH. With health effects of sex and age linked it is important to examine how these gender disparities in cardiovascular outcomes of patients with aTRH differ between subgroups of age[11,12]. Public health programs aimed at improving awareness of aTRH should make specific effort to target women and informing them of the dangerous health consequences associated. This study suggests that physicians should take special note in their treatment considerations when female patients are experiencing uncontrolled hypertension and understand the serious cardiovascular risks associated with developing aTRH. For example, because the interaction of age and aTRH on CVD did not change by sex, we would still endorse applying these recommendations to vigorously control aTRH in women of all ages instead of focusing on the older group only.

This study has several strengths. ALLHAT provides us with one of the largest datasets to test the impact of aTRH on CVD risk. Sample size is particularly important when analyzing effect modification as it utilizes subgroup analyses. We also deployed two methods (propensity score weighting and multiple imputation) to conserve power in our analyses. Similar findings from our original analysis and both sensitivity analyses indicate our study is adequately powered. Another strength provided by use of ALLHAT is in our classification of aTRH. BP was taken twice from a seated position and averaged for each study visit, medication adherence was maintained through pill counts at each study visit, and doses of antihypertensive medications were appropriately titrated up to the maximum tolerated dose prior to adding on an additional medication. All of these factors allow for accurate ascertainment of aTRH status and reduce the likelihood of false positives due to pseudoresistance[2-5].

While a strong study, there are also several limitations. As this study is limited to its analysis of variables collected in ALLHAT only, additional data could be included in the analysis. For example, dietary salt intake was not measured in ALLHAT, thus we could not adjust for this in multivariate models as it is suggested that aTRH is influenced by blood volume and salt intake[38,39]. However, because ALLHAT is a randomized clinical trial, potential unmeasured factors are balanced among the participants. The clinical trial nature of our data source, while a strength for validity of aTRH classification, is also a limitation as subjects were selected based on pre-determined criteria best fit for the goals of ALLHAT and thus further studies are needed to confirm the results among different study populations. The study participants consisted of older adults (≥ 55) and thus findings of the study in women should also be evaluated in women aged 55 and older, instead of interpretating the results to those aged < 55. Additionally, the impact of pseudoresistance can never be completely removed and "white coat" effect is always a possibility when examining BP readings.

aTRH increases the risk of CVD in patients with hypertension and this relationship is modified by age and sex independently on both the relative (multiplicative) and absolute (additive) scales. More research is needed to shed further light on these gender differences, especially with regard to women both pre and post menopause. Future research should focus on these sex and age differences and how it might impact treatment and control of aTRH as there is still much unknown about this specific relationship. Management of aTRH should take a patient's age and sex into consideration and more preventive interventions should be aimed at aging women as they represent the subgroup of aTRH patients with the highest combined risk of CVD.

CONCLUSION

aTRH was significantly associated with an increased risk of CVD and this association was modified by both sex and age. Further studies are warranted to test these mechanisms.

ARTICLE HIGHLIGHTS

Research background

A Limited number of studies have been conducted to test the magnitudes of the association between apparent treatment resistant hypertension (aTRH) and risk of cardiovascular disease (CVD).

Research motivation

aTRH is significantly associated with the risk of CVD. It is important to understand whether age and sex significantly modify this association. Findings of the study could add new evidence to the body of literature, and provide new insights into further mechanism studies.

Research objectives

To investigate the association between aTRH and risk of CVD and examine whether sex and age modify this association.

Research methods

We applied an observational analysis study design using data from the United States Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT recruited participants (n = 25516) from 625 primary care settings throughout the United States, Canada, Puerto Rico, and United States Virgin Islands, aged 55 and older with hypertension and at least one additional risk factor for heart disease. aTRH was assessed from the year 2 visit. CVD event was defined as one of the following from the year 2 follow-up visit: Fatal or non-fatal myocardial infarction, coronary revascularization, angina, stroke, heart failure, or peripheral artery disease. Cox proportional hazards regression was used to examine the effect of aTRH on CVD risk. Potential modifications of sex and age on this association were examined on the multiplicative scale by interaction term and additive scale by joint effects and relative excess risk for interaction.

Research results

Of the total study participants, 5030 experienced a CVD event during a mean of 4.7 years follow-up. aTRH was associated with a 30% increase in risk of CVD compared to non-aTRH [hazards ratio (HR) = 1.3]. Sex and age modified this relationship on both multiplicative and additive scales independently. Stratified by sex, aTRH was associated with a 64% increase in risk of CVD in women, and a 13% increase in risk of CVD in men. Stratified by age, aTRH had a stronger impact on the risk of CVD in participants aged < 65 than it did in those aged ≥ 65. Significant two-way interactions of sex and aTRH, and age and aTRH on risk of CVD were observed (P < 0.05). The observed joint effect of aTRH and ages ≥ 65 years in males was less than what was expected for both additive and multiplicative models, although three-way interaction of sex, age, and aTRH on the risk of CVD and CHD did not reach a statistical significance (P > 0.05).

Research conclusions

aTRH was significantly associated with an increased risk of CVD and this association was modified by both sex and age.

Research perspectives

Further studies are warranted to test these mechanisms.

FOOTNOTES

Author contributions: Nelson JT and Liu L contributed to the design and analysis of the study; Nelson JT prepared the written manuscript; Liu L critically reviewed and edited the manuscript.

Institutional review board statement: This study, using de-identified data from the National Heart, Lung, and Blood Institute, has been approved by Drexel University Institutional Review Board, No. 1608004781 (Principal Investigator: Longjian Liu).

Informed consent statement: This ALLHAT data is de-identified and publicly available for investigators to obtain through an IRB application process. Signed Informed Consent Forms are unavailable for the investigators conducting a secondary data analysis project.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The manuscript was prepared using ALLHAT Research Materials obtained from the National Heart, Lung, and Blood Institute (NHLBI).We are not allowed to share this dataset. For those who are

interested in using this dataset, they need to apply for it from the NHLBI directly.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: United States

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S-Editor: Fan JR
L-Editor: A
P-Editor: Yu HG

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World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2023 May 26; 15(5): 273-283

DOI: 10.4330/wjc.v15.i5.273

ISSN 1949-8462 (online)

META-ANALYSIS

Impact of erythropoietin therapy on cardiorenal syndrome: A systematic review with meta-analysis

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Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Wu YJ, China; Zhao XC, China

Received: December 19, 2022
Peer-review started: December 19, 2022
First decision: February 8, 2023
Revised: March 24, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 26, 2023

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Abstract

BACKGROUND

Heart and kidney dysfunction frequently coexist in patients with acute heart failure due to the overlap between these two organ systems. Cardiorenal syndrome (CRS) results from pathology occurring in the heart and kidneys along with the consequences of dysfunction in one organ contributing to dysfunction in the other and vice versa.

AIM

To evaluate the use of erythropoietin (EPO) in patients with CRS and its effects on hemoglobin (Hb), major cardiovascular (CV) events, and hospitalization rates.

METHODS

On February 24, 2022, searches were conducted using PubMed, MEDLINE, and EMBASE, and 148 articles were identified. A total of nine studies were considered in this systematic review. We assessed the included articles based on the National Heart, Lung, and Blood Institute quality assessment tools for controlled intervention and observational cohort or cross-sectional studies. An assessment of bias risk was conducted on the chosen studies, and data relevant to our review was extracted.

RESULTS

The systematic review of these studies concluded that most existing literature indicates that EPO improves baseline Hb levels and decreases myocardial remodeling and left ventricular dysfunction without reducing CV mortality. In addition, the effect of EPO on the hospitalization rate of patients with CRS needs

to be further studied since this relationship is unknown. Future studies, such as randomized controlled clinical trials and prospective cohort studies, should be conducted to enhance the literature on the potential of EPO therapy in patients with CRS.

CONCLUSION

Our systematic review suggests that EPO therapy may have a significant role in managing CRS. The review highlights the potential benefits of EPO in improving baseline Hb levels, reducing the risk of major CV events, improving cardiac remodeling, myocardial function, New York Heart Association class, and B-type natriuretic peptide levels. However, the effect of EPO treatment on hospitalization remains unclear and needs further exploration.

Key Words: Cardiorenal syndrome; Anemia; Cardiovascular disease; End-stage renal disease; Erythropoietin; Congestive heart failure

Core Tip: Erythropoietin improves baseline hemoglobin levels and decreases the risk of major cardiovascular.

Citation: Bhangal R, Cancarevic I, Nassar M, Umar Z. Impact of erythropoietin therapy on cardiorenal syndrome: A systematic review with meta-analysis. *World J Cardiol* 2023; 15(5): 273-283
URL: https://www.wjgnet.com/1949-8462/full/v15/i5/273.htm
DOI: https://dx.doi.org/10.4330/wjc.v15.i5.273

INTRODUCTION

Many patients with heart failure also experience kidney dysfunction and vice versa, as these two organs are closely related in their functions. Cardiorenal syndrome (CRS) describes a pathophysiological disorder of the heart and kidneys, whereby dysfunction of one system may contribute to dysfunction of another[1]. An estimated 50% of patients with congestive heart failure (CHF), who have both reduced and preserved left ventricular ejection fraction, have an estimated glomerular filtrate rate (eGFR) of less than 60 mL/min/1.73 m^2[2]. Even moderate renal insufficiency, defined as an eGFR less than 60 mL/min/1.73 m^2, is associated with an increased risk of cardiac failure, hospitalization, and all-cause mortality[2]. CRS was previously considered to indicate acute kidney injury resulting from acute cardiac disease; however, more recent research suggests that the relationship between these two organs is bi-directional, meaning either organ could be the primary culprit[1,3]. CRS is categorized into five categories: acute and chronic cardiorenal, acute and chronic nephrocardiac, and secondary cardiorenal syndrome[1,3]. Essentially, each sub-category of CRS describes the acuity and pathophysiology of cardiac and kidney dysfunction, how the two overlap, and the presence of other systemic disorders[3]. The most common subtype of CRS is type one (acute cardiorenal), with approximately 50% of patients diagnosed with this condition[4]. The risk factors associated with worsening renal function in CRS include existing chronic kidney disease, hypertension, history of heart failure, diabetes mellitus, coronary artery disease, ischemic cardiomyopathy, and history of acute kidney injury[4].

In addition, many studies have shown that kidney dysfunction in CHF is caused by poor renal plasma flow, which leads the kidneys to retain water and sodium, which in turn, allows for improved perfusion of all essential organs[1]. The presence of anemia can result in tissue hypoxia and peripheral vasodilation, resulting in lower blood pressure and renal blood flow, increased heart rate, stroke volume, renal vasoconstriction, and sodium and water reabsorption[5]. Poor renal blood flow causes increased release of renin, angiotensin, aldosterone, and antidiuretic hormone (ADH), further increasing renal vasoconstriction and sodium and water reabsorption[5]. Renin, angiotensin, aldosterone, and ADH are toxic to cardiac, renal, and endothelial cells, which results in dysfunction in these tissues[5].

Nevertheless, recent studies have revealed that kidney hemodynamic changes can occur independently of the heart's hemodynamic changes[1]. An initial response of the kidneys to CHF is to reduce renal plasma flow and eGFR, which results in a higher filtration fraction[1]. To maintain eGFR, both efferent arteriolar resistance and glomerular capillary hydrostatic pressure must be increased, severely impairing overall cardiac function[1]. Additionally, there is evidence of increased sodium reabsorption, specifically in the Loop of Henle, as well as activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) all play a role in the development of CRS[1,3]. Overactivation of the RAAS increases both preload and afterload, leading in the long-term to cardiac dysfunction.

The presence of anemia with kidney dysfunction has also been shown to exacerbate CHF's progression and increase the risk of morbidity and mortality[6]. Besides contributing to tissue dysfunction by potentiating hypoxia, anemia can also increase oxidative stress, which contributes to increased hyperdynamic blood circulation and heart failure development[6]. Hemoglobin (Hb) levels are less than or equal to 12 g/dL in approximately 40% of patients with CHF[5]. Moreover, anemia is more common in the elderly, diabetics, and patients with poor baseline cardiac and/or renal function [5]. Increasing Hb levels can limit the detrimental effects of oxidative stress on the kidney and cardiac function. In a study by Pagourelias *et al*[6], for every 1 g/dL increase in Hb, there was a 15.8% reduction in mortality and a 14.2% reduction in mortality plus hospitalization in patients with CHF[6]. Erythropoietin (EPO) is a hematopoietic growth factor, the major function of which is to stimulate the proliferation and differentiation of erythropoiesis. EPO treatment is an efficient approach to increase Hb levels in patients with CHF whose anemia is caused by reduced EPO production. EPO can also influence other cellular processes, such as cell integrity and angiogenesis[7]. EPO has been demonstrated to improve both renal and cardiac function. EPO can decrease marrow inflammation, which can reverse the myelosuppressive effects of cardiac dysfunction and coexisting uremia[6]. Furthermore, EPO may prevent myocardial ischemic injury in CHF patients by inhibiting the apoptosis of cardiac myocytes[6]. Iron therapy is unable to provide such effects on hematopoiesis due to the lack of hematological and immunological regulatory ability and its limited bioavailability[6].

It is of great significance to investigate the role of EPO in treating patients with CRS. Recombinant human EPO (rhEPO) is a drug routinely prescribed to treat anemia in patients with end-stage renal disease (ESRD), and rhEPO treatment has been demonstrated to be beneficial for improving patients' life quality and survival. It is reasonable to assume that rhEPO treatment is beneficial for patients with CRS. Given the high prevalence of CRS, searching for a treatment modality that can improve therapeutic responses is of high significance in clinical practice and will significantly decrease the mortality and hospitalization of CRS patients. Fewer hospitalizations would likely result in lower healthcare costs as well. Several studies are ongoing to examine the benefits of rhEPO treatment in patients with CRS. A two-part clinical trial conducted by the University of Alberta is currently examining whether treatment with EPO will increase cardiac performance and decrease renal disease progression in patients with CRS[8]. The failure to further investigate EPO for use in the treatment of CRS will result in the deprivation of a promising treatment option for many patients.

Through this systematic review, we aim to deepen our understanding of the role of EPO in managing CRS.

MATERIALS AND METHODS

Our article was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[9]. It was not registered as a systematic review and no separate protocol was written. On February 24, 2022, a literature search was conducted on PubMed, MEDLINE, and EMBASE databases. The literature search was conducted using the following search strategy consisting of medical subject headings (MeSH) terms and regular keywords: ("Cardio-Renal Syndrome"[Mesh] OR "cardio-renal syndrome" OR "cardiorenal" OR "cardiorenal syndrome" OR "CRS" OR "reno-cardiac syndrome" OR "renocardiac syndrome") AND ("Erythropoietin"[Mesh] OR "erythropoietin" OR "EPO" OR "epoetin alfa" OR "darbepoetin alfa" OR "colony-stimulating factors").

Subsequently, the search results were imported into the Covidence platform, which automatically removed duplicate articles. Two reviewers independently examined titles and abstracts as part of an initial screening, followed by a second screening of full-length articles. Conflicts in the selected articles were discussed directly between the two reviewers, and a conclusion was drawn after each conflict article's discussion. In the event that a conclusion could not be reached, a third reviewer was consulted to vote on the final decision. We included randomized controlled clinical trials, cross-sectional studies, prospective and retrospective case-control, and cohort studies exploring the use of erythropoietin in CRS management. The articles published up to February 24, 2022, were included. We excluded *in vitro* studies, animal studies, abstracts, case reports, case series, systematic reviews, and meta-analyses. Furthermore, we excluded articles in languages other than English.

Following this, a quality assessment was performed using the 2013 National Heart, Lung, and Blood Institute (NHLBI) quality assessment tools for controlled intervention studies and observational cohort or cross-sectional studies[10]. We included studies that scored 11 or higher on each quality assessment tool. Each study was then analyzed for obvious biases and confounding variables. Extrapolation of data was performed by one reviewer and displayed in a table (shown below). A qualitative analysis of the data was conducted following data extraction for the systematic review.

We performed a meta-analysis since there were a number of eligible studies. For studies included in the meta-analysis, an odds ratio (OR) was calculated. Due to the substantial heterogeneity in the concluded study, a random effects model was used for the meta-analysis. Meta-analysis was conducted using Review Manager 5.4.1 software. Meta-analysis studies with forest plots were included for the outcomes.

RESULTS

We selected 148 relevant articles from PubMed, MEDLINE, and EMBASE using an advanced search strategy combining MeSH terms and common keywords. We removed 11 duplicate articles. We screened 137 titles and abstracts before selecting 43 articles for full-text review. Of the 43 articles assessed for eligibility, 34 articles were excluded (7 were incorrect study designs, 3 were not retrievable, and 1 was an abstract). A total of nine studies were evaluated using the NHLBI quality assessment tools for controlled intervention studies and observational cohort studies or cross-sectional studies. Of the nine studies, six were randomized controlled trials, two were retrospective cohort studies, and one was a prospective cohort study. Articles that scored 11 or higher out of 14 on the assessment scale were considered high-quality articles, and therefore were included in the systematic review. Eight studies scored 11 points out of 14, whereas one study scored 12 points out of 14. A PRISMA flowchart of the reviewed literature and search strategies can be found in Figure 1. Table 1 summarizes the included studies and their statistical significance[11-19]. In addition, Table 1 illustrates how each study was scored according to the NHLBI quality assessment tools.

There were two studies included in the meta-analysis[11,12]. Study results showed a nonsignificant decrease in all causes of hospitalization (OR = 0.93 [95% confidence interval (CI), 0.23, 3.72]; P = 0.92). There was a high level of heterogeneity among the included studies (I^2 = 76%) (Figure 2). The asymmetry in the funnel plot indicates the existence of publication or selective reporting bias (Figure 3).

Elevated serum neutrophil-gelatinase-associated lipocalin (NGAL) is inversely correlated with baseline EPO levels, independent of renal function. Low-dose EPO treatment caused a moderate decrease in serum NGAL levels, therefore reflecting potential improvement in renal tubular damage.

DISCUSSION

Effects of EPO on Hb levels and predictors of EPO use

As expected, the majority of studies concluded that EPO therapy increased Hb levels in patients with CRS. Furthermore, it would be expected that lower Hb levels would be associated with a higher rate of EPO prescription. This was confirmed in a study by Jackevicius *et al*[12] that found EPO therapy to be inversely related to Hb levels, such that patients with lower Hb levels are more likely to be prescribed EPO. On average, Hb levels are found to increase approximately 6 wk after EPO treatment, at which point most patients experience symptomatic improvement[20]. The need for prolonged treatment was confirmed by Jie *et al*[16], who found that short-term EPO use (3 wk) did not result in any change in Hb levels in patients with CRS, whereas long-term EPO therapy (52 wk) resulted in a significant increase in both Hb and reticulocyte count. Further, the strongest predictors of EPO use include iron supplementation, markers of declining renal function, and patients taking hydralazine, nitrates, angiotensin II receptor blockers (ARBs), and/or aspirin concurrently[12]. Hydralazine and nitrates are typically prescribed to patients with heart failure once patients' renal function no longer permits RAAS inhibitor usage, at which point they are also far more likely to be prescribed EPO for advanced chronic kidney disease[12]. The temporal relationship is also important because hydralazine is a drug used to treat hypertension, and hypertension is a known side effect of EPO. No clear conclusions regarding aspirin or ARBs were drawn.

Likewise, in another study by Jie *et al*[18], EPO not only provided a significant rise in Hb levels compared to the non-EPO therapy but more interestingly, altered the monocyte transcriptomes that played a role in inflammation and oxidative stress. The increase in oxidative stress, in turn, increased the risk of cardiovascular (CV) events[18]. In this study, EPO's role in oxidative stress was found to be associated with improving Hb level and alterations in gene expression directly involved in the inflammatory response. The effects were, however, very variable and inconsistent between individuals. The authors were unable to demonstrate a beneficial non-hematopoietic effect of EPO, although no harmful effects were found[18].

Several studies have shown that Hb levels improve after sufficient treatment with EPO. Exogenous EPO stimulates erythropoiesis, which increases red blood cell production and Hb levels. By reducing the degree of anemia among patients with CRS, oxidative stress and inflammatory response can be reduced. As a result, anemia symptoms such as fatigue, malaise, weakness, and dizziness are also improved, thus enhancing patients' overall quality of life. Similarly, since the data presented clearly points towards increasing Hb levels, it is reasonable to expect that those suffering from symptomatic anemia would experience clinical improvement, likely prompting them to be compliant with EPO therapy. In our review, the degree of Hb improvement varied significantly between the studies that were analyzed, and it was highly dependent on the dose of EPO given and the frequency of EPO administration. There is still insufficient data to predict an individual's response to therapy.

EPO's effect on significant CV risk and mortality

The effect of EPO on CV mortality is at this time difficult to establish, considering the differences in outcomes reported by currently available studies[11,13-15]. The results of a randomized study by

Table 1 Summary of included studies

Ref.	Study design	No. of Patients	EPO dosage and treatment duration	Average Hb level (g/dL)			EPO's effect on			Other findings
				Before EPO therapy	After EPO therapy	Without EPO treatment	Hb level	Major CV event	Hospitalization rate	
Jackevicius *et al*[12], 2015	Retrospective cohort	2058	N/A	N/A	10.5	11.1	Inverse relationship between EPO therapy and Hb levels	N/A	N/A	The strongest predictors of EPO use include iron supplementation, markers of declining renal function, and patients concurrently taking hydralazine, nitrates, ARBs, and/or aspirin
Eisenga *et al* [13], 2019	Open-label, prospective, randomized trial	56	N/A	11.7	13.2	11.8	Increased Hb levels	Increased cFGFR23 and iFGFR23, increased risk of CV events and mortality	N/A	N/A
McMurray *et al*[14], 2011	Randomized trial	3847	N/A	N/A	N/A	N/A	N/A	Patients with CKD and anemia have an 11.2% higher risk for a major CV event. History of CHF was the highest-ranked predictor of future CV events, followed by age (hazard increase by 74% and 27%, respectively)	N/A	N/A
Fazlibegović *et al*[15], 2006	Prospective cohort	90	2000 to 6000 international units (I.U.) for 1-3 times per week, depending on the Hb level	8.7	10.1	N/A	Increased Hb levels	Improved functional ability of the myocardium, LV function, and quality of life	N/A	The average NYHA class before treatment with EPO was class II, with a range of I-IV; after treatment, the average class was I, with a range of I-II
Palazzuoli *et al*[11], 2007	A randomized, double-blind controlled study	51	6000 I.U. twice weekly	10.4	11.2	10.6	Increased Hb levels	Improved LV systolic function, LV remodeling, NYHA class, BNP levels, and quality of life compared to control group	N/A	N/A
Jie *et al*[16], 2011	Open-label randomized trial	65	N/A	7.5	8.4	6.9	Increased Hb levels with long term use	N/A	N/A	Reduced CD34+ KRD-EPC levels, which was associated with decreased vascular regenerative potential
Jackevicius *et al*[17], 2014	Retrospective cohort study	2058		10.5:		11.1	Increased Hb levels	Increased risk of major CV and acute coronary syndrome events	Increased risk of an all-cause hospitalization rate	EPO use increases the risk of mortality
Jie *et al*[18], 2012	Randomized trial	30	50 I.U./kg once weekly	11.8	12.3	N/A	Increased Hb levels	Modest alteration in monocyte transcriptomes, indicating imprints of inflammation and oxidative stress. The increase in oxidative stress, in turn, increased the risk of CV events	N/A	Variable response in gene expression. Unable to conclude whether EPO improved hematopoietic effects in CRS patients with such gene mutations
Emans *et al* [19], 2013	Open-label prospective	62	50 I.U./kg once weekly		13.7	11.8	Increased Hb levels	N/A	N/A	Elevated serum NGAL is inversely correlated with baseline EPO levels,

	randomized trial	independent of renal function. Low-dose EPO treatment caused a moderate decrease in serum NGAL levels, therefore reflecting potential improvement in renal tubular damage

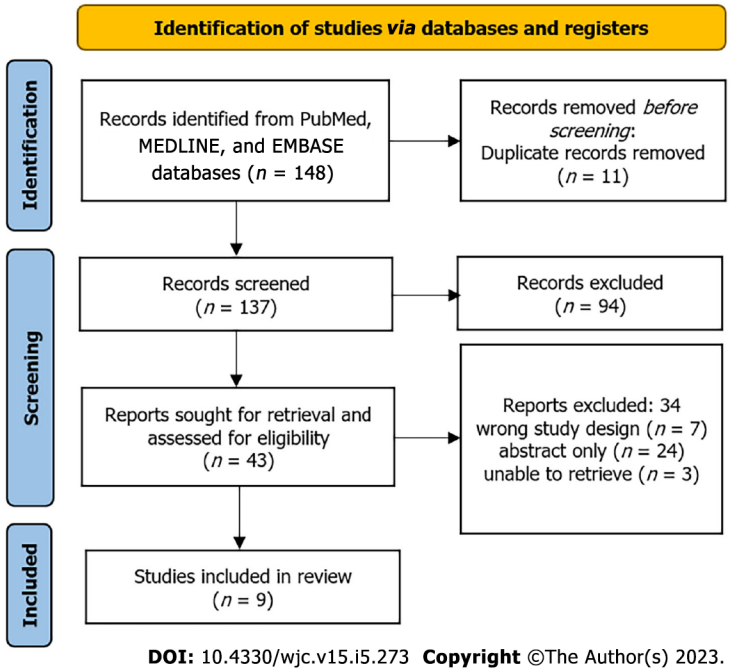
ARB: Angiotensin II receptor blocker; BNP: B-type natriuretic peptide; cFGF: C-terminal fibroblast growth factor; CKD: Chronic kidney disease; CHF: Congestive heart failure; CRS: Cardiorenal syndrome; CV: Cardiovascular; EPO: Erythropoietin; EPC: Endothelial progenitor cell: Hb: Hemoglobin; iFGFR: Intracellular fibroblast growth factor receptor; LV: Left ventricular; N/A: Not applicable; NGAL: Neutrophil-gelatinase-associated lipocalin; NYHA: New York Heart Association.

McMurray *et al*[14] revealed that patients with both chronic kidney disease and anemia are at an increased risk of major CV events by 11.2%. In addition, a history of CHF was the strongest predictor of CV events in the future (hazard increased by 74%), followed by age (hazard increased by 27%)[14]. Moreover, a prospective cohort study involving EPO therapy ranging from 2000 to 6000 international units (I.U.) for 1-3 times per week found that EPO treatment concurrently with iron supplementation improved the functional ability of the myocardium, left ventricular (LV) function, and overall quality of life among patients with chronic forms of the cardiorenal syndrome[15]. Palazzuoli *et al*[11] also compared the efficacy of combination therapy with EPO and iron to iron alone in patients with cardiorenal syndrome with anemia. They found that concurrent EPO and iron supplementation improved LV systolic function, LV remodeling, New York Heart Association (NYHA) class, B-type natriuretic peptide (BNP) levels, and quality of life compared to a control group that took only oral iron [11]. Eisenga *et al*[13] found that EPO caused a significant increase in C-terminal FGF23 (cFGF23) and a smaller increase in intact FGF23 (iFGF23). A higher level of cFGF23 has been associated with increased risk of CV events and mortality; however, the underlying mechanism remains unknown[13].

As demonstrated in this review, the exact effects of EPO supplementation, with or without iron supplementation, are difficult to determine. Some studies have even suggested worse CV outcomes, whereas others did not show statistically significant differences in CV mortality. The effects on myocardial function and the reported quality of life appear more promising.

EPO's effect on hospitalization rates

Our review included studies on the effects of EPO therapy on hospitalization rates in patients with CRS. For example, a study by Jackevicius *et al*[17] found that EPO use was associated with an increased risk of all-cause hospitalization, major CV events, acute coronary syndrome, and mortality. The risk of hospitalization may be due in part to patients receiving EPO having a poor renal function and/or myocardial dysfunction, which places them at an increased risk of hospitalization even before receiving EPO. However, a study by Emans *et al*[19] showed that baseline EPO levels inversely correlated with serum neutrophil gelatinase-associated lipocalin (NGAL) levels, regardless of renal function, and that low-dose EPO treatment caused a moderate decrease in serum NGAL levels, reflecting a potential improvement in renal tubular damage. NGAL is a protein from the lipocalin family that inhibits bacterial uptake of iron and is a biomarker reflective of tubular damage as it can detect early-stage acute kidney injury[19].



DOI: 10.4330/wjc.v15.i5.273

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for new systematic reviews, which included searches of databases and registers only.

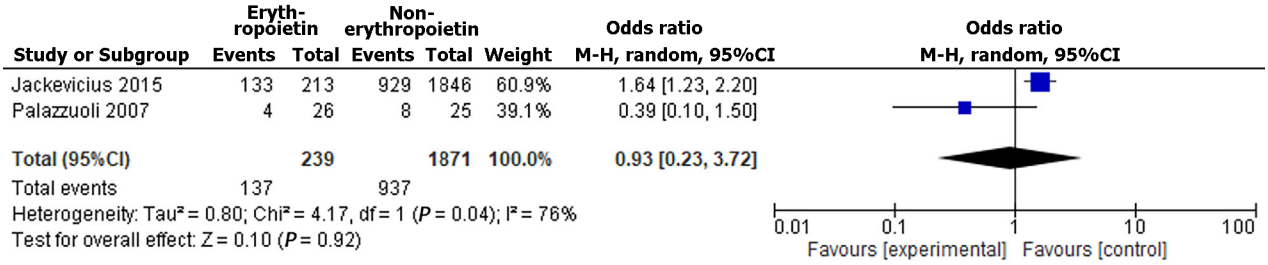


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Figure 2 Forest plot of all causes of hospitalization of erythropoietin *vs* non-erythropoietin.

The effects of EPO treatment on the hospitalization rates of patients with CRS remain variable and should therefore be further investigated. Interestingly, EPO reduces NGAL levels, thereby minimizing renal tubular destruction and increasing iron availability. Therefore, this is likely to minimize hospitalization rates as well. The effect of EPO on renal tubular function should be further explored, as this is a potentially significant benefit of EPO therapy in patients with CRS and other renal conditions. For the time being, physicians should determine whether the potential benefits of EPO use in patients with CRS outweigh the risks.

In summary, this systematic review studied the overall significance of EPO when managing patients with CRS. The literature demonstrates that not only does EPO increase patients baseline Hb levels but it also lowers the risk of major CV events from occurring in patients with CRS. EPO improves the heart failure aspect of CRS by both improving cardiac remodeling and overall myocardial function, and by doing so, EPO is able to minimize the CV mortality as well. Moreover, the reviewed literature does not demonstrate a clear effect of EPO on hospitalization rates and hence this effect should be further analyzed in future studies. Lowering hospitalization rates would potentially decrease healthcare expenses and, more importantly, improve the quality of life of patients with this condition. In conclusion, the literature included in this review clearly demonstrates how EPO has several significant benefits when used to treat patients with CRS.

Strengths

The strongest aspect of this systematic review is that it primarily focused on randomized controlled clinical trials and cohort studies, which provide a more accurate description of the temporal sequence among exposure, EPO treatment, and CRS effects.

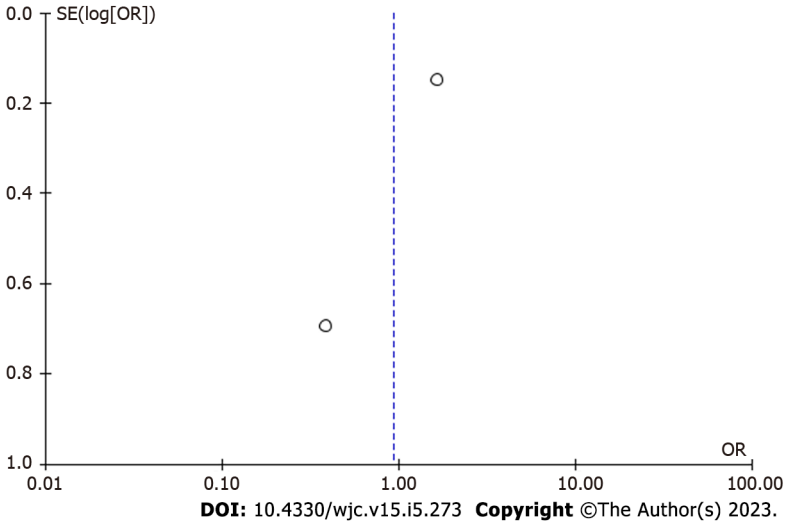

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Figure 3 Funnel plot of all causes of hospitalization of erythropoietin *vs* non-erythropoietin.

Limitations

This systematic review had some limitations that should be highlighted. A limited amount of total data available regarding this topic increased the risk of publication bias. In addition, some articles discussing this topic had small sample sizes, raising the possibility of cognitive bias. Moreover, the articles were selected from three separate databases with a constriction of only selecting articles written in English.

Future directions

The literature regarding patients with CRS and the use of EPO therapy should be expanded with more randomized controlled clinical trials and prospective cohort studies. Moreover, since the protocols used for EPO administration varied significantly between studies, further research should be conducted regarding EPO's most optimal dosage and treatment duration. The effect on mortality does not appear to reach statistical significance at this time, which may change with a larger sample size. It is also important for further research to be performed examining the effects of EPO treatment on hospitalization rates, as this association remains unknown at this time due to insufficient data.

CONCLUSION

We conducted a systematic review to investigate the role of EPO in CRS management. The benefits of EPO therapy in patients with ESRD and CHF are well-established. Thus, it is highly likely that EPO would also be beneficial for patients with CRS. The literature review indicates that EPO improves baseline Hb levels and decreases the risk of major CV events in patients with CRS. The ability of EPO to improve cardiac remodeling, myocardial function, NYHA class, and BNP levels is significant since this will improve the heart failure aspect of CRS and, more importantly, lower the likelihood of death for patients who have this condition. Additionally, the effect of EPO treatment on hospitalization remains unclear and should be further explored as it would benefit patients and potentially reduce healthcare costs. Our review had a few limitations, including the possibility of publication bias, cognitive bias, and the possibility of missing some studies due to the criteria used for selecting articles. Additionally, future randomized controlled clinical trials would benefit the medical community in assessing the use of EPO in treating patients with CRS and specifically examine different EPO dosages and their effects on CV risk, mortality risk, and hospitalization rates. Since CRS is a prevalent condition, the discovery of an effective adjunctive treatment option will significantly affect the clinical outcome of patients with this condition.

ARTICLE HIGHLIGHTS

Research background

Cardiorenal syndrome (CRS) describes a pathophysiological disorder of the heart and kidneys, whereby dysfunction of one system may contribute to dysfunction of another. Many patients with heart failure also experience kidney dysfunction and vice versa, as these two organs are closely related in their functions. Poor renal plasma flow in congestive heart failure (CHF) causes the kidneys to retain water

and sodium, which allows for improved perfusion of all essential organs, leading to kidney dysfunction.

Research motivation

Anemia exacerbates CHF's progression and increases the risk of morbidity and mortality, and increasing hemoglobin (Hb) levels can limit the detrimental effects of oxidative stress on the kidney and cardiac function. Erythropoietin (EPO) treatment is an efficient approach to increase Hb levels in patients with CHF whose anemia is caused by reduced EPO production. Investigating the role of EPO in treating patients with CRS is of great significance as it could significantly decrease the mortality and hospitalization of CRS patients and lead to lower healthcare costs.

Research objectives

This systematic review evaluated the use of erythropoietin (EPO) in patients with CRS and its effects on Hb, major cardiovascular (CV) events, and hospitalization rates. The study aimed to deepen our understanding of the role of EPO in managing CRS and whether it can be a promising treatment option for many patients. The primary objective was to assess the efficacy of EPO therapy in improving cardiac and renal function in CRS patients.

Research methods

The article was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The literature search was conducted on PubMed, MEDLINE, and EMBASE databases using a search strategy consisting of medical subject headings terms and regular keywords. Two reviewers independently examined titles and abstracts, followed by a second screening of full-length articles. Quality assessment was performed using the 2013 National Heart, Lung, and Blood Institute (NHLBI) quality assessment tools for controlled intervention studies and observational cohort or cross-sectional studies. A meta-analysis was performed using Review Manager 5.4.1 software, and meta-analysis studies with forest plots were included for the outcomes. *In vitro* studies, animal studies, abstracts, case reports, case series, systematic reviews, and meta-analyses were excluded. Furthermore, articles in languages other than English were excluded.

Research results

This study selected 148 relevant articles and narrowed them down to nine studies that were evaluated using the NHLBI quality assessment tools. The majority of the studies concluded that EPO therapy increased Hb levels in patients with CRS and reduced anemia symptoms such as fatigue, malaise, weakness, and dizziness. However, the degree of Hb improvement varied significantly between the studies and was highly dependent on the dose and frequency of EPO administration. The effect of EPO on CV mortality is difficult to establish as different studies have reported varying outcomes. EPO use was associated with an increased risk of hospitalization, major CV events, acute coronary syndrome, and mortality in some studies. However, other studies found potential benefits of EPO on myocardial function and quality of life. The study's strength lies in its focus on randomized controlled clinical trials and cohort studies, while its limitations include publication bias and small sample sizes.

Research conclusions

The literature review provides evidence supporting the use of EPO therapy as a potential treatment option for patients with CRS. The benefits of EPO treatment in improving Hb levels, reducing major CV events, and improving cardiac remodeling, myocardial function, NYHA class, and BNP levels are significant, indicating a positive impact on the heart failure aspect of CRS and lowering the likelihood of death for patients. However, further studies are needed to investigate the effect of EPO treatment on hospitalization rates and potential side effects. Overall, the findings of this review suggest that EPO therapy may be a promising adjunctive treatment option for CRS, and more research is needed to confirm its effectiveness and optimize its use in clinical practice.

Research perspectives

In terms of future research perspectives, it is crucial to investigate the potential long-term effects of EPO therapy in patients with CRS. Since CRS is a chronic condition, examining the long-term effects of EPO treatment will provide valuable insights into its efficacy and safety. Additionally, future studies should explore the potential of combining EPO therapy with other treatments for CRS, such as angiotensin-converting enzyme inhibitors and beta blockers, to determine if combination therapy could improve clinical outcomes. Finally, future research should also aim to identify biomarkers that can predict a patient's response to EPO therapy, which would allow for more personalized treatment approaches.

FOOTNOTES

Author contributions: All author contributed equally; All authors have read and approved the final version.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Liu JH
L-Editor: Filipodia
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