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OPINION REVIEW

# Metabolic and cardiovascular benefits with combination therapy of SGLT-2 inhibitors and GLP-1 receptor agonists in type 2 diabetes

Awadhesh Kumar Singh, Ritu Singh

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## Abstract

Both GLP-1 receptor agonists (GLP-1RA) and SGLT-2 inhibitors (SGLT-2I) are newer classes of anti-diabetic agents that lower HbA1c moderately and decrease body weight and systolic blood pressure (SBP) modestly. Combination therapy with GLP-1RA plus SGLT-2I have shown a greater reduction in HbA1c, body weight, and SBP compared to either agent alone without any significant increase in hypoglycemia or other side effects. Since several agents from each class of these drugs have shown an improvement in cardiovascular (CV) and renal outcomes in their respective cardiovascular outcome trials (CVOT), combination therapy is theoretically expected to have additional CV and renal benefits. In this comprehensive opinion review, we found HbA1c lowering with GLP-1RA plus SGLT-2I to be less than additive compared to the sum of HbA1c lowering with either agent alone, although body weight lowering was nearly additive and the SBP lowering was more than additive. Our additional meta-analysis of CV outcomes with GLP-1RA plus SGLT-2I combination therapy from the pooled data of five CVOT found a similar reduction in three-point major adverse cardiovascular events compared to GLP-1RA or SGLT-2I alone, against placebo. Interestingly, a greater benefit in reduction of heart failure hospitalization with GLP-1RA plus SGLT-2I combination therapy was noted in the pooled meta-analysis of two randomized controlled trials. Future adequately powered trials can confirm whether additional CV or renal benefit is truly exerted by GLP-1RA plus SGLT-2I combination therapy.

**Key Words:** GLP-1 receptor agonists; SGLT-2 inhibitors; Combination therapy, Metabolic outcomes; Cardiovascular outcomes; Renal outcomes

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**Core Tip:** GLP-1 receptor agonist (GLP-1RA) plus SGLT-2 inhibitor (SGLT-2I) dual therapy causes a greater reduction in HbA1c, body weight, and systolic blood pressure (SBP), compared to either agent alone with similar adverse events. However, lowering of HbA1c, body weight, and SBP with combination therapy appeared to be less, nearly equal, and more than additive, respectively, compared to the sum of either agent alone. Our meta-analysis from five cardiovascular outcome trials suggests a similar reduction in major adverse cardiovascular events with dual therapy compared to GLP-1RA or SGLT-2I alone, but an additional benefit in heart failure hospitalization is likely. Future trials are needed to confirm these findings.

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## INTRODUCTION

Type 2 diabetes mellitus (T2DM) has a complex nature of pathophysiology, and therefore, most patients will eventually require a combination of antidiabetic agents (ADD) with different mechanisms of action (MOA) to achieve optimal glycemic control. GLP-1 receptor agonists (GLP-1RA) are a newer class of ADD that lower plasma glucose both by enhancing insulin secretion and inhibiting glucagon secretion [1]. SGLT-2 inhibitors (SGLT-2I) are another newer class of ADD that lower plasma glucose by promoting urinary glucose excretion through the kidney by inhibiting glucose reabsorption[2]. Notably, both classes of these drugs have shown a favorable effect on body weight and blood pressure. Importantly, several recent cardiovascular (CV) outcome trials (CVOT) conducted with SGLT-2I or GLP-1RA have shown that certain agents within each class can reduce the incidence of CV events and mortality in people with T2DM[3,4]. In this comprehensive opinion review, we attempt to answer three contemporary questions: (1) What is the rationale of this combination therapy in the management of T2DM; (2) What additional metabolic control can we achieve with this combination therapy; and (3) Do we get an additional CV and renal benefit by combining both classes of drug?

## WHAT IS THE RATIONALE OF THIS COMBINATION THERAPY IN THE MANAGEMENT OF T2DM?

Since GLP-1RA and SGLT-2I work through different MOA in different organs, combination therapy with these agents is expected to have a complementary or perhaps synergistic effect on metabolic outcomes. Combination of GLP-1RA and SGLT-2I can potentially correct seven of the eight pathophysiologic defects (Ominous Octet) of T2DM[5]. GLP-1RA lower plasma glucose concentration by augmenting insulin secretion and inhibiting glucagon secretion *via* β-cells and α-cells in the pancreas, respectively, in a glucose-dependent manner[1,6]. SGLT-2I lower plasma glucose concentration by producing glucosuria, which in turn causes a compensatory and "paradoxical" increase in endogenous glucose production (EGP) accompanied by a significant increase in plasma glucagon as well as a significant decrease in the fasting plasma insulin concentration. Thus, SGLT-2I administration can lead to a marked increase in plasma glucagon-to-insulin ratio (GIR) by 50%-100%[7,8]. This increase in EGP by SGLT-2I appears to counterbalance or offset nearly 40%-50% of the amount of glucose that is lost in the urine during glucosuria and, therefore, attenuates the overall decrease in HbA1c caused by the SGLT-2I class of drugs[7]. Since increase in plasma GIR contributes to an increase in EGP caused by SGLT-2I (at least in part), any pharmacological agents that reverse this ratio and in turn prevent an increase in EGP would likely amplify the decrease in HbA1c by SGLT-2I[9,10]. This led to the belief that the addition of GLP-1RA to SGLT-2I would stimulate insulin secretion and inhibit glucagon secretion and, thus, prevent an increase in plasma GIR and, therefore, is expected to mitigate any increase in EGP caused by SGLT-2I. This would allow amplification of plasma glucose lowering with SGLT-2I in combination with GLP-1RA. Indeed, a study ($n$ = 36) that evaluated the acute effects of a single dose of liraglutide (GLP-1RA), canagliflozin (SGLT-2I), and combination of liraglutide plus canagliflozin on serum insulin, glucagon, and EGP found that acute administration of a single dose of liraglutide prevented the insulin decline and blocked the glucagon rise observed with canagliflozin, although it did not inhibit the increase in EGP[11]. Similarly, a 16-wk trial ($n$ = 45) that evaluated the chronic effect of

liraglutide, canagliflozin, and liraglutide plus canagliflozin combination therapy on serum insulin, glucagon, and EGP, found that canagliflozin caused a significant 9% increase in EGP ($P < 0.05$) accompanied by a significant 50% increase ($P < 0.05$) in plasma GIR, while liraglutide inhibited EGP and reduced plasma glucagon concentration. Interestingly, EGP increased by a significant 15% ($P < 0.05$) in canagliflozin plus liraglutide combination arm, despite the fact that canagliflozin induced plasma glucagon concentration was blocked by liraglutide and no change in plasma insulin from the baseline was observed[12]. These findings hint that factors other than insulin and glucagon may contribute to the stimulation of EGP with SGLT-2I induced glucosuria, and these include the contribution of renal gluconeogenesis, which is insensitive to plasma glucagon concentration[13].

Other logic of this combination therapy also stems from the fact that while SGLT-2I cause a significant reduction of body weight, chronic administration may lead to a plateau effect due to a compensatory increase in appetite that may partially offset weight reduction[14]. Contrarily, GLP-1RA delays gastric emptying and is associated with appetite suppression; therefore, combination therapy may overcome SGLT-2I induced hyperphagia. Figure 1 summarizes the potential effect of combined SGTL-2I and GLP-1RA therapy. Importantly, early initiation of GLP-1RA and SGLT-2I in combination does not potentiate hypoglycemia and adverse events significantly and will allow a timely achievement of glycemic goals. Consequently, this combination has the potential of lowering the risks of diabetes-related morbidity and mortality in patients with T2DM, especially in the light of positive CV and renal outcomes with these agents as demonstrated in their respective CV and renal outcome trials[15].

## WHAT ADDITIONAL METABOLIC CONTROL CAN WE ACHIEVE WITH THIS COMBINATION THERAPY?

Several short- and long-term randomized controlled trials (RCTs)[12,16-23] and observational studies [24-30] (ranging from 12-104 wk), and meta-analyses of RCTs[31-34] have assessed the efficacy and safety of GLP-1RA and SGLT-2I combination therapy, either simultaneously or sequentially. All these studies have demonstrated a significantly greater benefit on metabolic outcomes (HbA1c, body weight, and systolic blood pressure) with combination therapy compared to either agent alone or placebo. Table 1 summarizes the results from both randomized and observational studies, while Table 2 summarizes the results of meta-analyses. Collectively, reduction in HbA1c, body weight, and SBP was significantly greater with GLP-1RA plus SGLT-2I combination therapy compared to the placebo or GLP-1RA or SGLT-2I alone. However, in these RCTs, HbA1c lowering with simultaneous combination therapy of GLP-1RA and SGLT-2I was found to be less than additive compared to the sum of HbA1c lowering with either agent. Notably, body weight lowering appeared to be nearly additive, while SBP lowering was more than additive with simultaneous GLP-1RA and SGLT-2I combination therapy when compared to the sum effect with either agent alone across the RCTs. Table 3 summarizes these findings from RCTs. From the safety perspective, no obvious increase in odds of severe hypoglycemia was noted with combination therapy compared to either agent alone. Similarly, no obvious increase in gastrointestinal (GI) side effect or genital tract infection (GTI) was observed with GLP-1RA and SGLT-2I combination therapy compared with GLP-1RA or SGLT-2I alone, respectively.

The less than additive effect on HbA1c is commonly observed with many combination treatments including SGLT-2I plus metformin or SGLT-2I plus DPP-4 inhibitors or SGLT-2I plus GLP-1RA. It may be partly due to the "floor effect", as the efficacy of each individual agent depends on baseline HbA1c. When given in combination, one ADD would lower HbA1c more rapidly than the other due to the differential time to onset of action for each drug, thereby resulting in a smaller "effective baseline HbA1c" for the second ADD of combination therapy. Thus, the second ADD would then result in a smaller decline in HbA1c compared with its use in monotherapy, given the lower starting glycemic load. Second, it could be related to the MOA of the individual components. Third, despite a notable reduction in GIR and EGP with GLP-1RA alone, there was no decrease in EGP with combination therapy of GLP-1RA plus SGLT-2I, which can partly explain less than additive effect on HbA1c. Summarily, the overall effect on HbA1c with combination therapy depends upon multiple factors including onset of action and MOA of each drug and may not necessarily be synergistic despite having complimentary MOA. Another unique finding that has emerged about simultaneous GLP-1RA and SGLT-2I dual therapy compared to either therapy alone is weight reduction in short term *vs* long-term trials. In the longest conducted RCT (DURATION-8; 26-, 52- and 104-wk), Δweight reduction with GLP-1RA plus SGLT-2I dual therapy (exenatide QW and dapagliflozin combination) and GLP1-RA therapy (exenatide QW) alone decreased over time when compared to Δweight reduction at 28 wk[16-18]. Contrarily, SGLT-2I (dapagliflozin) recipients alone achieved greater Δweight reduction at 104 wk compared with Δweight reduction at 28 wk. This hint to a time-dependent diminution in body weight lowering is attributed to GLP-1RA rather than the SGLT-2I and, therefore, this finding defies the logic of "plateau" effect on body weight reduction with long-term use of SGLT-2I. Lastly, it is unclear whether simultaneous initiation or sequential administration of GLP-1RA and SGLT-2I has any difference in metabolic outcome based on available evidence. This is because all available studies that have evaluated sequential administration were primarily placebo-controlled trials. To know the metabolic outcome

**Table 1 Studies with GLP-1 receptor agonists plus SGLT-2 inhibitors *vs* SGLT-2 inhibitors or GLP-1 receptor agonists**

| Type of study | Ref. | Comparator agent | *n* | Duration | ΔHbA1c (%), (95%CI or mean ± SD) | ΔWeight (kg), (95%CI) | ΔSBP (mmHg), (95%CI) | OR for severe Hypo's (95%CI) | GI S/E | GTI |
|---|---|---|---|---|---|---|---|---|---|---|
| Simultaneous initiation of GLP-1RA plus SGLT-2I *vs* SGLT-2I | | | | | | | | | | |
| RCT, DB/ DURATION-8 | Frías *et al*[16], 2016 | EXE QW + DAPA *vs* DAPA | 695 | 28 wk | -0.6 (-0.8; -0.3) | -1.22 (-2.00; -0.44) | -2.4 (-4.5; -0.3) | 1.00 (0.02; 50.61) | EXENA + DAPA-16%; DAPA-12% | EXENA + DAPA-4%; DAPA- 6% |
| RCT | Ikonomodis *et al* [19], 2018 | LIRA + EMPA *vs* EMPA | 40 | 12 wk | -0.70 (-2.55; 1.15) | NR | 0.00 (-5.70; 5.70) | NR | NR | NR |
| RCT, OL | Ali *et al*[12], 2020 | LIRA + CANA *vs* CANA | 45 | 16 wk | -0.78 (-1.52; -0.04) | -2.50 (-4.35; -0.65) | -8.90 (-16.19; -1.61) | 1.00 (0.02; 53.66) | NR | NR |
| Sequential addition of GLP-1RA to SGLT-2I *vs* SGLT-2I | | | | | | | | | | |
| RCT, DB/AWARD-10 | Ludvik *et al*[20], 2018 | DULA + SGLT-2I *vs* PBO + SGLT-2I | 424 | 24 wk | -0.73 (-0.88; -0.58) | -0.75 (-1.47; -0.03) | -2.45 (-4.78; -0.12) | 2.50 (0.06; 104.85) | DULA + SGLT-2I-26.5%; PBO-17% | DULA + SGLT-2I-0%; PBO-1% |
| RCT, DB/SUSTAIN-9 | Zinman *et al*[21], 2019 | SEMA + SGLT-2I *vs* PBO + SGLT-2I | 302 | 30 wk | -1.40 (-1.58; -1.22) | -3.80 (-4.67; -2.93) | -6.30 (-9.07; -3.53) | 9.27 (0.50; 173.02) | SEMA + SGLT-2I-37.3%; PBO-13.2% | NR |
| RCT, DB/LIRA-ADD2SGLT2i | Blonde *et al*[22], 2020 | LIRA + SGLT-2I *vs* PBO + SGLT-2I | 303 | 26 wk | -0.68 (-0.89; -0.47) | -0.82 (-1.67; 0.03) | 1.40 (-1.65; 4.45) | 1.00 (0.02; 64.81) | LIRA + SGLT-2I-26%[1]; PBO-6.0%[1] | NR |
| Simultaneous initiation of SGLT-2I plus GLP-1RA *vs* GLP-1RA | | | | | | | | | | |
| RCT/DURATION-8 | Frías *et al*[16], 2016 | DAPA + EXE QW *vs* EXE QW | 695 | 28 wk | -0.4 (-0.6; -0.1) | -1.87 (-2.66; -1.08) | -2.9 (-5.0; -0.8) | 1.00 (0.02; 50.61) | EXENA + DAPA-16%; DAPA-15% | EXENA + DAPA-4%; EXENA-2% |
| RCT | Ikonomodis *et al* [19], 2018 | EMPA + LIRA *vs* LIRA | 40 | 12 wk | -0.20 (-2.16; 1.76) | NR | -1.00 (-6.57; 4.57) | NR | NR | NR |
| RCT | Ali *et al*[12], 2020 | CANA + LIRA *vs* LIRA | 45 | 16 wk | -0.23 (-1.18; 0.72) | -4.10 (-6.32; -1.88) | -9.00 (-18.49; 0.49) | 1.00 (0.02; 53.66) | NR | NR |
| Sequential addition of SGLT-2I to GLP-1RA *vs* GLP-1RA | | | | | | | | | | |
| RCT, DB/CANVAS | Fulcher *et al*[23], 2016 | CANA + GLP-1RA *vs* PBO + GLP-1RA | 95 | 18 wk | -1.03 (-1.34; -0.72) | -2.72 (-3.70; -1.74) | -8.05 (-14.13; -1.97) | 2.5 (0.05; 114.6) | NR | CANA + GLP-1RA-12.3%; PBO-5.3% |
| Non-randomized studies (all Δ from baseline) | | | | | | | | | | |
| Simultaneous initiation of SGLT-2I plus GLP-1RA | | | | | | | | | | |
| Obs | Goncalves *et al*[28, 29], 2017 | SGLT-2I with LIRA | 33 | 62 | -2.0 | -10.0 | -13.0 | NR | NR | NR |
| Sequential addition of SGLT-2I to GLP-1RA | | | | | | | | | | |
| Obs | Saroka *et al*[24], | CANA added to GLP- | 75 (60 on insulin) | 10.7 mo (mean) | -0.39 ± 0.88 | -4.6 ± 4.3 | -4.0 ± 12 | NR | 1.3% | GTI: 8% |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2015 | 1RA | | | | | | | | |
| Retro, Obs | Curtis *et al*[25], 2016 | DAPA added to GLP-1RA | 14 (10 on insulin) | 48 wk | -4.4 (-5.7; -2.7) | -5.47 (-22.9; -5) | NR | NR | NR | NR |
| Retro, Obs | Deol *et al*[26], 2016 | SGLT-2I added to GLP-1RA | 37 (DAPA = 36, CANA = 1) | 3-6 mo 139 d (mean) | -1.05 (-1.41; -0.69) | -3.07 (-4.36; -1.78) | -1.16 (-6.01; 8.42) | NR | NR | NR |
| Non-R, OL, PMS | Harashima *et al*[27], 2017 | CANA added to LIRA | 71 | 52 wk | -0.7 (-0.89; -0.51) | -3.29 (-3.86; -2.72) | -7.9 (-10.7; -5.1) | 9.9% (mild) | NR | 7.1% |
| Obs | Goncalves *et al*[28, 29], 2017 | SGLT-2I added to LIRA | 46 | 76 wk | -0.9 | -4.0 | -7.0 | NR | NR | NR |
| Non-R | Seino *et al*[30], 2018 | LUSEO added to LIRA | 76 | 52 wk | -0.68 (-0.87; -0.49) | -2.71 (-3.18; -2.23) | -7.1 (-10.4; -3.9) | 6.6% (mild) | 13.2% | 3.9% |

[1]Nausea. CANA: Canagliflozin; DAPA: Dapagliflozin; DB: Double blind; EMPA: Empagliflozin; EX QW: Exenatide once weekly; GI: Gastrointestinal; GLP-1RA: GLP-1 receptor agonists; GTI: Genital tract infections; Hypo's: Hypoglycemia; LIRA: Liraglutide; LUSEO: Luseogliflozin; Non-R: Non-randomized; NR: Not reported/retrievable; Obs: Observational; OL: Open label; OR: Odds ratio; PBO: Placebo; PMS: Post marketing study; RCT: Randomized controlled trial; Retro: Retrospective; SBP: Systolic blood pressure; SGLT-2I: SGLT-2 inhibitors; S/E: Side effect; SEMA: Semaglutide.

difference between simultaneous *vs* sequential approach, one requires comparison of three-arm trials - arm with simultaneous GLP-1RA plus SGLT-2I combination *vs* arm with GLP-1RA initiation and subsequent addition of SGLT-2I *vs* arm with SGLT-2I initiation and subsequent addition of GLP-1RA.

Several other studies with combination therapy with GLP-1RA plus SGLT-2I are currently in progress that can further enlighten their synergistic metabolic effect as compared to either therapy alone. Dapagliflozin plus exenatide on central regulation of appetite in diabetes type 2 (DECREASE; NCT03361098) is a double-blind, 16-wk RCT ($n$ = 65) investigating the separate and combined actions of GLP-1RA plus SGLT-2I on food intake, body weight, activity within the central satiety and reward circuits in response to food-related stimuli, and whether the combination can prevent the increased intake observed with SGLT2-I in obese T2DM[35]. Effects of combined dapagliflozin and exenatide *vs* dapagliflozin and placebo on ectopic lipids in patients with uncontrolled type 2 diabetes mellitus (EXENDA, NCT003007329) is a triple-blind, 24-wk RCT ($n$ = 34) investigating the effect of combination therapy *vs* SGLT-2I alone on hepatic lipid content (primary outcome) and myocardial and pancreatic lipid content (secondary outcome) as measured by magnetic resonance spectroscopy[36]. Another randomized, controlled, double blind study is ongoing to assess mechanistic effects of combination therapy of dapagliflozin with exenatide QW *vs* dapagliflozin alone in obese (BMI > 30 kg/m$^2$) patients with type 2 diabetes mellitus (RESILIENT; EudraCT 2015-005242-60). This study is evaluating the effect of exenatide QW plus dapagliflozin *vs* dapagliflozin alone compared with placebo on adjusted mean reduction in total body fat mass (as determined by dual-energy X-ray absorptiometry, DEXA) after 32 wk of treatment ($n$ = 110)[37]. A 6-wk ($n$ = 17), open-label, randomized, cross-over study to evaluate the albuminuria lowering effect of dapagliflozin, exenatide, and their combination in patients with type 2 diabetes (DECADE, EudraCT 2017-004709-42) is also currently underway[38]. Results from these studies of GLP-1RA plus SGLT-2I dual therapy would further add to our knowledge.

**Table 2 Meta-analysis of randomized controlled trials comparing GLP-1 receptor agonists + SGLT-2I *vs* SGLT-2I or GLP-1 receptor agonists**

| Ref. | Types of studies included, *n* | Comparator arm | *N* | ΔHbA1c (%), (95%CI) | ΔWeight (kg), (95%CI) | ΔSBP (mmHg), (95%CI) | Adverse events (GI, GTI, Hypo's) with SGLT-2I + GLP-1RA *vs* SGLT-2I |
|---|---|---|---|---|---|---|---|
| Zhou *et al* [31], 2019 | RCT, 3 | GLP-1RA + SGLT-2I *vs* SGLT-2I | 1421 | -0.80 (-1.14; -0.45) | -1.46 (-2.38; -0.54) | -2.88 (-4.52; -1.25) | Increased risk of GI S/E (RR: 1.68; 95%CI: 1.14-2.47) but similar GTI (RR: 0.82; 95%CI: 0.39-1.75) and hypo's (RR: 2.10; 95%CI: 0.75-5.90) in combo arm |
| Castellana *et al*[32], 2019 | RCT, 4 | GLP-1RA + SGLT-2I *vs* SGLT-2I | 1610 | -0.74 (-1.15; -0.33) | -1.61 (-2.83; -0.38) | -3.32 (-4.96; -1.68) | Similar hypo's (RR: 1.43; 95%CI: 0.46-4.52). GTI and GI S/E not reported |
| Patoulias *et al* [33], 2019 | RCT, 3 | GLP-1RA + SGLT-2I *vs* SGLT-2I | 1042 | -0.91 (-1.41; -0.42) | -1.95 (-3.83; -0.07) | -3.64 (-6.24; -1.03) | Increased risk of nausea (RR: 3.21; 95%CI: 1.36-7.54) and hypo's (RR: 2.62; 95%CI: 1.15-5.96) in combo arm. GTI not reported |
| Mantsiou *et al* [34], 2020 | RCT, 7 | GLP-1RA + SGLT-2I *vs* SGLT-2I | 1913 | -0.85 (-1.19; -0.52) | -1.46 (-2.94; +0.03) | -2.66 (-5.26; -0.06) | No difference in severe hypo's (OR: 2.39; 95%CI: 0.47-12.27). GTI and GI S/E not reported |
| | | GLP-1RA + SGLT-2I *vs* GLP-1RA | | -0.61 (-1.09; -0.14) | -2.59 (-3.68; -1.51) | -4.13 (-7.28; -0.99) | No difference in severe hypo's (OR: 1.38; 95%CI: 0.14-13.14). GTI and GI S/E not reported |

GI: Gastrointestinal; GLP-1RA: GLP-1 receptor agonists; GTI: Genital tract infections; Hypo's: Hypoglycemia; OR: Odds ratio; RR: Risk ratio; RCT: Randomized controlled trial; SBP: Systolic blood pressure; S/E: Side effect; SGLT-2I: SGLT-2 inhibitors.

**Table 3 Effect of simultaneous application of GLP-1 receptor agonists + SGLT-2I therapy on HbA1c (%), body weight (kg), and systolic blood pressure (mmHg) in randomized controlled trialx**

| Ref. | Parameters studied | Duration (wk) | (A) ΔGLP-1 RA | (B) ΔSGLT-2I | (C) ΔGLP-1 RA + SGLT-2I | (A + B) ΔSum of GLP-1 RA and SGLT2i | Effect of (C) compared to (A + B) |
|---|---|---|---|---|---|---|---|
| Frías *et al*[16], 2016; Jabbour *et al* [17], 2018; Birnbaum *et al*[18], 2018 | HbA1c | 28 | -1.60 | -1.40 | -2.00 | -3.00 | Less than additive |
| | | 52 | -1.38 | -1.23 | -1.75 | -2.61 | Less than additive |
| | | 104 | -1.29 | -1.06 | -1.70 | -2.35 | Less than additive |
| Ikonomidis *et al*[19], 2018 | HbA1c | 12 | -1.30 | -0.80 | -1.50 | -2.10 | Less than additive |
| Ali *et al*[12], 2020 | HbA1c | 16 | -1.44 | -0.89 | -1.67 | -2.33 | Less than additive |
| Frías *et al*[16], 2016; Jabbour *et al* [17], 2018; Birnbaum *et al*[18], 2018 | Body weight | 28 | -1.56 | -2.22 | -3.55 | -3.78 | Nearly additive |
| | | 52 | -1.51 | -2.28 | -3.31 | -3.79 | Nearly additive |
| | | 104 | -0.80 | -3.00 | -2.50 | -3.80 | Less than additive |
| Ikonomidis *et al*[19], 2018 | Body weight | 12 | NR | NR | NR | NR | NR |
| Ali *et al*[12], 2020 | Body weight | 16 | -1.90 | -3.50 | -6.00 | -5.40 | More than additive |
| Frías *et al*[16], 2016; Jabbour *et al* [17], 2018; Birnbaum *et al*[18], 2018 | SBP | 28 | -1.20 | -1.80 | -4.30 | -3.00 | More than additive |
| | | 52 | -0.70 | -2.70 | -4.50 | -3.40 | More than additive |
| | | 104 | -0.10 | -1.10 | -3.10 | -1.20 | More than additive |
| Ikonomidis *et al*[19], 2018 | SBP | 12 | -3.00 | -4.00 | -4.00 | -7.00 | Less than additive |
| Ali *et al*[12], 2020 | SBP | 16 | -5.10 | -5.20 | -14.10 | -10.30 | More than additive |

GLP-1RA: GLP-1 receptor agonists; HbA1c: Glycated haemoglobin; NR: Not reported; SBP: Systolic blood pressure; SGLT-2I: SGLT-2 inhibitors.

## DO WE GET AN ADDITIONAL CV AND RENAL BENEFIT BY COMBINING BOTH CLASSES OF DRUGS?

The mechanism by which both SGLT-2I and GLP-1RA exert their CV benefit appears to be mostly independent of glucose lowering and likely to be complementary owing to their differential MOA and

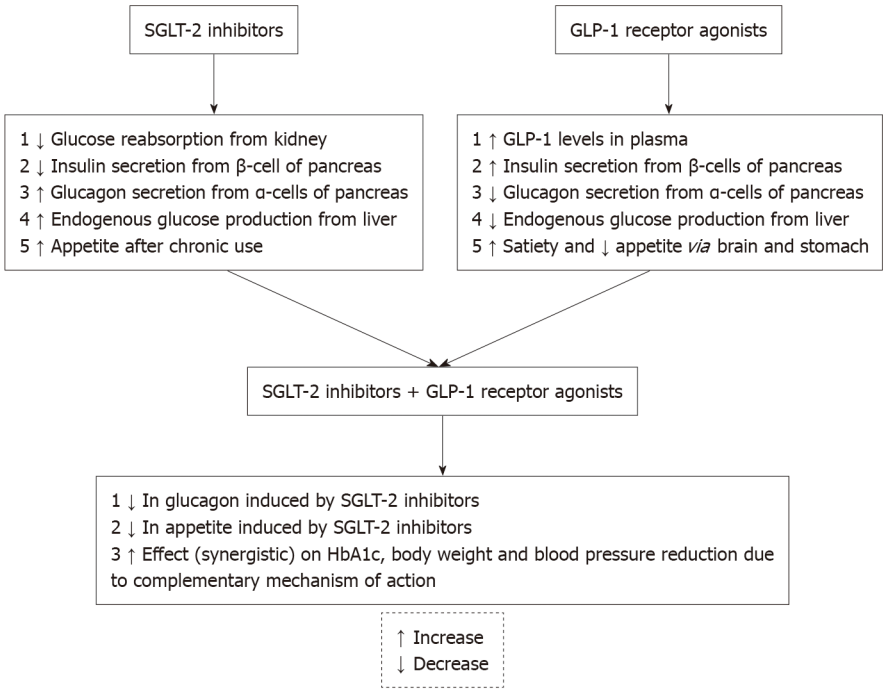


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**Figure 1 Complementary mechanism of action of SGLT-2 inhibitor and GLP-1 receptor agonist dual therapy.**

differential CV benefits. Available data from CVOT and renal outcome trials do hint that GLP-1RA primarily reduce the risk of atherosclerotic cardiovascular diseases (ASCVD) (ischemic stroke benefits being greater) with a modest effect on kidney function and minimal effect on heart failure, whereas SGLT-2I significantly reduced the risk of heart failure hospitalizations (HHF) and improved kidney function with a modest effect on ASCVD. Consequently, it is alluring to consider that combination therapy of SGLT-2I and GLP-1RA would achieve greater metabolic and cardio-renal benefits in patients with T2DM, compared with either class of drugs alone. This has gained further importance in the light of the latest American Diabetes Association and the European Association for the Study of Diabetes consensus report[39] and the European Society of Cardiology guidelines[40] that have put SGLT-2I, GLP-1RA, and their combination therapy much early in hierarchy in the presence of high CV risk, despite the lack of clarity on whether beneficial CV effects of individual GLP-1RA and SGLT-2I are retained, enhanced, or mitigated in combination therapy. To date, no dedicated randomized CVOT have yet evaluated the cardio-renal outcome with combination therapy of these two drug classes. A real-world propensity-matched study ($n$ = 25168) using insurance claims databases from the United States has found addition of SGLT-2I to GLP-1RA therapy to be associated with lower rates of major adverse cardiovascular events (MACE) and HHF compared to initiation with sulfonylureas, in people with T2DM[41]. Another 12-mo randomized blinded study ($n$ = 160) reported a significant increase of global myocardial work index with GLP-1RA plus SGLT-2I combination therapy (17.4%) or GLP-1RA alone (12.7%) compared with insulin (3.1%) or SGLT-2I (2%). Similarly, a significantly ($P$ < 0.05 for all comparisons) greater decline of pulse wave velocity (PWV), including central and brachial systolic blood pressure, was observed with GLP-1RA plus SGLT-2I combination therapy (PWV, 13%) or SGLT-2I (PWV, 10.1%) as compared with GLP-1RA (PWV, 8.6%) or insulin (PWV, 3.6%). The dual therapy of GLP-1RA plus SGLT-2I showed a significantly ($P$ < 0.05) greater effect on all measured markers in patients with left ventricular ejection fraction < 55%[42]. Summarily, GLP-1RA and SGLT-2I dual therapy showed a significantly better improvement of endothelial glycocalyx thickness (a marker of endothelial dysfunction) and myocardial work index and a larger reduction in arterial stiffness compared with insulin therapy despite a similar glucose reduction.

The study of combination therapy with GLP-1RA plus SGLT-2I in the recently conducted CVOT has been rare. The prevalence of baseline SGLT-2I use in GLP-1RA CVOT ranged from 0% to 5.3%, with the exception being AMPLITUDE-O study of efpeglenatide, where 15.2% ($n$ = 618) were using SGLT-2I at the baseline[43-45]. Likewise, the prevalence of baseline GLP-1RA use in SGLT-2I CVOT ranged from 2.5% to 4.4% (CANVAS, $n$ = 407; DECLARE-TIMI, $n$ = 750; VERTIS-CV, $n$ = 277)[45-48]. To understand the CV effect of GLP-1RA plus SGLT-2I combination therapy, we systematically reviewed the literature and pooled the data of the primary three-point MACE (3P-MACE) outcomes from five CVOT that reported the results against placebo[43,45-48]. Figure 2 represents the search criteria and flow diagram according to PRISMA statements. Additionally, we also pooled the data of HHF and renal composite that were available for two RCTs - AMPLITUDE-O and DECLARE-TIMI[45,47]. Table 4 summarizes the

**Table 4 Meta-data of three-point composite of major adverse cardiovascular events, heart failure hospitalization, and renal outcome in cardiovascular outcome trials of SGLT-2 inhibitors and GLP-1 receptor agonists**

| Trial eponym, drugs | Background GLP-1RA + SGLT-2I therapy; *n* | Active arm (*n*/*N*), % or rate-per 100-patient-yr[1] | Placebo arm (*n*/*N*), % or rate-per 100-patient-yr[1] | HR, (95%CI) | *P* value of interaction |
|---|---|---|---|---|---|
| 3-point composite of major adverse cardiovascular events outcome | | | | | |
| CANVAS[46], Canagliflozin | Yes; 407 | NR | NR | 0.73 (0.36-1.46) | 0.94 |
| | No; 9735 | NR | NR | 0.86 (0.76-0.98) | |
| DECLARE-TIMI[47], Dapagliflozin | Yes; 750 | 31/397, 7.8% | 31/353, 8.8% | 0.87 (0.53-1.43) | 0.84 |
| | No; 16410 | 725/8185, 8.9% | 772/8225, 9.4% | 0.94 (0.85-1.04) | |
| VERTIS-CV[48], Ertugliflozin | Yes; 277 | 21/192, 3.54[1] | 9/85, 3.79[1] | 0.94 (0.43-2.05) | NR |
| | No; 7961 | 632/5301, 3.91[1] | 318/2660, 4.02[1] | 0.97 (0.85-1.11) | |
| EXSCEL[43], Exenatide QW | Yes; 1144[2] | NR/572, 3.29[1] | NR/572, 4.81[1] | 0.68 (0.39-1.17) | NR |
| | No | NR | NR | NR | |
| AMPLITUDE-O[45], Efpeglenatide | Yes; 618 | 25/412, 6.1%, 3.4[1] | 17/206, 8.3%, 5.0[1] | 0.70 (0.37-1.30) | 0.68 |
| | No; 3458 | 164/2305, 7.1%, 4.0[1] | 108/1153, 9.4%, 5.4[1] | 0.74 (0.58-0.94) | |
| Heart failure hospitalization outcome | | | | | |
| DECLARE-TIMI[47], Dapagliflozin | Yes; 750 | 4/397, 1.0% | 18/353, 5.1% | 0.20 (0.07-0.60) | 0.01 |
| | No; 16410 | 208/8185, 2.5% | 268/8225, 3.3% | 0.77 (0.64-0.92) | |
| AMPLITUDE-O[45], Efpeglenatide | Yes; 618 | 3/412, 0.7%; 0.4[1] | 6/206, 2.9%, 1.6[1] | 0.23 (0.05-0.97) | 0.35 |
| | No; 3458 | 37/2305, 1.6%, 0.9[1] | 25/1153, 2.2%, 1.2[1] | 0.70 (0.42-1.17) | |
| Renal outcome | | | | | |
| DECLARE-TIMI[47], Dapagliflozin[3] | Yes; 750 | 4/397, 1.0% | 10/353, 2.8% | 0.36 (0.11-1.15) | 0.49 |
| | No; 16410 | 123/8185, 1.5% | 228/8225, 2.8% | 0.54 (0.43-0.67) | |
| AMPLITUDE-O[45], Efpeglenatide[4] | Yes; 618 | 37/412, 9.0%, 5.1[1] | 34/206, 16.5%, 10.0[1] | 0.52 (0.33-0.83) | 0.38 |
| | No; 3458 | 316/2305, 13.7%, 8.2[1] | 216/1153, 18.7%, 11.9[1] | 0.70 (0.59-0.83) | |

[1]Rate-per 100-patient-yr.
[2]Open-label, propensity-matched.
[3]Renal composite outcome consist of sustained decrease of 40% or more in eGFR to less than 60 mL/min/1.73 $m^2$, new end-stage renal disease, or death from renal causes.
[4]Renal composite outcome consists of incident macroalbuminuria (UACR > 300 mg/g or 33.9 mg/mmol) plus ≥ 30% rise of UACR from baseline, a sustained ≥ 30 d decrease in eGFR by ≥ 40%, renal replacement therapy, and a sustained (≥ 30 d) eGFR < 15 mL/min/1.73 $m^2$.
3P-MACE: Three-point composite of major adverse cardiovascular events; CVOTs: Cardiovascular outcome trials; HHF: Heart failure hospitalization; GLP-1RA: Glucagon-like petide-1 receptor agonists; HR: Hazard ratio; *n*: Number of events; *N*: Total number of patients; NR: Not reported/retrievable; PBO: Placebo; SGLT-2I: Sodium glucose transporter-2 inhibitors.

findings from five CVOT that reported the outcomes stratified on combination therapy users. Subsequently, a meta-analysis was conducted by applying the inverse variance-weighted averages of pooled logarithmic hazard ratio (HR) using a fixed-effects model with Comprehensive Meta-Analysis software Version 3, Biostat Inc., Englewood, NJ, United States. A two-sided *P* value of < 0.05 was considered statistically significant. Heterogeneity was measured using Higgins $I^2$ and Cochrane *Q* statistics and it was considered low ($I^2$ ≤ 25%) or moderate (> 25%-50%) or high (> 50%)[49]. While we did not use Cochrane tool to assess the bias risk assessment considering the robust quality of trials included in this meta-analysis, publication bias for CV outcome was evaluated by applying funnel plot using the "trim and fill" adjustment, rank correlation test, and the Egger's test. A sensitivity exclusion analysis was additionally performed to determine whether any subgroups included in this meta-analysis could have influenced the aggregate result or changed the heterogeneity significantly. Our meta-analysis of five CVOT (*n* = 40, 760) that reported the outcome with or without combination therapy, found a significant reduction in composite of 3P-MACE (hazard ratio [HR] = 0.90; 95% confidence interval [CI]: 0.85-0.96; *P* = 0.001), without any heterogeneity. This finding was similar regardless of baseline GLP-1RA or SGLT-2I use: GLP-1RA without SGLT-2I (1 RCT; *n* = 3458; HR = 0.74; 95%CI: 0.58-0.94; *P* = 0.02), SGLT-2I without GLP-1RA (3 RCT; *n* = 34106; HR = 0.92; 95%CI: 0.86-0.99; *P* = 0.02), and GLP-1RA plus SGLT-2I combination therapy (5 RCT; *n* = 3196; HR = 0.77; 95%CI: 0.59-1.01;

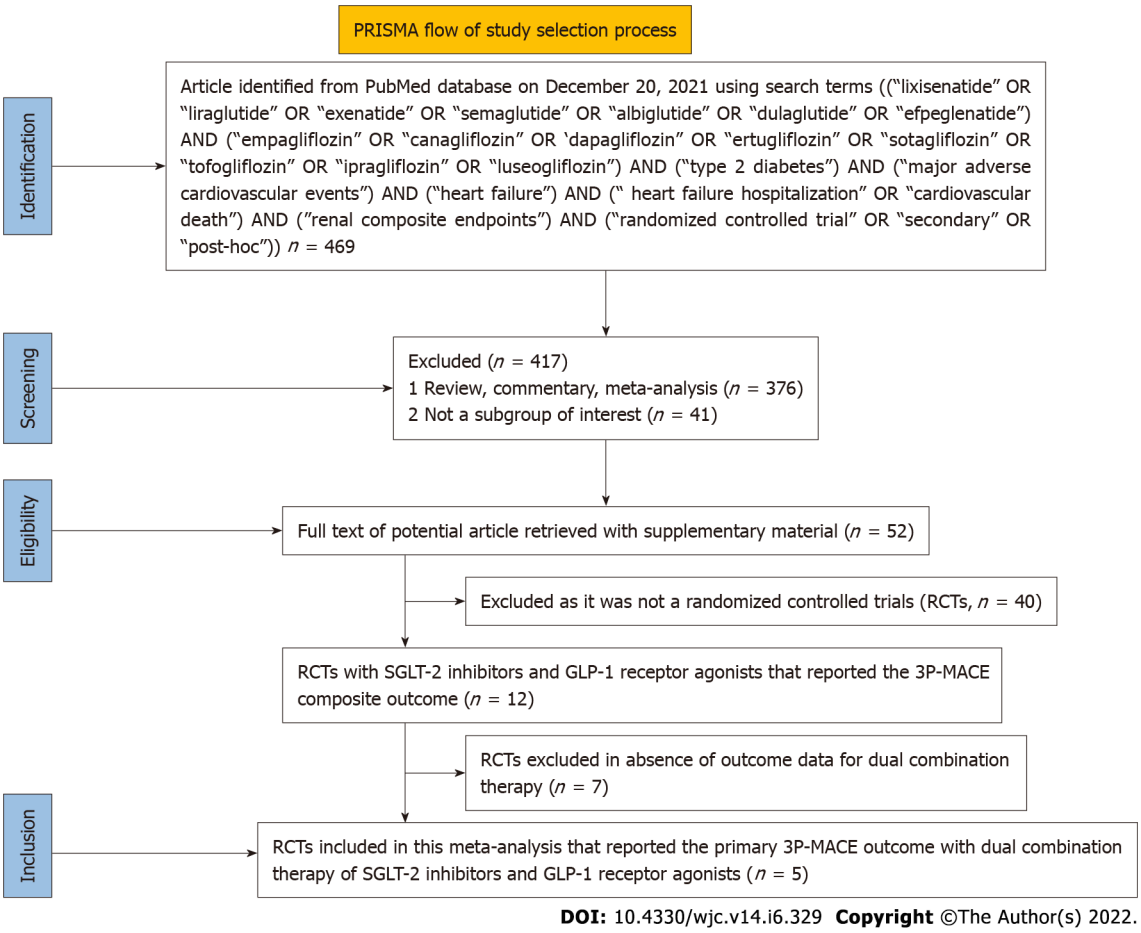


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**Figure 2 PRISMA flow diagram for randomized controlled trials chosen for meta-analysis.** RCT: Randomized controlled trial.

$P$ = 0.06), without any significant heterogeneity and interaction ($P_{interaction}$ = 0.12) (Figure 3). Sensitivity analysis showed that no individual subgroup significantly affected the aggregate results or heterogeneity (Supplementary Table 1). No obvious publication bias was noted amongst the three subgroups, and Trim and Fill imputed point estimates were similar to the final results (Supplementary Figure 1). Our analysis suggests no incremental or attenuated 3P-MACE benefits with GLP-1RA plus SGLT-2I combination therapy, although that needs to be confirmed through large adequately powered clinical trials. Our findings are congruent to two recent network meta-analyses that did not report additional CV benefit with GLP-RA and SGLT-2I combination therapy[50,51].

Unlike 3P-MACE, a possible additive beneficial effect on heart failure and renal events with GLP-1RA and SGLT-2I combination therapy is very likely mechanistically because both drug classes have shown a consistent reduction in urinary protein excretion and rate of estimated glomerular filtration rate (eGFR) decline. Since both classes of drugs cause natriuresis (albeit by different mechanisms), a synergistic effect on HHF reduction is also mechanistically possible. Indeed, in a *post hoc* subgroup analysis of DECLARE-TIMI ($n$ = 750) stratified by baseline GLP-1RA use, a greater benefit ($P_{interaction}$ = 0.014) on HHF was noted in patients with baseline dapagliflozin plus GLP-1RA user (HR = 0.20; 95%CI: 0.07-0.60) compared to dapagliflozin alone (HR = 0.77; 95%CI: 0.64-0.92)[47]. Similarly, a greater benefit ($P_{interaction}$ = 0.03) on composite of CV death/HHF was also noted in DECLARE-TIMI in patients with baseline dapagliflozin plus GLP-1RA use (HR = 0.37; 95%CI: 0.18-0.78) compared with dapagliflozin alone (HR = 0.86; 95%CI: 0.75-0.98)[47]. However, the benefit of dapagliflozin on renal endpoints in DECLARE-TIMI was similar ($P_{interaction}$ = 0.49) amongst baseline dapagliflozin plus GLP-1RA users (HR = 0.36; 95%CI: 0.11-1.15) compared to dapagliflozin alone or GLP-1RA non-users (HR = 0.54; 95%CI: 0.43-0.67)[47]. A *post hoc* analysis of the CANVAS program also noted a similar effect on the composite renal outcome in canagliflozin plus GLP-1RA users *vs* GLP-1RA non-users ($P_{interaction}$ = 0.43)[46].

Similar trends were also noted in GLP-1RA CVOT although it was inconsistent. In an exploratory analysis of AMPLITUDE-O with GLP-1RA efpeglenatide ($n$ = 618), a nonsignificant trend ($P_{interection}$ = 0.35) of greater HHF reduction was observed in baseline efpeglenatide plus SGLT-2I users (HR = 0.23; 95%CI: 0.05-0.97) *vs* SGLT-2I non-users (HR = 0.70; 95%CI: 0.42-1.17)[45]. Similarly, improvement in renal composite outcome in AMPLITUDE-O was insignificantly ($P_{interection}$ = 0.38) greater in baseline efpeglenatide plus SGLT-2I users (HR = 0.52; 95%CI: 0.33-0.83) compared to SGLT-2 non-users (HR = 0.70; 95%CI: 0.59-0.83)[45]. Notably, a propensity matched *post hoc* analysis ($n$ = 1144) of EXSCEL

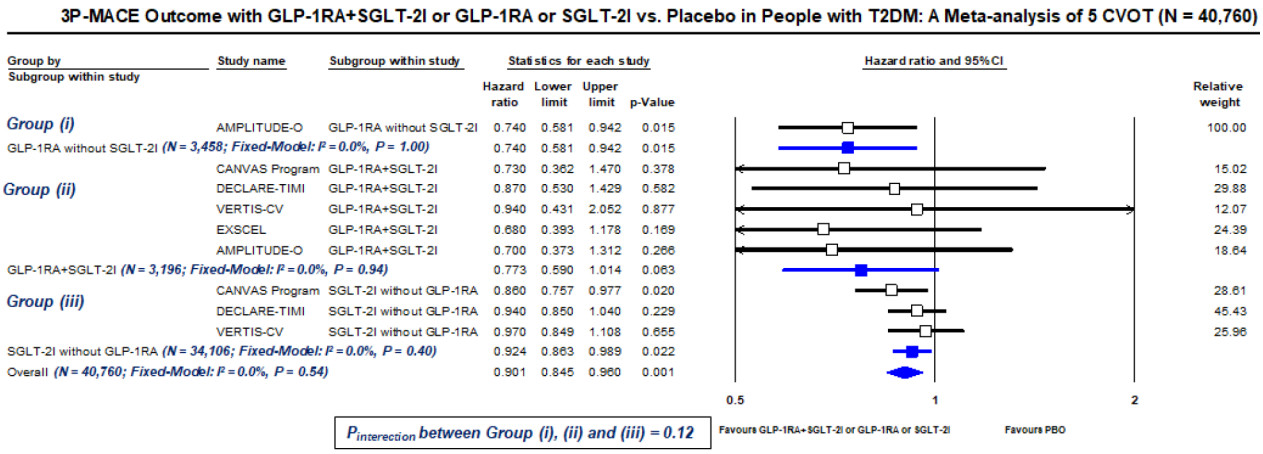


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**Figure 3 Three-point major adverse cardiovascular event outcome with GLP-1 receptor agonist plus SGLT-2 inhibitor dual therapy or GLP-1 receptor agonists or SGLT-2 inhibitors *vs* placebo: A meta-analysis of five cardiovascular outcome trials.**

reported a nominally significant reduction in all-cause mortality (adjusted HR = 0.38, 95%CI: 0.16-0.90) and CV death (adjusted HR = 0.17; 95%CI: 0.04-0.77) and improvement in estimated eGFR slope (adjusted HR = +1.94 mL/min; 95%CI: 0.94-2.94 mL/min/1.73 m$^2$/year) with exenatide QW plus SGLT-2I combination therapy compared to the placebo[43]. Importantly, exenatide QW plus SGLT-2I combination also demonstrated a nominally significant reduction in all-cause mortality (HR = 0.41; 95%CI: 0.17-0.95) and CV death (HR = 0.21; 95%CI: 0.05-0.93) and improved eGFR slope (HR = +2.38 mL/min; 95%CI: 1.40-3.35 mL/min/1.73 m$^2$/year) as compared to exenatide QW alone in a propensity-matched analysis of 1150 participants[43].

Our meta-analysis from the pooled data of two RCTs that reported the outcomes of HHF and renal composite suggested a greater benefit ($P_{interaction}$ = 0.02) on HHF outcomes with GLP-1RA plus SGLT-2I dual therapy (HR = 0.21; 95%CI: 0.08-0.50, $P$ < 0.001) compared with GLP-1RA without SGLT-2I (HR = 0.70; 95%CI: 0.42-1.17; $P$ = 0.17) and SGLT-2I without GLP-1RA (HR = 0.77; 95%CI: 0.64-0.92; $P$ = 0.005) against placebo (Figure 4). No significant difference ($P_{interection}$ = 0.11) was noted on the composite of renal outcome between the combination therapy (HR = 0.50; 95%CI: 0.32-0.76; $P$ = 0.001), GLP-1RA without SGLT-2I (HR = 0.70; 95%CI: 0.59-0.83, $P$ < 0.001), or SGLT-2I without GLP-1RA (HR = 0.54; 95%CI: 0.43-0.67; $P$ < 0.001) against placebo (Figure 5). Collectively, these findings hint to a possible synergistic CV and renal effect of GLP-1RA plus SGLT-2I combination therapy. Nevertheless, some caution must be exercised while interpreting these findings in the light of following limitations: Exploratory, *post hoc* analysis with a small number of participants in each subgroup compounded by a very small number of events (9 events of HHF in AMPLITUDE-O and 14 events for renal outcome in DECLARE-TIMI in combination arm); uncategorized type of heart failure; results with wide confidence interval (imprecise point estimates); allocation bias; applying the aggregate trial-level results for the meta-analysis in the absence of individual patient data; inclusion of adjusted HR from propensity-matched analysis of EXSCEL; and no correction made for multiplicity in the subgroups analysis. Moreover, baseline GLP-1RA or SGLT-2I addition in SGLT-2I or GLP-1RA CVOT, respectively, may have been determined by the patient preference, cost, availability of treatment, and local guidelines, and thus, precludes true randomization. Future randomized trial PRECIDENTD (PREvention of CardIovascular and DiabEtic kidNey disease in Type 2 Diabetes), which has been planned to evaluate cardiovascular and renal outcomes with either SGLT-2I or GLP-1RA or both, in nearly 9000 T2DM having high CV risk, will further enlighten the effect of combination therapy[52].

## CONCLUSION

GLP-1RA plus SGLT-2I combination therapy lower HbA1c, body weight, and SBP significantly greater than GLP-1RA or SGLT-2I therapy alone. While HbA1c lowering with this combination therapy is less than additive compared to the sum of HbA1c lowering with individual agents, body weight lowering seems to be nearly additive and SBP lowering is found to be more than additive. Importantly, combination therapy with GLP-1RA and SGLT-2I does not potentiate hypoglycemia, GI side effects, or GTI compared to either agent alone. While 3P-MACE risk reduction with GLP-1RA plus SGLT-2I combination therapy appears to be similar compared with either GLP-1RA or SGLT-2I alone, improvement in HHF and possibly renal outcomes could be likely additive. Future adequately powered large RCT are needed to confirm additional benefit of GLP-1RA plus SGLT-2I combination therapy on

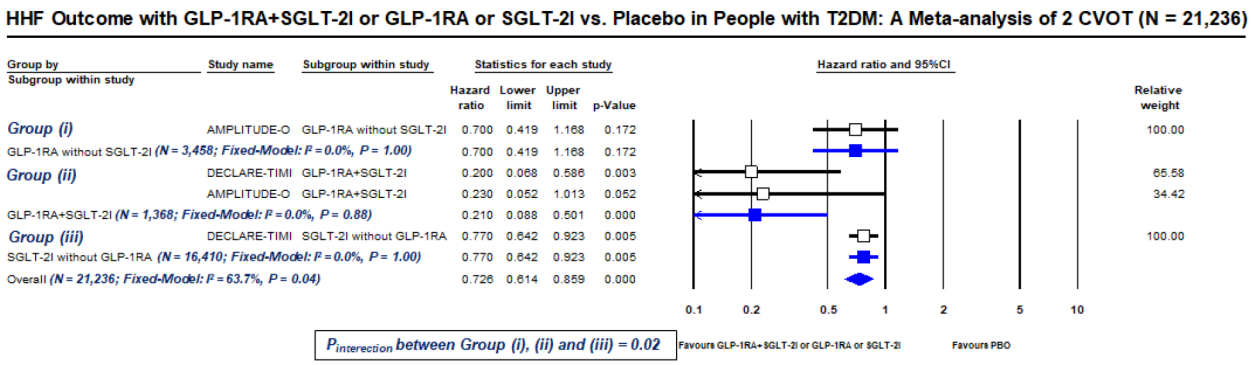


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**Figure 4 Heart failure hospitalization outcome with GLP-1 receptor agonist plus SGLT-2 inhibitor dual therapy or GLP-1 receptor agonists or SGLT-2 inhibitors *vs* placebo: A meta-analysis of two cardiovascular outcome trials.**

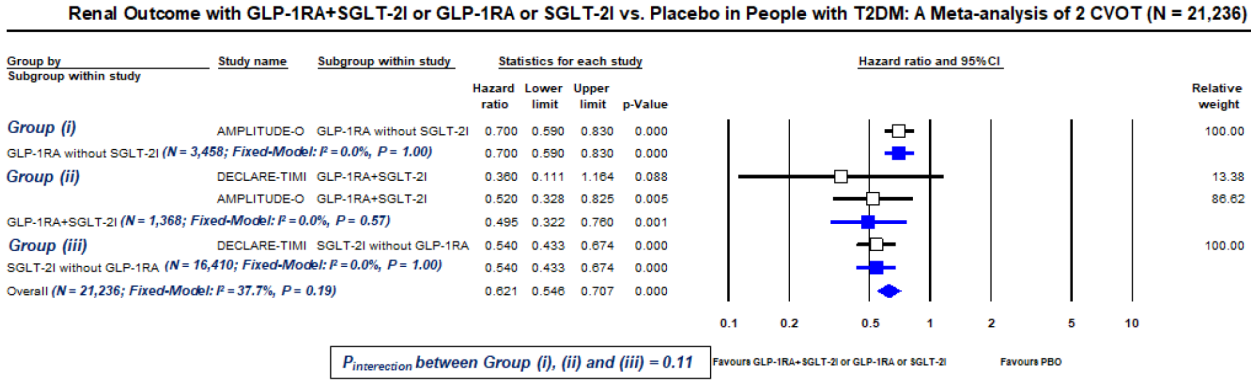


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**Figure 5 Renal outcome with GLP-1 receptor agonist plus SGLT-2 inhibitor dual therapy or GLP-1 receptor agonists or SGLT-2 inhibitors *vs* placebo: A meta-analysis of two cardiovascular outcome trials.**

CV, renal, and mortality outcomes.

## FOOTNOTES

**Author contributions:** Singh AK made conception and design of the study and collected the data; Singh AK and Singh R did the statistical calculations, drafted the manuscript, and revised the manuscript critically; all authors read and approved the final manuscript.

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

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*MINIREVIEWS*

# COVID-19 vaccination and cardiac dysfunction

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## Abstract

The coronavirus disease 2019 (COVID-19) mRNA vaccine against severe acute respiratory syndrome coronavirus 2 infections has reduced the number of symptomatic patients globally. A case series of vaccine-related myocarditis or pericarditis has been published with extensive vaccination, most notably in teenagers and young adults. Men seem to be impacted more often, and symptoms commonly occur within 1 wk after immunization. The clinical course is mild in the majority of cases. Based on the evidence, a clinical framework to guide physicians to examine, analyze, identify, and report suspected and confirmed cardiac dysfunction cases is needed. A standardized workup for every patient with strongly suspicious symptoms associated with the COVID-19 mRNA vaccine comprises serum cardiac troponin measurement and a 12-lead electrocardiogram (ECG). For patients with unexplained elevation of cardiac troponin and pathologic ECG, echocardiography is recommended. Consultation with a cardiovascular expert and hospitalization should be considered in this group of patients. Treatment is primarily symptomatic and supportive. Deferring a 2$^{nd}$ dose of the COVID-19 mRNA vaccination in individuals with suspected myocarditis or pericarditis after the 1$^{st}$ dose is suggested until further safety data become available.

**Key Words:** Cardiac dysfunction; Myocarditis; Pericarditis; COVID-19; mRNA vaccine; Electrocardiography; Echocardiography; SARS-CoV-2

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**Core Tip:** A possible hypersensitivity myocarditis with a consistent relationship to administering an mRNA coronavirus disease 2019 (COVID-19) vaccination was reported. While the actual prevalence of this adverse event is unclear at this time, the clinical manifestation and pathological findings point to a link with an inflammatory reaction to a COVID-19 immunization. However, acute myocarditis following mRNA COVID-19 vaccination was very low and mostly self-limited. Moreover, the high efficacy of mRNA COVID-19 vaccines in preventing further pandemic conditions, reducing disease severity, and the occurrence of a very low incidence of myocarditis following immunization should be a strength of an mRNA COVID-19 vaccine for public trust.

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## INTRODUCTION

Myocarditis or pericarditis is an inflammatory heart condition caused by infections, drug exposure, or immune system activation[1,2]. It has a wide range of clinical manifestations and courses, with most cases resolving spontaneously. However, it is also a cause of sudden cardiac death in young people. Furthermore, in some instances, inflammation can induce significant scarring, which causes left ventricular (LV) remodeling and finally leads to dilated cardiomyopathy or a predominant hypokinetic nondilated phenotype of cardiomyopathy[3,4]. Myocarditis has previously been reported following non-mRNA vaccine immunization. The incidence of myocarditis after a live smallpox vaccination was 2.2-7.8 *per* 100000, which occurred within 30 d after immunization[5,6]. The majority of adverse events that occur after vaccination in these people resolve without long-term consequences. Measles-mumps-rubella, chickenpox, yellow fever, and oral polio vaccine, have a 0.24 *per* 100000 immunization risk of pericarditis or myocarditis in the 42 d following vaccination[7].

During post-marketing pharmacovigilance surveillance, a considerably higher incidence of myocarditis or pericarditis than predicted was detected after coronavirus disease 2019 (COVID-19) immunization using mRNA vaccines[8]. As a result, the United States Food and Drug Administration, followed by the European Medicines Agency, listed myocarditis and pericarditis as extremely uncommon adverse drug reactions in the product information for Moderna and Pfizer-BioNTech[9,10]. Myocarditis or pericarditis is becoming more common as an unusual consequence of the COVID-19 mRNA vaccines, particularly in young adults and adolescent men. This article delves deeper into this phenomenon and its possible pathophysiology. We also examine the trade-off between the danger of myocarditis or pericarditis from mRNA vaccination and the cardiac and other hazards associated with COVID-19.

## INCIDENCE AND CLINICAL MANIFESTATIONS OF MYOCARDITIS AFTER COVID-19 VACCINATION

Witberg *et al*[11] analyzed Clalit Health Services, Israel's biggest health care organization, for the myocarditis patients who had been immunized with one dose of the mRNA vaccine BNT162b2 (Pfizer–BioNTech). Clalit Health Services provided health care for 4.7 million patients (52% of the total population) regarding socioeconomic status and prevalence of co-existing diseases. They explored 2558421 members who were vaccinated with one dose of the mRNA vaccine; along with 2401605 members who were vaccinated with 2 doses. They discovered 54 patients who satisfied the research criteria for myocarditis. There were 41 mild cases, 12 moderate cases, and 1 fatal case. The median age of these patients was 27 (21-35) years, with 94% of them being males. Within 42 d of the first dosage, the incidence of myocarditis *per* 100000 vaccinated people was 2.13 (1.56-2.70) (mild = 1.62, intermediate = 0.47, and severe = 0.04). There was a higher incidence among male patients than female patients, with 4.12 (2.99-5.26) and 0.23 (0-0.49) *per* 100000 vaccinations, respectively (Table 1). Among all patients aged 16 years to 29 years, the incidence was 5.49 (3.59-7.39) *per* 100000 vaccinations. The incidence was reduced to 1.13 (0.66-1.60) *per* 100000 vaccinations among the patients who were 30 years of age or older. Male patients between the ages of 16 and 29 had the greatest incidence, with 10.69 (6.93-14.46) occurrences *per* 100000 immunizations. The most common clinical presentation was chest pain in 82% of the patients. Only 1 patient presented with hemodynamic instability. The electrocardiogram (ECG) showed 53% ST-segment elevation, 24% minor abnormalities, and a 21% normal pattern at presentation. All available data for cardiac troponin T (41 cases) showed a median peak of troponin T of 680 ng/L

**Table 1 Incidence and clinical manifestations of myocarditis after coronavirus disease 2019 mRNA vaccination**

| Ref. | Type of vaccine | Study population | Incidence | Cardiac assessment methods | Main findings and clinical outcomes |
|---|---|---|---|---|---|
| Witberg *et al* [11], Israel | Pfizer-BioNTech | 54/2558421 (21-63 yr) | 2.13/100000 | Clinical presentation, ECG, ECHO, MRI, Troponin T | Myocarditis = 10.69/100000 in male ages 16-29 yr, 25.92% had LV dysfunction, 76% = mild, 22% = intermediate, 1 case had cardiogenic shock, 1 case died of unknown cause, 0.51/100000 after 1st dose and 2.15/100000 after 2nd dose |
| Mevorach *et al* [12], Israel | Pfizer-BioNTech | 136/9289765 (≥ 16 yr) | 1.46/100000 | Clinical presentation, ECHO, MRI, Troponin T, Endomyocardial biopsy | Myocarditis = 15.07/100000 in male ages 16-19 yr, 0.35/100000 after 1st dose, 2.28/100000 after 2nd dose, 94.85% = mild, 4.41% = intermediate, 1 case was fatal, endo-interstitial edema with neutrophils and mononuclear-cells infiltrates with no giant cells |
| Montgomery *et al*[13], United States | Pfizer-BioNTech/Moderna | 23/2810000 (20-51 yr) | 0.82/100000 | Clinical presentation, ECG, ECHO, MRI, Troponin T | Myocarditis = 1.88/100000 after 1st dose, 3.49/100000 after 2nd dose, and 4.36/100000 in male after 2nd dose |
| Perez *et al* [14], United States | Pfizer-BioNTech/Moderna/Johnson and Johnson | 7/175472 (12-106 yr) | 55.35/100000, Person-yr | Clinical presentation, ECG, ECHO, MRI, Troponin T | The overall incidence rate was 55.35 (22.25–114.00) *per* 100000 person-yr during the 2 wk after a dose of vaccine. The IRR for myocarditis following COVID-19 mRNA vaccination was increased for males at 6.69 (2.35–15.52), but it was not statistically significant for females at 1.41 (0.03–8.45) |
| Das *et al*[15], United States | Pfizer-BioNTech | 25/7735071 (12-17 yr) | 0.32/100000 | Clinical presentation, ECG, ECHO, MRI, Troponin T, CRP | Myocarditis = 0.04/100000 after 1st dose, 0.28/100000 after 2nd dose, and 0.26/100000 in male after 2nd dose |
| Li *et al*[16], United States | Pfizer-BioNTech/Moderna/Janssen | Age ≥ 12 yr | 0.598/100000 | VAERS | Pfizer–BioNTech had a higher incidence rate of 0.670/100000 than the rate of 0.498/100000 found for Moderna. The incidence rate following the 2nd dose was twice that of the 1st dose and was the highest in adolescents aged 12-17 yr, at 2.094/100000. The Janssen vaccine was not associated with myocarditis or pericarditis |
| Patone *et al* [17], United Kingdom | Pfizer-BioNTech/Moderna/AstraZeneca | 1615/38615491 (Age ≥ 16 yr) | 4.18/100000 | NIMS | The IRR of myocarditis = 1.76, 1.45, 8.38 after 1st dose of AstraZeneca, Pfizer-BioNTech, Moderna. IRR of myocarditis = 1.75, 23.10 after 2nd dose of Pfizer-BioNTech, Moderna. There was an increase in the risk of myocarditis within 1 wk after 1st dose of adenovirus and mRNA vaccines and a higher increased risk after 2nd dose of both mRNA vaccines, especially in under 40 yr |
| Simone *et al* [18], United States | Pfizer-BioNTech/Moderna | 15/2392924 (Age ≥ 18 yr) | 0.63/100000 | KPSC members with clinical presentation, ECG, ECHO, Troponin I | Myocarditis = 0.08/100000 after 1st dose, 0.58/100000 after 2nd dose over a 10-d period, all were men aged 20-32 yr. The IRR of myocarditis = 0.38 after 1st dose and 2.7 after 2nd dose |
| Nygaard *et al* [19], Denmark | Pfizer-BioNTech | 15/261334 (12-17 yr) | 5.74/100000 | Clinical presentation, ECG, ECHO, MRI, Troponin | Myocarditis = 3.06/100000 after 1st dose, 2.68/100000 after 2nd dose mostly in male (M:F = 6:1) |
| Husby *et al* [20], Denmark | Pfizer-BioNTech/Moderna | 269/4931775 (Age ≥ 12 yr) | 5.45/100000 | Danish Vaccination Register | HR of myocarditis/pericarditis = 1.34, 3.92 within 28 d from the vaccination of Pfizer-BioNTech, Moderna respectively. Myocarditis or pericarditis occurred at 1.4/100000 for Pfizer-BioNTech and 4.2/100000 for Moderna. Vaccination with Moderna vaccine was associated with an increased risk of myocarditis or pericarditis, especially in aged 12-39 yr |
| Diaz *et al*[21], United States | Pfizer-BioNTech/Moderna/Janssen | 57/2000287 (26-70 yr) | 2.85/100000 | Clinical presentation, ECG, | Myocarditis = 1.0/100000 and pericarditis = 1.8/100000. Myocarditis and pericarditis |

| | | | | | |
|---|---|---|---|---|---|
| | | | | ECHO, Troponin | were observed after the COVID-19 vaccination. Myocarditis developed rapidly in younger patients, mostly after the 2nd dose. Pericarditis affected older patients later, after either the 1st or 2nd dose |
| Chouchana *et al*[22], WHO | Pfizer-BioNTech/Moderna | 2277/716576 reports | NA | VigiBase | Over all myocarditis = 3.57/100000 with 12–17 yr = 3.69/100000, 18–29 yr = 1.97/100000, and ≥ 30 yr = 0.21/100000. Younger male aged 12–17 yr were more prone to report myocarditis or pericarditis with 22.3/100000. The median time to onset for myocarditis was 3 d after vaccine injection |
| Barda *et al* [23], Israel | Pfizer-BioNTech | 21/938812 | 2.23/100000 | Clinical presentation, ECG, ECHO, Troponin | Vaccination was most strongly associated with an elevated risk of myocarditis [risk ratio, 3.24 (1.55-12.44)]. Alternatively, SARS-CoV-2 infection was associated with a substantially increased risk of myocarditis [risk ratio, 18.28 (3.95-25.12)]. The BNT162b2-mRNA vaccine increased the incidence of a few adverse events over a 42-d follow-up period |

ECG: Electrocardiography; ECHO: Echocardiography; HR: Hazard ratio; IRR: Incidence rate ratio; KPSC: Kaiser Permanente Southern California; M:F: Male to female; MRI: Magnetic resonance imaging; NA: Not available; NIMS: The English National Immunisation; ROR: Reporting odds ratio; VAERS: Vaccine Adverse Events Reporting System; VigiBase: World Health Organization (WHO) global safety database; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

(275-2075). One patient's cardiac biopsy revealed perivascular lymphocyte and eosinophil infiltration. On admission, ECG findings (48 cases) showed 71% normal LV function. Fourteen patients (29%) showed some degree of LV dysfunction. Seventeen percent presented with mild symptom, four percent had mild symptom, four percent had moderate symptom, two percent had moderate-to-severe symptom, and two percent had severe symptom. Fifteen patients underwent cardiac magnetic resonance imaging (MRI) and showed normal LV function (Table 2). They concluded that the highest incidence of myocarditis after BNT162b2 mRNA vaccination was among male patients aged 16-29 years. The majority of myocarditis cases were mild to moderate in severity.

Mevorach *et al*[12] retrospectively reviewed data regarding myocarditis cases. During the surveillance period, 9289765 Israeli residents were included. Of those, 5442696 individuals received the 1st dose and 5125635 received two BNT162b2 mRNA vaccines. They found that 136 cases were confirmed as diagnoses of myocarditis. In most cases, the clinical presentations in 129 cases were mild with a resolution of myocarditis. The overall incidence of myocarditis *per* 100000 vaccinated people was 1.46. A comparison of risks 21 d after the 1st and 2nd doses based on age and gender revealed a risk difference of 1.76 *per* 100000 people. Male recipients had a risk difference of 3.19, while female recipients had a risk difference of 0.39. The highest difference was observed among male patients aged 16 and 19, at 13.73 *per* 100000 people. These findings pointed out that the 1st wk after the 2nd dose of vaccination was the leading risk period.

Myocarditis symptoms usually appear within a few days of receiving the 2nd dose of the vaccine. After the 2nd dose of vaccine, they estimated that definite cases of myocarditis occurred at a rate of 1 in 26000 males and 1 in 218000 females in the general Israeli population. The majority of the patients had normal or mildly reduced ejection fraction (EF), but the EF in 4 patients was severely reduced. MRIs were performed on 48 people who had a positive result from a T2-based sequence or a T1-based sequence that indicated myocarditis. They concluded that the myocarditis incidence that occurred after 2 doses of the mRNA vaccine was very low, although the incidence was higher than in unvaccinated people. Myocarditis was mostly discovered in young male recipients after the second dose of the vaccine.

Montgomery *et al*[13] retrospectively studied a United States Military Health System case series that experienced myocarditis after COVID-19 vaccination (BNT162b2-mRNA and mRNA-1273 vaccines). The authors found that 23 male patients aged 20-51 years were evaluated for acute-onset chest pain following 2810000 mRNA COVID-19 vaccinations and confirmed acute myocarditis. The overall incidence was 0.82 *per* 100000 doses of vaccination. Myocarditis was reported at 1.88 *per* 100000 vaccinations after the 1st dose, at 3.49 *per* 100000 vaccinations after the 2nd dose, and at 4.36 *per* 100000 vaccinations in males after the 2nd dose. T-wave inversions, ST-segment elevations, and nonspecific ST changes were reported in 83% of patients as abnormal ECG findings. In 17% of the recipients, echocardiography (ECHO) demonstrated reduced LVEFs (40% to 50%). They concluded that the number of cases of myocarditis observed in the Military Health System exceeded some estimates of expected numbers, particularly when considering the subset of the population who received the 2nd dose of the mRNA vaccine. It's time to pay more attention to myocarditis as a potential side effect of the mRNA COVID-19

**Table 2 Characteristic of acute myocarditis patients after coronavirus disease 2019 mRNA vaccination**

| Ref. | Type of vaccine | No. of myocarditiscases | Male/Female (%) | Median age in yr (IQR) | Myocarditis after 1st dose (%) | Myocarditis after 2nd dose (%) | Clinical severity F/I/M |
|---|---|---|---|---|---|---|---|
| Witberg *et al*[11], Israel | Pfizer-BioNTech | 54 | 51/3 (94/6) | 27 (21–35) | 17 (31.48) | 37 (68.52) | 1/12/41 |
| Mevorach *et al* [12], Israel | Pfizer-BioNTech | 136 | 118/18 (87/13) | - (16-> 30) | 19 (13.97) | 117 (86.03) | 1/6/129 |
| Montgomery *et al* [13], United States | Pfizer-BioNTech/Moderna | 23 | 23/0 (100/0) | 25 (20-51) | 3 (13.04) | 20 (86.96) | 0/7/16 |
| Perez *et al*[14], United States | Pfizer-BioNTech/Moderna | 7 | 6/1 (86/14) | 44 (22-71) | 1 (14.29) | 6 (85.71) | 0/6/1 |
| Das *et al*[15], United States | Pfizer-BioNTech | 25 | 22/3 (88/12) | 15 (12-17) | 3 (12.00) | 22 (88.00) | 0/22/3 |
| Simone *et al*[18], United States | Pfizer-BioNTech/Moderna | 15 | 15/0 (100/0) | 25 (20-32) | 2 (13.33) | 13 (86.67) | 0/15/0 |
| Nygaard *et al*[19], Denmark | Pfizer-BioNTech | 15 | 13/2 (87/12) | 17 (13-17) | 8 (53.33) | 7 (46.67) | 0/1/14 |
| Diaz *et al*[21], United States | Pfizer-BioNTech/Moderna | 20 | 15/5 (75/25) | 36 (26-48) | 4 (20.00) | 16 (80.00) | 2/17/1 |

F/I/M: Fulminant/intermediate/mild; IQR: Interquartile range.

vaccination.

Perez *et al*[14] used the Mayo Clinic COVID-19 Vaccine Registry to conduct a retrospective case series study to assess post-immunization myocarditis. They discovered that a total of 7 people were diagnosed with myocarditis after receiving at least one dose of a COVID-19 mRNA vaccine (BNT162b2-mRNA and mRNA-1273 vaccines). The COVID-19 registry contained 175472 individuals (aged 12 years to 106 years), of whom 718 (0.4%) were adolescents aged 12 years to 15 years. Myocarditis was found to be 55.35 *per* 100000 person-years in the two weeks following a dose of COVID-19 mRNA vaccination. The incidence rate ratio (IRR) of myocarditis after mRNA vaccinations in males was 6.69 (2.35–15.52) which was higher than the Rochester Epidemiology Project during the years 2016–2020. However, the myocarditis IRR in females was 1.41 (0.03–8.45) which was not statistically significant. The most common presenting symptoms were chest pain, dyspnea, and fatigue, with a baseline troponin T of 486.5 ng/L (222.5–965.0). Seventy one percent of the patients had ECG abnormalities, including ST-segment changes. On ECHO examination, 3 patients (60%) were noted to have a reduced LVEF. Cardiac MRI was performed in 6 patients (86%) and showed myocardial delayed enhancement. Pericardial involvement was seen in 3 (50%) patients. Myocarditis is a rare side effect of COVID-19 mRNA vaccines, according to the authors. It affects adult males at a significantly higher rate than the general population.

Das *et al*[15] performed a study of 25 cases aged between 12 and 18 years who developed myopericarditis following the mRNA vaccine in 7735017 children and adolescents. The incidence of myopericarditis after COVID-19 mRNA vaccination was 0.32 *per* 100000 people. Myopericarditis has occurred in 0.04 *per* 100000 people after the 1st dose, 0.28 *per* 100000 persons following the 2nd dose, and 0.26 *per* 100000 males following the 2nd dose. The most common presenting symptom was chest pain. Sixty percent and seventy-two percent of patients reported the development of symptoms within 2 and 3 d of getting the second dosage of the vaccine, respectively. All 25 patients had elevated plasma troponin concentrations. Abnormal ECG was found in 84% of the patients, including 60% of the elevation of ST-segment, 24% of the isolation of nonspecific ST-segment changes, 4% of the depression of ST-segment, and 4% of the depression of PR interval. An ECHO was performed in all patients and showed normal LV function in 92% of the individuals. Cardiac MRI was done on 16 of 25 patients (64%) and revealed late gadolinium enhancement in 94% of cases. Myocardial edema on T2 mapping was found in 37.5% of the patients, and a small pericardial effusion was found in 19% of the patients. They concluded that the complication of mRNA vaccine-related myopericarditis has been observed primarily in men. It has not been thoroughly investigated if hormonal or other variables have a role in the manifestation of this disease.

Li *et al*[16] employed the Vaccination Adverse Event Reporting System, a nationwide early warning system that monitors potential vaccine safety issues, as the major data source. The COVID-19 mRNA vaccines and viral vector vaccinations were the vaccines studied in this study. They found that the incidence rate of myocarditis or pericarditis following COVID-19 vaccination was 0.598 (0.573–0.624) *per* 100000 doses of vaccinations. The incidence rate was highest in adolescents aged 12-17 years, with an incidence rate of 2.09 (1.90–2.30) *per* 100000 vaccinations. It decreased with increasing age to 0.59

(0.56–0.62) *per* 100000 in adults aged 18-64, and 0.19 (0.16–0.22) *per* 100000 aged 65 years and over. The incidence rate was higher for different vaccine types in the mRNA vaccines, at 0.59 (0.57–0.62) *per* 100000, than for a viral vector vaccine, at 0.56 (0.44–0.70) *per* 100000 vaccinations. Among mRNA vaccines, BNT162b2-mRNA vaccines had a higher incidence rate of 0.67 (0.63–0.70) cases *per* 100000 than the rate of 0.49 (0.46–0.53) cases *per* 100000 of the mRNA-1273 vaccine. Moreover, the incidence rate after the 2nd dose was twice that of the 1st dose of mRNA vaccinations. Fifty percent of myocarditis or pericarditis cases were reported 2 to 7 d after vaccinations, with 58.67% of cases having chest pain symptoms. They also found that reporting odds ratios (RORs) of the mRNA-1273 vaccine were 2.91 (2.21–3.83) compared with the RORs of the BNT162b2-mRNA vaccine at 5.37 (4.10–7.04). They concluded that the BNT162b2-mRNA vaccine was associated with significant risks of myocarditis or pericarditis in adolescents aged 12 to 17, with RORs ranging from 8.19 (4.37–15.36). A viral vector vaccine may be an alternative for consideration for individuals with myocardial injuries after mRNA vaccination.

Patone *et al*[17] conducted the study to find out the incidence of myocarditis or pericarditis after COVID-19 vaccinations in the United Kingdom using the English National Immunisation Database of COVID-19 vaccinations. During that period, 38615491 individuals received one dose of a viral vector vaccine ChAdOx1 ($n$ = 20615911), an mRNA vaccine BNT162b2 ($n$ = 16993389), or an mRNA vaccine 1273 ($n$ = 1006191). Results showed an increased myocarditis risk at 1–7 d after the 1st dose of ChAdOx1-viral vector vaccine as an IRR of 1.76 (1.29-2.42), of BNT162b2-mRNA vaccine as an IRR of 1.45 (0.97-2.12), and of mRNA-1273 vaccine as an IRR of 8.38 (3.53-19.91). For the 2nd dose of the BNT162b2-mRNA vaccine, the IRR was 1.75 (1.13-2.70), the IRR of the mRNA-1273 vaccine was 23.10 (6.46-82.56). Over the 1–28 d post-vaccination, they observed an association with the 1st dose of ChAdOx1-viral vector vaccine, whose IRR was 1.29 (1.05-1.58), with BNT162b2-mRNA vaccine, whose IRR was 1.31 (1.03-1.66) and with mRNA-1273 vaccine, whose IRR was 2.97 (1.34-6.58). After a 2nd dose, the mRNA vaccine 1273 had higher risk [IRR = 9.84 (2.69–36.03)] compared with the BNT162b2-mRNA vaccine [IRR = 1.30 (0.98–1.72)]. They observed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunization in adults was linked with a low myocarditis risk after 1 wk of getting the 1st immunization of a viral vector vaccine and a mRNA vaccine, as well as after receiving the 2nd dose of both mRNA vaccines. COVID-19, on the other hand, was linked to an increased risk of hospitalization or mortality from myocarditis, pericarditis, and cardiac arrhythmia.

Simone *et al*[18] performed a study using Kaiser Permanente Southern California (KPSC) as a case study. The KPSC members' database (2392924) was used to evaluate acute myocarditis incidence and clinical outcomes among adults following mRNA vaccinations. In the vaccinated group, the authors discovered 15 cases of confirmed myocarditis (2 after the 1st dose and 13 after the 2nd dose). Over a 10-d observation period, the observed incidence after the 1st dosage was 0.08 cases *per* 100000 and 0.58 cases *per* 100000 after the 2nd dose. The IRR for myocarditis was 0.38 (0.05–1.40) after the 1st dose and 2.7 (1.4–4.8) after the 2nd dose. The most common clinical manifestation was chest pain (93%), which occurred between 1 and 5 d after vaccination. They determined that acute myocarditis following COVID-19 immunization was uncommon, with a prevalence of 5.8 occurrences in 1000000 people following the 2nd immunization (1 occurrence in 172414 fully immunized people). They proposed that the higher risk of myocarditis in adolescence males needs more research.

Nygaard *et al*[19] performed a prospective population-based cohort study to evaluate the incidence of myopericarditis after COVID-19 vaccination in Danish adolescents. They discovered that among 133477 males and 127857 females aged 12–17 years who got the first dose of the BNT162b2-mRNA vaccination, the incidence of myopericarditis was 97 and 16, respectively, *per* 1000000, corresponding to 1 in 10000 males and 1 in 63000 females. In contrast, 16900 males and 16044 females aged 12–17 years old infected with SARS-CoV-2 showed multisystem inflammatory syndrome in children, including myocarditis at an incidence of 1 in 2800 men and 1 in 5300 women, which was substantially more than the prevalence of myopericarditis following the immunization of the COVID-19 vaccine in both men and women. They determined that the frequency of myopericarditis in male adolescents following BNT162b2-mRNA immunization is greater than previously reported, and that more severe cases are more common.

Husby *et al*[20] conducted a study using the Danish Vaccination Register to evaluate the incidence of myocarditis or myopericarditis after BNT162b2-mRNA and mRNA-1273 vaccinations in Denmark. Among the cohort participants, 3482295 were vaccinated with BNT162b2-mRNA vaccines, whereas 498814 were immunized with mRNA-1273. Individuals who received the BNT162b2-mRNA vaccine exhibited a non-substantially higher risk of myocarditis in the 28-d following immunization compared to unvaccinated follow-up [hazard ratio (HR) = 1.34 (0.90–2.00)]. Individuals aged 12–39 years had a non-significantly higher rate in the 28-d following vaccination compared non-immunization people [HR = 1.48 (0.74–2.98)]. Individuals vaccinated with mRNA-1273, on the other hand, exhibited a substantially higher risk of myocarditis or myopericarditis compared to unvaccinated follow-up [HR = 3.92 (2.30–6.68)]. Furthermore, people aged 12–39 years had substantially higher rates of myocarditis or myopericarditis when compared to unvaccinated controls [HR = 5.24 (2.47–11.12)]. Myocarditis occurred at a rate of 1.7 (1.3-2.2) *per* 100000 vaccinated people. Within 28 d, the incidence rate of myocarditis following BNT162b2-mRNA vaccination or mRNA-1273 immunization was 1.4 (1.0–1.8) and 4.2 (2.6–6.4), respectively. Within 28 d of immunization, the equivalent rates of myocarditis from BNT162b2 vaccination was 1.6 (1.0-2.6) *per* 100000 people compared with mRNA-1273 vaccination was

5.7 (3.3-9.3) *per* 100000 people. The authors found that mRNA-1273 immunization was linked with a higher risk of myocarditis or myopericarditis compared to uninfected people, whereas BNT162b2-mRNA vaccination was related to a higher rate of myocarditis or myopericarditis among females. Furthermore, clinical outcomes following myocarditis or myopericarditis episodes were mostly modest, lending credence to the general safety of COVID-19 mRNA vaccinations.

Diaz *et al*[21] conducted a retrospective study to evaluate the incidence of myocarditis and pericarditis after COVID-19 vaccinations among 2000287 individuals who received at least one COVID-19 vaccination (52.6% received the BNT162b2-mRNA vaccine, 44.1% were given the mRNA-1273 vaccine, while 3.1% were given the Ad26.COV2.S vaccine). They found that 20 individuals had vaccine-related myocarditis [1.0 (0.61-1.54)] *per* 100000 vaccinations, and 37 individuals had pericarditis [1.8 (1.30-2.55)] *per* 100000 vaccinations, which occurred 3.5 d after being vaccinated. They concluded that mRNA vaccination was linked to myocarditis, particularly in adolescence males, within 3 d following the 2nd dose of immunization. Additionally, pericarditis may be more common than myocarditis among older patients.

Chouchana *et al*[22] conducted an observational retrospective analysis on inflammatory cardiac events that were reported regarding mRNA immunizations in the global safety database of the World Health Organization using a case–non-case methodology (VigiBase). Among the 26258646 reports in the VigiBase, 716576 were associated with the mRNA COVID-19 vaccination as a suspected medication, with 2277 cases of inflammatory heart responses identified as 1241 (54.5%) myocarditis, 851 (37.3%) pericarditis, and 167 (7.3%) myopericarditis. The majority of myocarditis cases have been observed in male patients aged between 12 and 29. Overall, the median duration from the beginning of myocarditis following immunization was 3 (2–14) d. When compared to myocarditis, a median onset of pericarditis was delayed to be 8 (3–21) d. Most of the myocarditis (81.8%) and pericarditis (57.8%) reported cases that required hospitalization, and 21.5% of myocarditis and 20.5% of pericarditis were life threatening. The overall incidence rate of myocarditis or pericarditis was 0.61 (0.57–0.65) *per* 100000 fully vaccinated individuals. In 2 doses of immunization, they found a significant increase in incidence rates in 12–17–year–old patients [3.69 (3.25–4.18) *per* 100000 people] and 18–29–year–old patients [1.97 (1.80–2.16) *per* 100000 people], while patients older than 30 years were 0.21 (0.19–0.24) *per* 100000 patients. Male patients had an elevated chance of reporting myocarditis with RORs = 9.4 (8.3–10.6) and diagnosed pericarditis with RORs = 3.7 (3.2–4.2). Age category analysis revealed a significant decrease in myocarditis reporting after mRNA immunizations in 12- to 17-year-olds [RORs = 22.3 (19.2–25.9)] and 18–to–29-year-olds [RORs = 6.6 (5.9–7.5)] individuals when compared to individuals older than 30 years. Across all age groups, this increased reporting was more significant in male patients than in female patients. While there was a considerable disproportionate reporting of myocarditis in teens and young adults, particularly in male patients, and it was an uncommon event, they discovered that it did not appear to compromise the vaccines' favorable benefit-risk balance.

Barda *et al*[23] evaluated the safety of the BNT162b2-mRNA COVID-19 vaccine using the largest health care organization in Israel. They discovered that the vaccinated and control groups each had an average of 884828 people. Vaccination was the strongest predictor of an increased risk of myocarditis [risk ratio, 3.24 (1.55–12.44)]. By contrast, infection with SARS-CoV-2 was linked to a significantly higher myocarditis rate [risk ratio, 18.28 (3.95–25.12)]. They concluded that the BNT162b2-mRNA vaccine increased the occurrence of a few side effects over a 42-d period of follow-up. Whereas the majority of these incidents were minor, myocarditis has the potential to be life-threatening. According to the findings, SARS-CoV-2 infection is a significant risk factor for myocarditis, as well as a number of other adverse outcomes.

Table 2 summarizes the characteristics of acute myocarditis patients, such as sex, age, occurrence after the 1st or 2nd dose of mRNA COVID-19 vaccination, and clinical severity. Many investigators' data indicated the same result: Acute myocarditis was more prevalent in younger males, and over 90% occurred after the 2nd dose of immunization. Furthermore, practically all patients had mild to moderate clinical presentation and prognosis. Figure 1 shows the number of acute myocarditis cases after the 1st and 2nd doses of the Pfizer-BioNTech mRNA COVID-19 vaccine. According to these data, the majority of the cases occurred shortly after the 2nd dose of immunization, generally within 5 d. Close observation and monitoring of vaccination recipients are critical during this period.

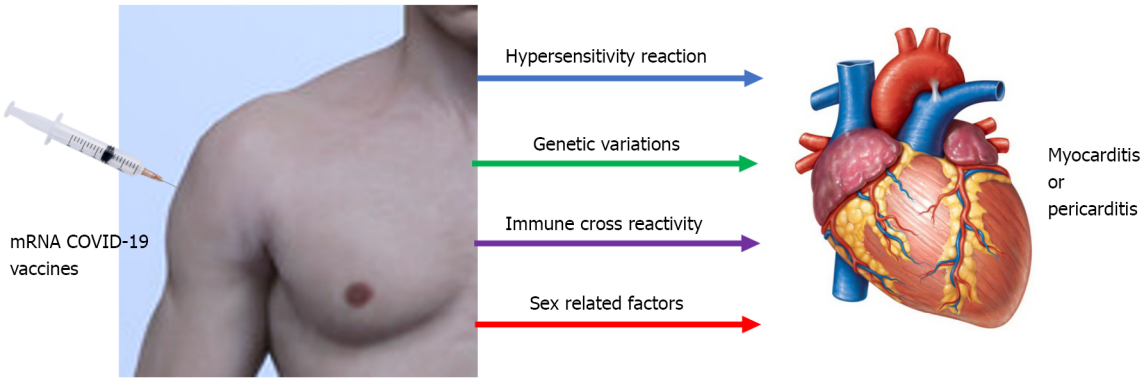
Table 3 shows the clinical presentation of the patients with acute myocarditis after mRNA COVID-19 vaccinations, which usually included chest pain, myalgia, fatigue, and fever. The common ECG abnormalities were ST-elevation, non-specific ST/T changes, PR depression, T-wave inversion, and ventricular fibrillation. ECHO showed the reduction of LVEF. Laboratory findings demonstrated the elevation of cardiac troponin and C-reactive protein. The imaging studies of acute myocarditis patients after mRNA COVID-19 vaccination showed myocardial inflammation, myocardial edema, and delayed iodine enhancement.

Despite the fact that the majority of the findings of various studies demonstrated the occurrence of acute myocarditis following mRNA COVID-19 immunization, the incidence was quite low. Furthermore, there were significant disparities across these trials in terms of ethnicity, age, underlying disorders, inherent immunity to the SARS-CoV-2 virus, and other genetic variables. More research should be conducted to understand this problem.

**Table 3 Clinical presentation of the patients with acute myocarditis after coronavirus disease 2019 mRNA vaccination**

| | Clinical presentation of acute myocarditis |
|---|---|
| 1 | Chest pain, Myalgia, Fatigue, Fever |
| 2 | Abnormal ECG: ST-elevation, Non-specific ST/T changes, PR depression, T-wave inversion, Ventricular fibrillation |
| 3 | Elevation of cardiac troponin |
| 4 | Elevation of CRP |
| 5 | Abnormal ECHO: LVEF reduction |
| 6 | Abnormal cardiac MRI: Myocardial inflammation, Myocardial edema |
| 7 | Abnormal cardiac spectral CT: Delayed iodine enhancement |

CRP: C-reactive protein; CT: Computerized tomography; ECG: Electrocardiogram; ECHO: Echocardiogram; LVEF: Left ventricular ejection fraction; MRI: Magnetic resonance imaging.




**DOI:** 10.4330/wjc.v14.i6.343 **Copyright** ©The Author(s) 2022.

**Figure 1 Timelines of acute myocarditis occurrence after Pfizer-BioNTech and Moderna mRNA coronavirus disease 2019 vaccination.** COVID-19: Coronavirus disease 2019.

## HISTOPATHOLOGICAL FINDINGS OF MYOCARDITIS AFTER MRNA COVID-19 VACCINATION

Ameratunga *et al*[24] reported a 57-year-old woman who died of fulminant necrotizing myocarditis after receiving the first dose of the BNT162b2 mRNA vaccine. The clinical manifestations were lethargy, fatigue, breathlessness, stiff neck, and upper limb pain. After that, she complained of back pain, a sore throat, and hematuria without palpitation or chest pain. The autopsy findings showed that the heart was normal without pericardial effusion and intra-cardiac thrombosis. There was a large thymoma mass (710 g) in the left pleural cavity. The histopathology demonstrated fulminant necrotizing eosinophilic myocarditis. Multifocal aggregates of lymphoid cells, histiocytes, and many eosinophils with isolated myocyte necrosis were seen in the free walls of both ventricles, the interventricular septum, and throughout the conduction system (sinoatrial and atrioventricular nodes) (Table 4). They concluded that the danger of myocarditis and other deadly consequences of COVID-19 infection outweighed the risk of these uncommon vaccine-related side effects. The advantages of immunization substantially outweigh the hazards of COVID-19 infection. Choi *et al*[25] published the autopsy results of a 22-year-old man who had chest discomfort 5 d after receiving the 1$^{st}$ dose of the BNT162b2-mRNA vaccination and died 7 h later. He developed ventricular fibrillation on ECG before cardiopulmonary resuscitation in the emergency department. The autopsy findings showed the heart weighed 470 g with multiple petechial hemorrhages on its surface.

There was no fibrin buildup or exudate in the pericardium. The coronary arteries were patent, and the cardiac valves were in good condition. Within the heart, histology revealed a diffuse inflammatory infiltrate with neutrophils and histiocyte predominance. Inflammatory infiltrates were more common in the atria and around the sinoatrial and atrioventricular nodes, but there were few or no inflammatory cells in the ventricular area. They concluded that the major cause of mortality was myocarditis, which was linked to the BNT162b2-mRNA vaccination. Schneider *et al*[26] conducted an autopsy of 18 deceased people after COVID-19 vaccinations and found that only 1 case was related to the BNT162b2-mRNA vaccine. The autopsy findings showed severe coronary sclerosis, massive cardiac hypertrophy,

**Table 4 Gross and histopathological findings of the heart after coronavirus disease 2019 mRNA vaccination**

| Ref. | No. of cases (age, sex)/vaccine | Gross findings | Histopathological findings |
|---|---|---|---|
| Ameratunga *et al*[24] | 1 (57, F)/Pfizer-BioNTech | The heart was normal without pericardial effusion and intra-cardiac thrombosis. There was a large thymoma mass (710 g) in the left pleural cavity | The heart sections showed fulminant necrotizing eosinophilic myocarditis. There were multifocal aggregates of lymphoid cells, histiocytes, and abundant eosinophils with focal myocyte necrosis in the free walls of both ventricles, interventricular septum, and around the conduction system (sino-atrial and atrioventricular nodes) |
| Choi *et al*[25] | 1 (22, M)/Pfizer-BioNTech | The heart weighed 470 g with multiple petechial hemorrhages on its surface. The pericardium was smooth with no fibrin deposition or exudate. The coronary arteries were patent, and the heart valves were unremarkable | The myocardial sections showed a diffuse inflammatory infiltration with neutrophils and histiocytes predominance. The inflammatory infiltrates dominant in the atria and around the sinoatrial and atrioventricular nodes with no inflammatory cells in the ventricular muscles |
| Schneider *et al*[26] | 1 (65, M)/Pfizer-BioNTech | The heart showed severe coronary sclerosis, massive cardiac hypertrophy, myocardial infarction scars | The myocardial sections showed myocarditis with lymphocytic and plasmacytoid infiltration of the perivascular space and the myocardium |

F: Female; M: Male.

and myocardial infarction scars. The histopathology showed myocarditis with lymphocytic and plasmacytoid infiltration of the perivascular space and the myocardium.

## PATHOPHYSIOLOGY OF CARDIAC DYSFUNCTION AFTER MRNA COVID-19 VACCINATIONS

The mRNA COVID-19 vaccines are made up of the mRNA which was modified with nucleosides that codes for the spike protein of SARS-CoV-2 and is enclosed in nanoparticles of lipid that do not have live virus particles or DNA of virus. When the spike protein of a virus is created on the cell surface during the entry of mRNA-vaccine, it activates an adaptive immune response that detects and kills viruses expressing the spike protein. SARS-CoV-2 attachment to the host cell is blocked by vaccine-induced spike-protein IgG antibodies, which bind to the angiotensin-converting enzyme 2 receptor and destroy the virus[27].

Myocarditis caused by enterovirus or human herpesvirus infection is often severe in young adolescents and adult males. Genetic polymorphisms in genes producing HLA factors and, in a minority of individuals, genetic variants in genes encoding cytoskeletal, desmosomal, or sarcomeric proteins are related to this kind of myocarditis, which raises the chance of developing acute myocarditis following viral infection[28]. Myocarditis and pericarditis have previously been documented following immunization, particularly with smallpox and influenza vaccinations with shallow incidence rates[5]. There are sex-specific hormone alterations in COVID-19 mRNA-vaccination-related myocarditis and non-COVID-19 viral myocarditis[29].

Although potential processes are unclear, various ideas may be possible. mRNA immune reactivity, cross reactivity with cardiac proteins, SARS-CoV-2 spike protein antibodies, and hormonal alterations are the four main mechanisms by which COVID-19 mRNA vaccines might induce hyper-immunity. Immune–genetic background, age, and sex can all impact these processes. The immune system may detect the vaccine's mRNA as an antigen, triggering immunological pathways and pro-inflammatory cascades in the heart. Despite the fact that nucleotide changes to mRNA diminish its innate immunogenicity, the mRNA immune response could induce an abnormal innate and acquired immunity, explaining why mRNA vaccinations induce a stronger immune response than other COVID-19 immunization approaches[30]. Another proposed mechanism is molecular mimicry between the SARS-CoV-2 spike protein and cardiac self-antigen presentation. Antibodies against SARS-CoV-2 spike proteins may cross-react with myocardial-myosin heavy chain. These autoantibodies might be inadvertent bystanders that cause myocardial inflammation and damage (Figure 2).

Moreover, they could represent a specific immune–genetic background that predisposes to hyper-immunity and myocarditis in response to any stimulus[31,32]. Furthermore, while COVID-19 mRNA-vaccination-related myocarditis is more common in men, changes in hormone signaling may play a role in its etiology. Testosterone has the capacity to reduce anti-inflammatory immune cells while increasing the aggressiveness of T helper cell-type immune responses. On the other hand, estrogen suppresses pro-inflammatory T cells, leading to a reduction in cell-mediated immune response. As a result, testosterone may still promote an abnormal acquired and innate immune response, which may explain why mRNA immunizations produce a larger immunological response than other methods of COVID-19

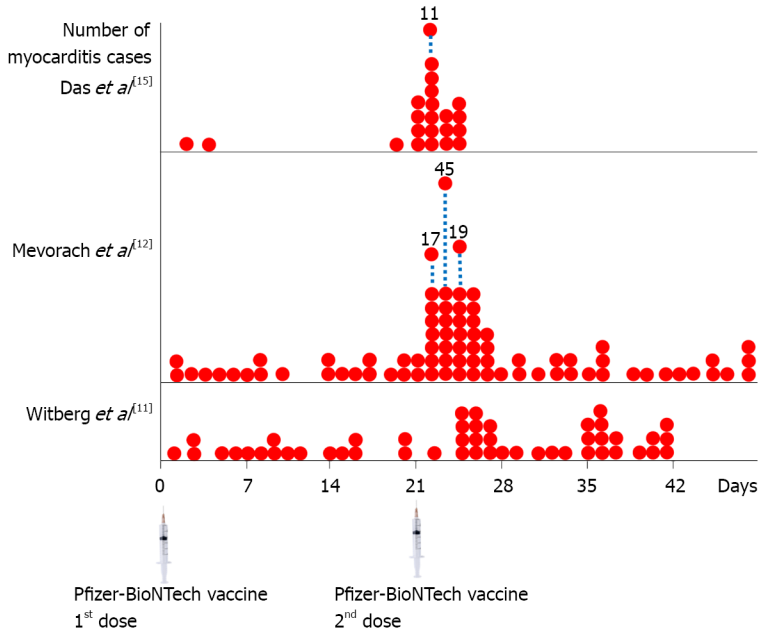



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**Figure 2 Coronavirus disease 2019 mRNA vaccine associated with myocarditis.**

immunization in males than females[33-36].

## CONCLUSION

Post-mRNA vaccination myocarditis is most common in young boys under 21 years old. The majority of instances appear within a few days of receiving the 2nd immunization dose. The most common symptom is chest pain, followed by fever or myalgia. The majority of patients have an abnormal ECG. Elevated cardiac troponin and inflammatory markers are mainly laboratory abnormalities. On cardiac MRI, most individuals have evidence of myocardial edema, or inflammation of the cardiac muscles. Possible causes of myocarditis or pericarditis following mRNA COVID-19 vaccines include antibodies to SARS-CoV-2 spike proteins, immune response to mRNA, cross reaction with cardiac proteins, and alteration in hormones. A more rigorous investigation was required to resolve this issue. Despite a few incidences of self-limited myocarditis, the risk-benefit evaluation for COVID-19 vaccination shows a positive balance for all age and gender categories; hence, COVID-19 vaccination is now recommended for all people aged 12 and above.

## FOOTNOTES

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*MINIREVIEWS*

# Takotsubo cardiomyopathy: A comprehensive review

Walker Barmore, Himax Patel, Sean Harrell, Daniel Garcia, Joe B Calkins Jr

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## Abstract

Takotsubo cardiomyopathy (TCM), also known as stress cardiomyopathy, occurs in the setting of catecholamine surge from an acute stressor. This cardiomyopathy mimics acute myocardial infarction in the absence of coronary disease. The classic feature of TCM is regional wall motion abnormalities with characteristic ballooning of the left ventricle. The etiology of the stressor is often physical or emotional stress, however iatrogenic causes of TCM have been reported in the literature. In our review, we discuss medications, primarily the exogenous administration of catecholamines, and a wide array of procedures with subsequent development of iatrogenic cardiomyopathy. TCM is unique in that it is transient and has favorable outcomes in most individuals. Classically, beta-blockers and ACE-inhibitors have been prescribed in individuals with cardiomyopathy; however, unique to TCM, no specific treatment is required other than temporary supportive measures as this process is transient. Additionally, no improvement in mortality or recurrence have been reported in patients on these drugs. The aim of this review is to elucidate on the iatrogenic causes of TCM, allowing for prompt recognition and management by clinicians.

**Key Words:** Takotsubo; Cardiomyopathy; Iatrogenic; Heart Failure; Myocardial Infarction

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**Core Tip:** The aim of this review is to elucidate on the iatrogenic causes of Takotsubo cardiomyopathy (TCM). To date, there are individual case reports of iatrogenic TCM but there is not a comprehensive review article. In this review article, we discuss medication and procedure-induced TCM as well as an in-depth review of the current pathophysiology behind TCM.

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## INTRODUCTION

Takotsubo cardiomyopathy (TCM) was first identified in Japan in 1991. The term "Takotsubo" originates from the Japanese word for octopus trap as cardiac morphology in this disease process often resembles the shape of these traps. Since its identification, TCM has also been referred to as stress cardiomyopathy, apical ballooning syndrome, or broken heart syndrome. This complex disease mimics acute myocardial infarction in the absence of obstructive coronary disease and is characterized by transient left ventricular dysfunction. The main feature of TCM is regional wall motion abnormalities with a characteristic ballooning of the left ventricle during systole. The wall motion abnormalities are unique as they extend beyond a single vascular territory and are usually localized to the apex of the left ventricle; however, non-apical variants exist[1]. Although TCM itself is often underdiagnosed, its clinical relevance, recognition, and understanding have progressively accelerated in the recent years. The cardiomyopathy occurs in the setting of a catecholamine surge from an acute stress leading to cardiac dysfunction. The etiology of the stressor is often physical or emotional stress; however, less commonly iatrogenic causes of TCM have been reported as well. Iatrogenic TCM can classified as either medication or procedure related. The aim of this review article is to focus on the reported iatrogenic causes of TCM and to make clinicians aware of this disease process and its complications, allowing for prompt recognition and possibly reducing morbidity and mortality from this rare process.

## CLINICAL PRESENTATION

Before discussing iatrogenic causes of TCM, it is important to review the clinical presentation of TCM. Patients frequently present with chest pain, dyspnea, and syncope, and less commonly with arrhythmias, cardiogenic shock, and cardiac arrest. These symptoms are triggered most often by acute physical or emotional stress and infrequently by medical procedures and medication administration. Patients may have elevated cardiac biomarkers (NT-proBNP, troponin T), which complicates differentiating TCM from acute myocardial infarction. High NT-proBNP/troponin T ratio has a sensitivity of 91% and specificity of 95%, is suggestive of TCM, and is helpful in differentiating TCM from ST-elevation myocardial infarction[2]. Typical electrocardiographic findings in TCM include ST-elevation, ST depression, QTc prolongation, and T-wave inversions[3]. On the echocardiogram, left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) can be observed as apical ballooning or midventricular, basal, or focal wall motion abnormalities[4]. TCM predominantly affects the apex; however, non-apical variants may occur. The incidence of such non-apical variants ranges from 8%-40%, with the mid-ventricular variant accounting for approximately 20%, and the basal form for approximately 3%[1]. This cardiomyopathy is unique because it is associated with a nonischemic etiology of acute, but transiently decreased, systolic function with wall motion abnormalities extending beyond a single vascular territory. Angiography often reveals the absence of coronary atherosclerotic disease without dissection, plaque rupture or thrombus formulation. If ventriculography is performed, an apical nipple sign (Figure 1) may be visualized with regional wall motion abnormalities. Lastly, on cardiac magnetic resonance imaging these patients often have reveal wall motion abnormalities, apical ballooning (Figure 2A), late gadolinium enhancement and edema (Figure 2B) on T2 weighted imaging in the dysfunctional left ventricle (LV) regions[1]. Therefore, given that its presentation can mimic that of an acute myocardial infarction, it is critical to diagnose and treat this disease appropriately to allow for rapid recovery and improve long term outcomes in patients.

## PATHOPHYSIOLOGY

The pathophysiology of TCM is not completely understood. One of the most well-known and accepted hypotheses concerning the etiology of ventricular dysfunction in this condition is the catecholamine theory[5]. Amariles and Cifuentes suggested that acute stressors lead to an increase in the concentration of neuropeptides and catecholamines (dopamine, epinephrine, norepinephrine) during the acute phase of TCM, contributing to LV dysfunction[6]. These elevated levels of catecholamines contribute not only to myocardial dysfunction, but also cause coronary microvascular vasospasm, increasing cardiac workload and leading to a supply-demand mismatch. This acute mismatch is followed by post-ischemic stunning of the myocardium, resulting in the typical apical ballooning the left ventricle. However, the

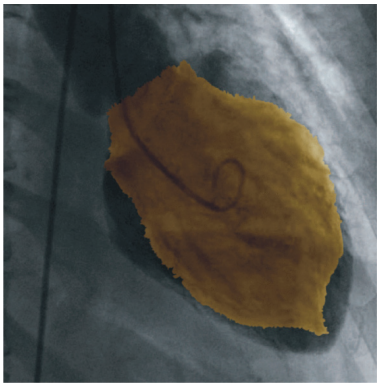

**Figure 1 Ventriculogram with apical ballooning with presence of apical nipple sign[31].** Citation: Walter Desmet, Johan Bennett, Bert Ferdinande, Dries De Cock, Tom Adriaenssens, Mark Coosemans, Peter Sinnaeve, Peter Kayaert, Christophe Dubois. The apical nipple sign: a useful tool for discriminating between anterior infarction and transient left ventricular ballooning syndrome. *Eur Heart J Acute Cardiovasc Care* 2013; 3: 264-267. Copyright The European Society of Cardiology 2013. Published by Oxford University Press.

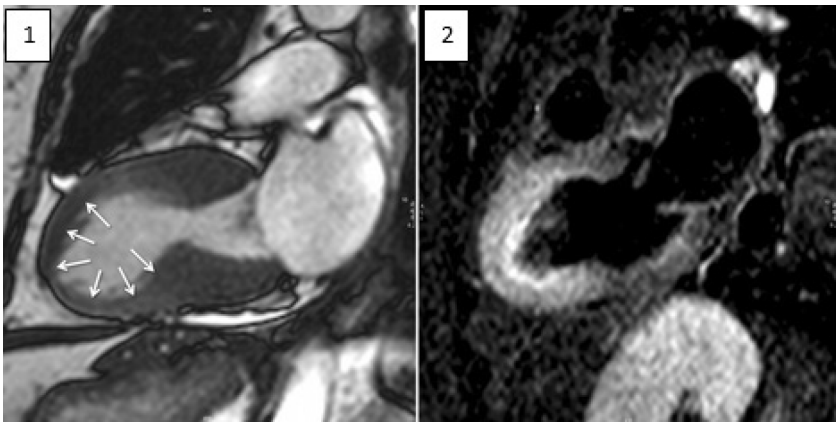


**Figure 2 Cardiac magnetic imaging noting (1) apical ballooning (2) myocardial edema in the mid-apical region of the left ventricle[36].** Citation: Plácido R, Cunha Lopes B, Almeida AG. The role of cardiovascular magnetic resonance in takotsubo syndrome. *J Cardiovasc Magn Reson* 2017; 18: 68. Copyright The Authors 2017. Published by Springer Nature.

stunning is temporary and the transient ballooning and is typically followed by complete recovery of the left ventricular contractility after a short period of time in most cases.

In TCM, stress leads to an acute increase in primarily two catecholamines, norepinephrine and epinephrine. Most of the norepinephrine and all of the epinephrine is released from the adrenal medulla [7]. Interestingly, only some of these secreted catecholamines are released into the circulation; most is released directly by the sympathetic nerve endings into the nerve terminals and is presented directly to the adrenoreceptors in the myocardium. This direct release of catecholamines into the myocytes leads to decreased myocardial viability through cAMP mediated calcium overload resulting in myocardial toxicity and myocardial contraction band necrosis[8]. Similar toxicity and necrosis is seen in acute neurovascular events such as subarachnoid hemorrhage as well as in patients with pheochromocytoma, and those dying from violent assaults, or drowning, thus confirming the link between acute stress and cardiac injury[8]. The pattern of contraction band necrosis is considered one of the hallmark signs of TCM[9].

A protective method that the myocardium implements against excessive catecholamines to prevent myocardial necrosis and LV dysfunction is "stimulus-trafficking". During a catecholamine surge, myocardial adrenoreceptors undergo a switch from Gs to Gi coupling leading to a negative inotropic response[10]. If not for this switch, the catecholamine surge would activate the Gs protein pathway, causing increased myocardial contractility and workload, ultimately leading to myocardial injury and toxicity as described earlier. Additionally, the characteristic apical ballooning pattern can be explained by the regional differences in the presence of adrenoreceptors in the myocardium. B2-adrenoreceptors are more densely distributed in the apical region than the basal segment of the LV, whereas B1-adrenoreceptors are expressed more at the base than the apex[11]. Therefore, with high levels of catecholamines, the classic pattern of enhanced basal contraction and reduced apical contractility is seen. This theory was confirmed in rat models in which a bolus of epinephrine to mimic a catecholamine surge resulted in reversible depression of apical contraction and basal hypercontractility[12].

In addition to activation of negative inotropic signaling, catecholamines have been shown to cause epicardial coronary vasospasm and microvascular coronary dysfunction. Decreased radioactive tracer uptake during positron emission tomography perfusion scans in the acute phase of TCM confirms the involvement of microvascular coronary dysfunction as a trigger for myocardial dysfunction[5]. Additionally, Angelini performed acetylcholine testing of the coronaries which led to transient LV dysfunction, confirming a potential role of vasospasm in TCM[13].

Lastly, estrogen deficiency has also been identified as a contributing factor to TCM. In menopause, there is an increased sympathetic drive noted from the lack of estrogen in the circulation. This increases the risk of post-menopausal females to TCM and explains the high incidence of (approximately 89.8%) of TCM in elderly women[14]. Similar to post-menopausal females, the lack of estrogen in males places them at a higher risk of developing TCM and they are noted to have worse outcomes than their female counterparts. To further support estrogen's role in TCM, animal models have demonstrated that estrogen pre-treatment prevents stress-induced LV apical ballooning[5].

## CASE REPORTS: MEDICATION-INDUCED TCM

TCM has been widely reported following medication administration with a much higher incidence occurring after catecholamine administration[15-18]. Most of the case reports listed in Table 1, with the exception of Teixeria *et al*[19], discuss an acquired TCM after receiving a prolonged administration of catecholamines. Laínez *et al*[16] present the case of a 61-year-old female who was to undergo resection of a urinary neoplasm. Following anesthesia induction, she experienced fictitious hypotension that was initially believed to be anaphylactic shock. High-dose epinephrine and norepinephrine were administered, and she was found to have a new left bundle branch block on ECG. Further evaluation revealed septal, lateral, and apical dyskinesia with subsequent angiogram revealing non obstructive coronary artery disease. These findings were consistent with TCM, and she had full ventricular recovery over the following four d. As mentioned, Teixeria *et al*[19] stands alone from other case reports listed in Table 1 in that the offending agent was a beta-blocker and not a catecholamine. This case involved a 47-year-old female presenting with severe gastrointestinal symptoms who was given a beta blocker (esmolol) for sinus tachycardia and shortly thereafter developed cardiogenic shock in the setting of elevated cardiac biomarkers. Subsequent evaluation revealed nonobstructive coronaries, preserved apical contractility, and basal akinesis consistent with a non-apical TCM variant. She had full ventricular recovery over the next two d, and her clinical course is unique as it was likely the result of sympathetic stimulation from severe gastrointestinal illness and exacerbated by esmolol administration, likely mimicking the switch from Gs to Gi as seen in "stimulus-trafficking". Additional cases have been reported in the literature involving medication induced TCM following catecholamine administration and can be found in Table 1.

## CASE REPORTS: PROCEDURE-INDUCED TCM

In addition to medication induced TCM, there are several cases documenting post-procedural TCM. With the exception of a patient incidentally receiving undiluted norepinephrine, Table 2 lists post-procedural development of TCM in patients who did not receive catecholamines prior to or during a procedure[20]. Table 2 highlights a wide range of procedures associated with TCM including electroconvulsive therapy, endoscopy, valve replacement and bronchoscopy. In one case report, Narayanan *et al* presented the case of a middle-aged female with refractory depression who developed TCM after receiving electroconvulsive therapy[21]. She had been receiving long term therapy with a beta-blocker (bisoprolol) and an ace-inhibitor (lisinopril), both of which were believed at that time to offer protection against the development of TCM[22]. However, Brunettii *et al*[23] subsequently reanalyzed and ultimately refuted this assertion. Most of the cases presented in Table 2 involved anesthetic induction which may have been a contributing factor in the subsequent development of TCM in these patients.

## RISK FACTORS, TREATMENT AND PREVENTION

TCM is transient and has favorable outcomes in the large majority of patients. Significant adverse events such as free wall rupture, or cardiac arrest occurs infrequently. Therefore, no specific treatment is recommended. TCM has been known to have a relatively low recurrence rate, at 4% per El-battrawy *et al* [24] Beta-blockers and ACE-inhibitors (ACEi) are commonly used in patients with LV dysfunction given their cardioprotective nature; however, no consensus is available for their use in TCM. Isogai *et al*[25] established that early introduction of beta-blockers in individuals with TCM did not lower their 30-day inpatient mortality. However, lower rates of cardiac rupture were noted in patients with TCM on beta-blockers by Kumar *et al*[26].

**Table 1 Medication-induced takotsubo cardiomyopathy case reports**

| | Sundbøll *et al*[15], 2014 | Laínez *et al*[16], 2009 | Azouzi *et al*[17], 2019 | Ward *et al*[18], 2019 | Teixeira *et al*[19], 2014 |
|---|---|---|---|---|---|
| Electrocardiogram findings | STE II, III, I, aVL, V2-6 | New LBBB | Anterolateral STE | TWI | QTc prolongation (479ms) |
| Peak troponin I (μg/L) | 0.773 | N/A | 0.08 | N/A | 8.2 |
| Echocardiogram | Apical ballooning | Septal, apical, lateral akinesia | 40%; apical hypokinesis | Basal hypokinesis | Mid-to base akinesis w/severe systolic dysfunction; preserved apical contractility |
| Angiography | Nonobstructive | Nonobstructive | Nonobstructive | Nonobstructive | Nonobstructive |
| Administered medication | Mucosal E, cocaine | NE, E | E gtt(BB overdose) | NE | Esmolol |
| LV Recovery Time | 4 d | 5 d | [a] | [a] | 2 d |

[a]Recovered left ventricle function without documented time. N/A: Not reported; E: Epinephrine; NE: Norepinephrine; TWI: T-wave Inversion; BB: Beta-blocker; STE: ST-elevation; LV: Left ventricle.

**Table 2 Iatrogenic-takotsubo cardiomyopathy after procedure case reports**

| | Narayanan *et al*[21], 2014 | Yeow *et al*[27], 2020 | Chen *et al*[20], 2011 | Kim *et al*[32], 2011 | Yu *et al*[33], 2016 | Blázquez *et al*[4], 2010 | Hui *et al*[34], 2019 | Tori *et al*[35], 2008 |
|---|---|---|---|---|---|---|---|---|
| Procedure | ECT | ECT | Percutaneous coronary intervention | Upper, lower endoscopy | Upper endoscopy | Mitral valve replacement | Bronchoscopy | cholecystectomy and choledocholithotomy |
| Procedure medication | Propofol, succinyl choline | N/A | Undiluted NE | Pentazocine, Midazolam | Lidocaine spray, Midazolam | N/A | N/A | N/A |
| Electrocardiogram findings | ST depression and TWI V5-V6 | Left anterior fascicular block, TWI III | STE V2-V6 | STE V2-3 | normal | TWI V1-6 | Anterior TWI | TWI V2-5 |
| Peak troponin I (ng/mL) | 2.847 | N/A | 15.11 | 2.0 | 3.79 | N/A | N/A | normal |
| Echocardiogram | 52%, mid-segment and apical hypokinesia with ballooning | Mid-ventricular and apical akinesis | 20-40%, severe apical and septal hypokinesis | Hyperkinetic basal LV; rest of LV akinetic | 45%, Hypokinetic mid-LV | 15-20%; severe mid-ventricular dysfunction, apical akinesis, with hyperdynamic basal segments | 10-15%, apical ballooning and hypokinesis | apical akinesis, basal hyperkinesis |
| Angiography | NOB | NOB | NOB. | NOB. | NOB. | NOB. | NOB. | N/A |
| LV recovery time | [a] | 3 wk d | 2 d | 2 mo | 6 d | 11 d | [a] | 14 d |

[a]Recovered left ventricle function without documented time. N/A: Not reported; E: Epinephrine; NE: Norepinephrine; TWI: T-wave Inversion; BB: Beta-blocker; STE: ST-elevation; LV: Left ventricle; NOB: Nonobstructive.

Singh *et al*[22] performed a meta-analysis evaluating the efficacy of beta-blockers and ACEi in preventing recurrent TCM. They concluded that ACEi were superior to beta-blocker in recurrent TCM. A case report by Yeow *et al*[27] supports the use of both ACEi and beta-blockers. It involves a 61-year-old male who was admitted suicidal ideation and underwent ECT with subsequent development of TCM. This patient was started on a beta-blocker (metoprolol succinate) and ACEi (lisinopril) while hospitalized and re-evaluated in the outpatient setting three weeks later. He was found to have full ventricular recovery and underwent ECT four additional times over the following six mo without recurrence of TCM, which supports the findings of Singh *et al*[22]. However, Brunetti *et al*[23] reanalyzed the data of Singh *et al*[22] a year later, and suggested that the lower rates of TCM were noted in patients treated with ACEi than beta-blockers; however, this difference was not secondary to the drugs' cardioprotective effect, but rather due to the fact that the patients in the ACEi cohort were

prescribed the drug at a higher rate and these patients had closer follow-up than patients in the beta-blocker cohort. Lastly, a recent study by Kim *et al*[28] failed to show a survival benefit or prevent recurrence in patients with TCM treated with ACE inhibitors or beta-blockers.

A recent study by Deshmukh *et al*[29] collected data from the Nationwide Inpatient Sample database in order to analyze potential risk factors for TCM. They identified that age, gender, tobacco or alcohol use, dyslipidemia, hypertension, and external stressors, such as physical or emotional stress, contributed to an increased risk in the development of TCM[29]. Age and gender appear to the be the strongest risk factors as Deshmukh *et al*[29] revealed that women over the age of fifty-five had 4.8 times higher odds of developing TCM when compared to younger women. This increased risk is likely due to decreased circulating levels of estrogen levels and resultant increased sympathetic drive as noted previously in the findings of Templin *et al*[14].

## LIMTATIONS

Although iatrogenic medication-induced TCM is likely related to excessive catecholamine administration based on the case reports listed in Table 1, procedure-induced TCM appears to be an associated but rare complication. It is likely that the patients involved in Table 2 experienced an endogenous catecholamine surge that resulted in transient cardiac dysfunction. With the exception of Chen *et al*[20], the case reports in Table 2 did not involve pre-procedural catecholamine administration; however, all patients experienced post-procedural TCM. Case reports listed in Table 2 did not elucidate on potential complications during procedures, such as transient hypotension or the administration of vasopressor support resulting in a catecholamine surge causing iatrogenic TCM. In addition, case reports did not consistently include their home medications. Withdrawal of certain medications could theoretically precipitate a catecholamine surge (*i.e.*, clonidine[30]) or render the patient more susceptible to the endogenous effects of catecholamines.

## CONCLUSION

Although Takotsubo cardiomyopathy was first described in 1991, this specific type of cardiomyopathy has only recently gained increased recognition throughout the medical community. TCM is largely provoked by extreme, acute physical or emotional distress but there are now several iatrogenic cases involving catecholamine administration and post-procedural complications highlighted in Table 1 and Table 2. There are many aspects of TCM that are still not completely understood; however, future research should increase our understanding of this disease. It is important to acknowledge this clinical syndrome and its association with medications and procedures in order to better predict complications and potentially prevent further iatrogenic cases of Takotsubo cardiomyopathy.

## FOOTNOTES

**Author contributions:** Barmore W, Patel H and Harrell S performed the majority of the writing, prepared the figures and tables; Barmore W and Patel H performed data accusation and writing; Barmore W, Patel H, Harrell S and Garcia D performed the majority of literature review; Calkins Jr JB provided the input in writing the paper; Harrell S designed the outline and coordinated the writing of the paper.

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ORIGINAL ARTICLE

Observational Study

# Association of obesity anthropometric indices with hypertension, diabetes mellitus and hypertriglyceridemia in apparently healthy adult Nigerian population

Anil Sirisena, Basil Okeahialam

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## Abstract

### *BACKGROUND*

Hypertension, hyperglycemia and hypertriglyceridemia are chronic conditions associated with cardiometabolic diseases. Certain anthropometric indices are known to predict them.

### *AIM*

To investigate the association of anthropometric indices with these chronic diseases and which anthropometric index predicts them best.

### *METHODS*

In this study, 221 apparently healthy individuals who never received treatments for cardiovascular disease (CVD), diabetes or other chronic diseases participated. The age of the participants ranged from 20-75 years with mean age of 36.9 ± 11.4 years. The risk factors of these diseases namely systolic blood pressures (SBP) and diastolic blood pressures (DBP), fasting blood glucose (FBG) and triglycerides (TG) were determined for all the participants using standard clinical procedures. The obesity anthropometric indices, waist circumference, waist-to-height ratio, waist-to-hip ratio and body mass index as well as abdominal height (AH) and body surface index were determined. The association between each of them with the risk factors were determined by the Pearson correlation method.

### *RESULTS*

From the results, it was found that AH showed superiority over the rest for SBP ($r$ = 0.301, $P$ < 0.01), DBP ($r$ = 0.370, $P$ < 0.01), FBG ($r$ = 0.297, $P$ < 0.01) and TG ($r$ = 0.380, $P$ < 0.01). Using the receiver operating characteristic curves, cut-off values of AH for SBP, DBP, FBG and TG were determined to be 24.75 cm, 24.75 cm, 25.25 cm and 24.75 cm respectively.

*CONCLUSION*
The indices of anthropometry used in this study correlated significantly with the studied CVD risk factors, with AH emerging as the most predictive.

**Key Words:** Hypertension; Hyperglycemia; Hypertriglyceridemia; Abdominal height; Anthropometric indices

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**Core Tip:** In this work, we used common anthropometric indices and some novel ones to correlate with cardiometabolic diseases in an attempt to identify the best anthropometric index that accurately predicts risk of cardiometabolic diseases in apparently normal individuals.

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## INTRODUCTION

It has been identified that chronic disease conditions such as hypertension, hyperglycemia and hypertriglyceridemia are important public health challenges often encountered in Sub-Saharan Africa and worldwide with hypertension considered a major risk factor leading to stroke, myocardial infarction, heart failure and even ultimate death[1,2]. Metabolic conditions associated with abdominal obesity such as elevated blood pressure, impaired glucose tolerance, insulin resistance and elevated triglycerides (TG) are all contributing factors of metabolic syndrome (MetS) and cardio-metabolic diseases (CMD)[3-5]. For a long time, excess adiposity, especially the visceral fat is identified as one of the major risk factors of these chronic diseases[6]. Moreover, visceral fat has a more significant impact on diabetes and other related conditions than subcutaneous fat[7]. The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. An increased intake of energy-dense food high in fat; and an increase in physical inactivity due to the increasingly sedentary lifestyle is responsible for this energy imbalance[8]. In most population based cardiovascular risk evaluation studies found in the literature, researchers have chosen two or more of traditional obesity anthropometric indices among waist circumference (WC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHR) and body mass index (BMI) to establish the risk level of cardiovascular disease (CVD). This is because they are simple, non-invasive and cost effective measuring procedures. However, as shown in the literature, none of these adiposity anthropometric indices has been found to be systematically better than the others in the discriminatory power of CVDs[9] because, they can have some inherent clinical deficiencies associated with them in getting accurate diagnosis. For decades, BMI has been the most widely accepted index of adiposity and most commonly used for defining obesity recommended by the WHO[10] but it can be affected by age, gender, and ethnicity[11]. Some studies found statistical evidence that supports the superiority of measures of abdominal obesity (WC, WHR, or WHtR) over BMI, for discriminating cardiovascular risk factors in both genders[12,13]. Moreover, it has been shown that BMI cannot distinguish between visceral (abdominal) adiposity and overall (general) adiposity and therefore, found to be incapable of differentiating body fat and lean body mass[14]. Although WC takes abdominal obesity into account but it includes both visceral and transcutaneous fat in its measurements. Some studies have proposed WHtR and WHR as the better anthropometric parameters than BMI for predicting cardiometabolic risk[15-17]. Another study showed that although WC and WHR could indicate relative abdominal shape more clearly, they still provided limited information on the fat distribution and can lead to inaccurate diagnosis[17]. Moreover, the predictive power of different anthropometric indices also depends on the ethnic origin of the studied population[18] and this suggests the need for regional studies to be carried out in order to determine the best adiposity discriminators unique to each of these population groups for more accurate community risk evaluations of cardiometabolic diseases. In this study, two other adiposity indices abdominal height (AH)[19] and body surface index (BSI)[20] were included along with BMI, WC, WHtR and WHR. The purpose of this study is to identify the best anthropometric index for each of the disease conditions; hypertension, diabetes mellitus (DM) and hypertriglyceridemia for our chosen cross-sectional population study group and to determine their respective cut-off values.

## MATERIALS AND METHODS

### *Materials*

After signing the consent form, the participants were given a questionnaire to fill indicating their sex, age, state of origin, smoking status (Yes or No), alcohol use (Yes or No), physical inactivity (Yes or No) and the family history of CVD (Yes or No). For the measurements to determine the anthropometric indices, Hana bathroom scale, a stadiometer, a non-flexible measuring tape and an abdominometer were used. The blood pressures were measured with an Omron M2 basic automatic digital blood pressure monitor while fasting blood glucose (FBG) and TG were determined with an SD lipidocare dual analyzer.

### *Methods*

**Study design:** A cross-section of apparently healthy adult Nigerians of multiple ethnicity participated in this study. All participants recruited for this study reside in Jos, which is the capital of Plateau State of Nigeria. By "apparently healthy" we meant people who assume themselves to be healthy because they feel no symptoms although they had never done routine medical check-ups or taken any type of medications for chronic diseases such as hypertension, DM and MetS in their life time. They may well be in some form of cardiometabolic disease incubation depending on their age, physical attributes and lifestyle. The minimum sample population size was determined statistically by using the formula, $N = (Z^2\ p\ q)/X^2$ to be 196. The prevalence of cardiometabolic diseases in Nigeria as reported in a previous literature was taken to be 15%[21]. This study was carried out at the Jos University Teaching Hospital, Jos, Nigeria after obtaining the ethical clearance from the hospital's ethical committee. Informed and written consents were obtained from each of the participants of this study. Demographic, behavioral and other risk factor information needed in this study were obtained by administering a questionnaire.

**Inclusion criteria:** Only the apparently healthy staff and students in Jos University Teaching Hospital who never received treatments for CVD, Diabetes or other chronic diseases were included in this study. The minimum age to qualify for this study was 18 years.

**Exclusion criteria:** Pregnant women and children were excluded from this study.

**Ethical consideration:** The study design and protocols were duly approved by the Ethical Committee of the Jos University Teaching Hospital, Jos; and the study lasted between August 2015 to January 2016.

**Measurements of anthropometric indices:** The body mass was measured using a Hana bathroom scale to the nearest 0.5 kg with subjects wearing light clothes as much as possible with empty pockets standing erect on the scale with both legs well placed on it without shoes. The height measurement was taken as the subject stands erect without shoes on a stadiometer in centimeters. Waist and hip circumferences were measured using a non-flexible tape in centimeters to the nearest 0.1 cm. WC was measured at the end of a normal expiration with arms relaxed at the sides over the light clothing in standing position at the mid-point between the lower margin of the last palpable rib and the top of the iliac crest. Hip circumference was measured with tape wrapped around the maximum circumference of the buttocks with the subjects standing with their feet together with body weight evenly distributed over the feet. WHR was determined by the ratio between the waist and the hip circumferences. Similarly, WHtR was determined by the ratio between the WC and height. The BMI and BSI were computed by dividing the body mass (kg) by the square of height ($m^2$) and dividing the body mass (kg) by the body surface area ($m^2$)[20]. The AH was measured using a locally constructed wooden instrument 'abdominometer' in centimeters with an accuracy of 0.5 cm by placing the instrument at the level of iliac crest which corresponds to the space between $4^{th}$ and $5^{th}$ lumber vertebrate and the anterior abdominal wall at the level of umbilicus as the subject stands erect[19].

**Measurements of blood pressures:** Both systolic and diastolic blood pressures (DBP) were measured using an Omron M2 Basic automatic digital blood pressure monitor. The subjects were asked to sit without crossing legs on a chair quietly and place his/her hands on the table after resting in a sitting position for about 15 min. The inflating cuff was fixed tightly on the upper left arm making sure that the lower edge of the cuff was placed about 2 cm above the inner side of the elbow joint. The measurements were taken 3 times within a 5-min interval and the average of both systolic and DBP of the last two measurements were recorded according to WHO guidelines[22].

**Measurements of TG and FBG:** SD lipidocare dual analyzer was used to determine the TG and FBG levels.

**High risk cut-off values of risk factors:** In clinical practice, hypertension is diagnosed when systolic blood pressure (SBP) ≥ 140 mmHg and DBP ≥ 90 mmHg[21]. Hyperglycemia which is also known as DM is clinically established when FBG level ≥ 7.0 mmol/L[23]. Hypertriglyceridemia is also diagnosed from the fasting blood serum when the level of TG ≥ 1.7 mmol/L[24].

**Statistical analysis:** In this study, all statistical analysis were carried out with IBM SPSS Version 22 software package. Correlations between risk parameters (SBP, DBP, FBG and TG) and obesity anthropometric indices (AH, WC, WHR, BSI, WHtR and BMI) were carried out using Pearson correlation method. Also, the correlation between AH and the rest of the anthropometric indices was determined. The receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values of AH for all the risk parameters including obesity.

## RESULTS

In this study, 221 consenting subjects (82 males and 139 females) of aged between 18-75 years with a mean age of 36.9 ± 11.4 years participated. Out of this, 67% were indigenes of Plateau state (Central Nigeria) while the rest of the 33% were from 18 other different states representing the North, South, East and West geographical regions of Nigeria.

From the questionnaires, the percentages of traditional risk factors such as status of smoking, alcohol use, physical inactivity and family history of CVD were found to be 2.3%, 17.2%, 31.7% and 24.4% respectively.

Table 1 shows the number of subjects from the study population and the percentage risk for each of the risk parameters considered in this study including the risk of obesity (BMI ≥ 30.0 kg/m$^2$).

Figure 1 shows the correlations between SBP, DBP, FBG and TG respectively with the selected obesity anthropometric indices.

Table 2 shows the order of correlation coefficients of the anthropometric indices from the highest to the lowest for each of the four risk parameters SBP, DBP, FBG and TG.

Table 3 shows the Pearson Correlation coefficients and *P* values between AH and other anthropometric indices used in this study.

Table 4 shows the ROC curve analysis with cut-off values of AH for all the risk parameters including obesity.

## DISCUSSION

Table 1 shows the summary of the prevalence of risk levels of chronic diseases among the apparently healthy cross section of adult Nigerians chosen in this study. Unknown to them, a significant percentage of these participants were at high risk for CMD. We found that 16.3% of the participants had SBP greater or equal to 140 mmHg while 10.0% had DBP greater or equal to 90 mmHg. However, only 2.7% had hyperglycemia but 19.0% had hypertriglyceridemia. Interestingly, 28.1% of these participants who claimed to be healthy were obese. Correlation coefficients of anthropometric indices WC, AH, BMI, BSI, WHtR and WHR with risk parameters SBP, DBP, FBG and TG were illustrated in Figure 1 and all the correlations were significant at $P < 0.01$ and showed a positive association between the anthropometric indices and risk parameters. Table 2 shows the order of correlation with each risk parameter from highest to lowest values. It was found that AH is superior to all the other obesity anthropometric indices considered in this study to discriminate hypertension (SBP and DBP), hyperglycemia (FBG) and hypertriglyceridemia (TG). This confirms the findings of an earlier pilot study by Okeahialam *et al*[25] that AH was superior to BMI in predicting hypertension and diabetes. This present study shows that even for hypertriglyceridemia AH is a better predictive anthropometric index. Although both WHO and American Heart Association recommend the use of WC in screening for cardiometabolic risk[26], in our study WC is positioned as the second best discriminator for SBP, DBP and FBG except for TG where BSI proved to be better. Previous studies also showed that AH, also known as sagittal abdominal diameter (SAD) correlates better with cardiovascular risk factors than WC and BMI[27-29]. However, in these studies SAD was measured with a subject lying in a supine position to allow loose subcutaneous fat to fall to the sides of the subject on the couch and more rigid visceral fat to remain in place to be measured using a caliper instrument. They also reported that the ability of SAD to index abdominal fat and high risk obesity more accurately is greater than that of the WC and BMI. We also noticed that BSI is superior to BMI in discriminating all the risk parameters considered in this study. The other two anthropometric indices WHtR and WHR can also be used as good discriminators of CMD. However, some inaccuracies can occur especially in finding the best anatomical site for WHR measurement[30]. Although all these six anthropometric indices are statistically found suitable for the risk evaluation studies of adult Nigerians, some uncertainties involved in differentiating of visceral fat from subcutaneous fat and abdominal obesity from general obesity can hinder the accuracy of these traditional anthropometric indices in diagnosing cardiometabolic diseases. Therefore, we propose AH to be the best discriminator of CMD for adult Nigerians in this locality taking into consideration both statistical superiority and clinical acceptability due to its ability to measure visceral fat more accurately. Table 3 shows the association of AH with the other five anthropometric indices. Incidentally, AH also shows very strong and positive correlations with all the other indices: WC (0.944), WHtR (0.905), BSI (0.892), BMI (0.872)

**Table 1 Number of risk subjects and percentage risk for study parameters**

| Risk cut-off of parameter | Number of subjects | Percentage risk |
|---|---|---|
| SBP ≥ 140 mmHg | 36/221 | 16.3 |
| DBP ≥ 90 mmHg | 22/221 | 10.0 |
| FBG ≥ 7.0 mmol/L | 06/221 | 2.7 |
| TG ≥ 1.7 mmol/L | 42/221 | 19.0 |
| BMI ≥ 30.0 kg/m$^2$ | 62/221 | 28.1 |

SBP: Systolic blood pressures; DBP: Diastolic blood pressures; FBG: Fasting blood glucose; BMI: Body mass index; TG: Triglycerides.

**Table 2 The order of correlation of the anthropometric indices with risk parameters**

| Risk-parameter | Order of correlation with anthropometric indices, highest (1) to lowest (6) | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| SBP | AH | WC | WHR | BSI | WHtR | BMI |
| DBP | AH | WC | BSI | WHtR | BMI | WHR |
| FBG | AH | WC | WHtR | WHR | BSI | BMI |
| Triglycerides | AH | BSI | WC | BMI | WHtR | WHR |

AH: Abdominal height; SBP: Systolic blood pressures; DBP: Diastolic blood pressures; FBG: Fasting blood glucose; BMI: Body mass index; WC: Waist circumference; WHtR: Waist-to-height ratio; WHR: Waist-to-hip ratio; BSI: Body surface index.

**Table 3 Correlation between abdominal height and other anthropometric indices**

| | WC | BMI | WHtR | WHR | BSI |
|---|---|---|---|---|---|
| AH | 0.944 | 0.872 | 0.905 | 0.682 | 0.892 |
| *P* value | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

AH: Abdominal height; BMI: Body mass index; WC: Waist circumference; WHtR: Waist-to-height ratio; WHR: Waist-to-hip ratio; BSI: Body surface index.

**Table 4 Receiver operating characteristic curve analysis with cut-off values of abdominal height for risk parameters**

| Disease condition | Risk value | AH cut-off (cm) | Sensitivity, % | Specificity, % | AUC | 95%CI |
|---|---|---|---|---|---|---|
| Hypertension (SBP) | ≥ 140 mmHg | 24.75 | 66.7 | 56.8 | 0.638 | 0.544-0.730 |
| Hypertension (DBP) | ≥ 90 mmHg | 24.75 | 77.3 | 56.3 | 0.664 | 0.551-0.778 |
| Hyperglycemia (FBG) | ≥ 7.0 mmol/L | 25.25 | 66.7 | 58.6 | 0.621 | 0.344-0.899 |
| Hypertriglyceridemia (TG) | ≥ 1.7 mmol/L | 24.75 | 83.3 | 61.5 | 0.751 | 0.675-0.827 |
| Obesity (BMI) | ≥ 30.0 kg/m$^2$ | 25.75 | 85.5 | 79.2 | 0.923 | 0.889-0.957 |

AH: Abdominal height; TG: Triglycerides; BMI: Body mass index; SBP: Systolic blood pressures; DBP: Diastolic blood pressures; FBG: Fasting blood glucose; AUC: Area under the curve; CI: Confidence interval.

and WHR (0.682). This shows the strong relationship of AH over the other anthropometric indices considered in this study for risk evaluations of CMD. From the ROC curve analysis, we found the cut-off values, area under the curve, 95% confidence interval of AH for all the risk parameters SBP, DBP, FBG, TG and obesity (using the BMI scale) as shown in Table 4. We established that the risk cut-off value of AH ≥ 24.75 cm for both hypertension and hypertriglyceridemia and AH ≥ 25.25 cm for hyperglycemia. Using BMI ≥ 30.0 kg/m$^2$ as the risk value of obesity, the cut-off value of obesity is found to be AH ≥ 25.75 cm. This means that, going by our findings, cardiometabolic disease risk can occur

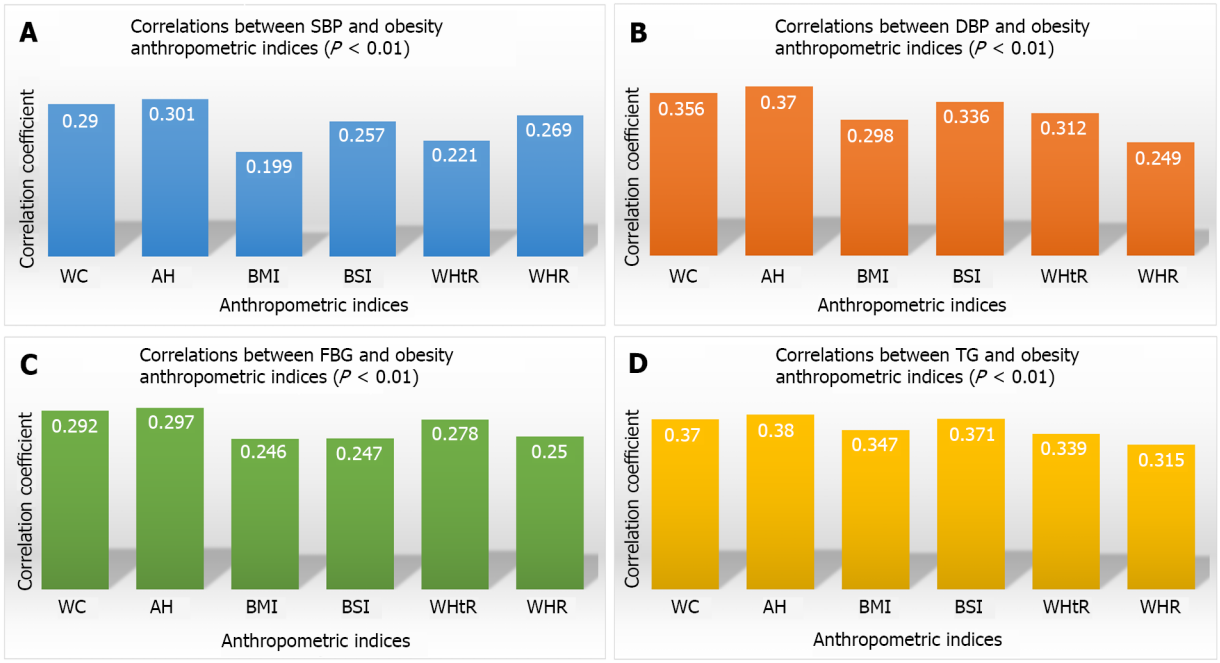


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**Figure 1 Correlation between each index and obesity anthropometric index.** A: Correlations between systolic blood pressures and obesity anthropometric indices; B: Correlations between diastolic blood pressures and obesity anthropometric indices; C: Correlations between fasting blood glucose and obesity anthropometric indices; D: Correlations between triglycerides and obesity anthropometric indices. AH: Abdominal height; WC: Waist circumference; BMI: Body mass index; BSI: Body surface index; WHtR: Waist-to-height ratio; WHR: Waist-to-hip ratio; SBP: Systolic blood pressures; DBP: Diastolic blood pressures; FBG: Fasting blood glucose; TG: Triglycerides.

without a person being classified as obese going by WHO BMI values.

## CONCLUSION

From this study, we have attempted to establish the clinical and statistical significance of the AH measured when a subject is standing in erect position at ease with our abdominometer in risk evaluation of cardiometabolic diseases over the other existing traditional obesity anthropometric indices such as WC, WHtR, WHR and BMI. Moreover, we also found that the BSI can be a better index than the BMI for cardiometabolic risk evaluations as a general obesity anthropometric index.

### *Recommendations*

Using this simple AH measurements, large scale community based population studies were recommended to predict and separate high risk individuals for possible life style modification procedures, clinical interventions and treatments to minimize the mortality and morbidity rates of cardiometabolic diseases as preventive measures. This is necessary given the relatively small size of our sample and the convenience approach to sampling; in order to improve external validity.

## ARTICLE HIGHLIGHTS

### *Research background*

For decades, body mass index (BMI) has been the most widely accepted index of adiposity and most commonly used for defining obesity recommended by the WHO but it can be affected by age, gender, and ethnicity.

### *Research motivation*

In most population-based cardiovascular risk assessment studies found in the literature, researchers selected two or more of traditional obesity among waist circumference, waist-to-height ratio, waist-to-hip ratio, and body mass index. Anthropometric measures (BMI) to determine the level of cardiovascular disease (CVD) risk. This is because they are simple, non-invasive and cost-effective measurement procedures. However, as shown in the literature, these anthropometric measures of

obesity have not been found to be systematically superior to others in terms of their discriminative power for CVD, as they may have some inherent clinical pitfalls associated with them in obtaining an accurate diagnosis.

### *Research objectives*

We sought to identify the best anthropometric index predictive of each of the disease conditions; hypertension, diabetes mellitus and hypertriglyceridemia for our chosen cross-sectional population study group and to determine their respective cut-off values.

### *Research methods*

This was a cross-sectional study that included 221 consenting apparently healthy adult Nigerians 18 years and above who were not pregnant at enrolment. After signing the consent form, the participants were given a questionnaire to fill indicating their sex, age, state of origin, smoking status (Yes or No), alcohol use (Yes or No), physical inactivity (Yes or No) and the family history of CVD (Yes or No). Height and weight were measured as well as the other anthropometric indices using a measuring tape and an abdominometer. The blood pressures were measured with an Omron M2 basic automatic digital blood pressure monitor while fasting blood glucose and triglycerides were determined with an SD lipidocare dual analyzer.

### *Research results*

In this study, 221 consenting subjects (82 males and 139 females) of aged between 18-75 years with a mean age of 36.9 ± 11.4 years participated. From the questionnaires, the percentages of traditional risk factors such as status of smoking, alcohol use, physical inactivity and family history of CVD were found to be 2.3%, 17.2%, 31.7% and 24.4% respectively.

### *Research conclusions*

Anthropometric measures used in this study were significantly associated with the CVD risk factors studied, with abdominal height (AH) emerging as the most predictive measure.

### *Research perspectives*

Using this simple measure of AH, large-scale community population studies are recommended to predict and differentiate high-risk individuals for possible lifestyle modification procedures, clinical interventions, and treatments to minimize cardiometabolic mortality and mortality. Morbidity as a preventive measure. This is necessary given our relatively small sample size and convenient sampling method.

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## FOOTNOTES

**Author contributions:** Sirisena A generated data, analyzed data and contributed to write up; Okeahialam B conceptualized and supervised project, wrote up the paper.

**Institutional review board statement:** The study was reviewed and approved by the Research and Ethics Committee of Jos University Teaching Hospital, No. JUTH/DCS/ADM/127/XIXI/6257.

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**Data sharing statement:** Technical appendix, statistical code and data set are available from the first author at shalom2k3@yahoo.com. Patients did not give consent for data sharing but the presented data are anonymized and risk of identification is nil.

**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.

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ORIGINAL ARTICLE

Observational Study

# Study of coronary sinus anatomy during levophase of coronary angiography

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## Abstract

### *BACKGROUND*

Coronary sinus (CS) imaging has recently gained importance due to increasing need for mapping and ablation of electrophysiological arrhythmias and left ventricular (LV) pacing during cardiac resynchronization therapy (CRT). Retrograde venogram is the current standard for imaging CS and its tributaries.

### *AIM*

To evaluate CS anatomy during levophase of routine coronary angiography to aid LV lead implantation during CRT.

### *METHODS*

In this prospective observational study, 164 patients undergoing routine coronary angiography for various indications (Chronic stable angina-44.5%, acute coronary syndrome- 39.5%, Dilated cardiomyopathy-11%, atypical chest pain-5%) were included. Venous phase (levophase) of left coronary injection was recorded in left anterior oblique - cranial and right anterior oblique -cranial views. Visibility of coronary veins, width and shape of CS ostium, angulations of proximal CS with body of CS were noted. Presence, size, take-off angle and tortuosity of postero-lateral vein (PLV), anterior interventricular veins (AIV) and middle cardiac vein (MCV) were also noted.

### *RESULTS*

During levophase, visibility grade (Muhlenbruch grade) for coronary veins was 3 in 74% and 2 in 26% of cases. Visibility of CS did not correlate with body mass index. The diameter of CS ostium was < 10 mm, 10-15 mm and > 15 mm in 48%, 42% and 10% of patients respectively. Proximal CS was tubular in 136 (83%)

patients and funnel-shaped in 28 (17%) patients. Sharp take-off angulation between ostium and body of CS was seen in 16 (10%) patients. Two or more PLV were present in 8 patients while PLV was absent in 52 (32%) patients. Angle of take-off of PLV with body of CS was favourable (0°-45°) in 65 (40%) patients. The angle was 45°-90° in 36 patients and difficult take-off angle (> 90°) was seen in 8 patients. Length of PLV reached distal third of myocardium in 84 cases and middle third in 11 cases. There was no tortuosity in 79 cases, a single bend in 29 cases and more than 2 bends in 4 cases. Thirty nine (24%) patients had other veins supplying posterior/Lateral wall of LV. There was a single vein supplying lateral/posterior wall in 31 (19%) patients. Diameter of MCV and AIV was significantly larger in patients with absent PLV as compared to patients with a PLV.

*CONCLUSION*

Levophase study of left coronary injection is effective in visualization of the CS in almost all patients undergoing coronary angiography and may be an effective alternative to retrograde venogram in patients with LV dysfunction or LBBB.

**Key Words:** Posterolateral vein; Ostium; Angiography; Sharp take off; Favourable angulation

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**Core Tip:** In this prospective, observational study, we assessed venous phase of coronary angiogram ($n$ = 164) with the intent to evaluate coronary sinus anatomy for purpose of left ventricular (LV) lead placement during cardiac resynchronization therapy. Levophase analysis showed excellent visibility of coronary sinus and its tributaries irrespective of body mass index. Shape of ostium & angulations within body of coronary sinus could be delineated reliably. Number, size, take off angle and any tortuosity within postero-lateral vein could be well identified. We found levophase study of coronary angiography an acceptable alternative to retrograde venography for LV lead placement assessment.

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## INTRODUCTION

Imaging of the coronary venous system is usually overshadowed by that of the coronary arteries. However, imaging of coronary venous system has gained importance in recent past, as many cardiac interventions currently use the coronary sinus *e.g.*, mapping and ablation of various arrhythmias, left ventricular (LV) pacing, targeted drug delivery, and stem cell therapy. The coronary sinus (CS) is the largest cardiac venous structure and is frequently cannulated during electrophysiologic and interventional procedures. Thus, detailed knowledge of its normal anatomy and anomalies is of paramount importance to avoid any complications[1,2].

The cardiac veins are classified, according to the region they drain viz. the CS and its tributaries, the anterior cardiac veins, and the thebesian veins[3-6]. The anterior cardiac veins are the primary venous return for the anterior wall of the right ventricle. They include three or four small veins which drain directly into the right atrium either separately or after forming a common venous trunk before emptying into the right atrium[5]. The right marginal vein is a relatively constant vein which ascends along the right margin of the heart. The right marginal vein can also drain into the small cardiac vein, which runs in the right atrioventricular groove which eventually terminates by draining into the CS or directly into the right atrium[5]. The thebesian veins (venae cordis minimae) are several small veins that drain the subendocardium.

The major tributaries of the CS include: (1) The anterior interventricular vein; (2) The great cardiac vein (GCV); (3) The left marginal vein and posterior vein; and (4) the middle cardiac vein or posterior interventricular vein. The CS is variable in size. It varies 45 to 63 mm in length, and the size of the ostium ranges from 4 mm × 5 mm to 9 mm × 16 mm[7-10].

Cardiac resynchronization therapy (CRT) involves LV pacing in patients with LV systolic dysfunction to improve synchronization of LV conduction. It yields the best results when the LV lead is implanted in area of latest mechanical activation, with the lateral and posterior branches being the usual target veins for this procedure[3]. Hence, CS imaging can play an important role in planning LV lead implantation

strategy and help identify suitable veins in area of interest. The most co mmonly employed technique to visualize CS anatomy is occlusive retrograde venography. In this study, we evaluated venous phase (levophase) of coronary angiography to assess its utility in studying CS anatomy.

## MATERIALS AND METHODS

All patients above 18 years of age undergoing coronary angiography for various indications between November 2017 and October 2018 were considered for inclusion. Patients who were in cardiogenic shock, had congestive heart failure, had eGFR < 50 mL/min, those having severe left main disease or complex congenital heart disease were excluded from the study.

Our study included patients who were undergoing invasive coronary angiography for different reasons such as acute coronary syndromes or stable angina. A written informed consent was taken from all patients in our study. Baseline characteristics were recorded in all patients which included age, sex, height, weight, NYHA functional class, cardiovascular risk factors like diabetes mellitus, hypertension, smoking, prior history of coronary artery disease (CAD) and left ventricular ejection fraction (LVEF).

Patients underwent a coronary angiogram from either the radial route using a 5F tiger catheter or femoral route with a 5F/6F Judkins left diagnostic catheter. A non-ionic, low osmolarity, iodide contrast medium - Iohexol (Omnipaque, GE Healthcare, Chicago, Illinois, United States) was used through manual injection in all cases. After canulating the left coronary ostium, a left anterior oblique (LAO) caudal view was recorded to detect patients with severe left main disease or any abnormality affecting the safety of the procedure. Further coronary angiogram was done with necessary angiographic view as per detected lesions. LAO with cranial angulation (LAO 40 degrees, cranial 30 degrees) and right anterior oblique (RAO) with cranial angulation (RAO 30 degrees, cranial 30 degrees) views were recorded for all patients. These are the views in which venous anatomy was studied. Venous phase (levo-phase) of injection was recorded beyond the initial 5-10 seconds to visualise the coronary venous anatomy in these LAO- cranial and RAO-cranial views. Recording was done on cine mode at rate of 15 frames per second. The rest of the coronary angiogram and all other procedure including intervention, post-procedure care was done as per routine. In some cases, the coronary venous anatomy could also be seen in other views taken during the study. When this revealed additional information, they were also included in our analysis.

### *Analysis of coronary venogram*

Visibility of the coronary veins was classified on the 0-3 point scale described by Muhlenbruch *et al*[10] (Table 1).

Measurements were taken on the CAAS QCA software based on pixel size and comparison with the catheter diameter. Width of the coronary sinus ostia was measured. Shape of the coronary sinus: tubular, funnel-shaped or other was recorded (Figure 1). The proximal portion of the coronary sinus was studied subjectively for factors that affect sheath selection such as angulation and presence of a thebesian valve. Superior angulation of the proximal portion of the coronary sinus with the body of the coronary sinus was measured in the LAO cranial view and classified into 3 groups: (Figure 2) Group 1: 0°-30°; Group 2: 31°-60° and Group 3: > 60°. The presence of posterior angulation of the coronary sinus ostia with the body of the coronary sinus was recorded in the RAO cranial view. LAO cranial view was studied for the presence of a Thebesian valve. A Thebesian valve was detected by noting an upward direction of outflow into the right atrium (RA) from the coronary sinus, and by a smooth inferior border of the outflow jet.

Other anomalies in venous anatomy such as posterior lateral vein (PLV) draining near the coronary sinus ostia or directly into the RA, left superior vena cava (SVC) were also recorded when relevant. Number of suitable (> 2 mm diameter) PLVs were noted. Veins with a diameter of > 2 mm measured 2cms distal to its ostium were considered favourable. Veins tapering or dividing into venules of less than 2 mm size before running 2 cms as seen in two recorded views were classified as unfavourable. The diameter of the PLV, measured at 2 cms distal to its ostia with the coronary sinus was noted. In cases with > 1 PLV, the diameter of the largest PLV was recorded. The angle made by the PLV with body of CS was also noted in the LAO cranial view and classified into 3 groups: (Figure 3) - Easy take-off: (0° to 45°); Medium difficulty: 45° to 90°; Difficult take-off: > 90°.

When a PLV was absent, the incidence of other tributaries draining the posterior-lateral part of the LV was studied. Diameter of the anterior interventricular vein (AIV) and the middle cardiac vein (MCV) was recorded in all cases. Comparisons were made of the diameters of the AIV and MCV in patients with and without a PLV. Tortuosity of the PLV most suitable for the purpose of CRT LV lead was studied, and the number of bends were also recorded.

### *Statistical analysis*

Demographic data were reported as percentages, mean and median were calculated when applicable. Chi square test and the student t-test were used for statistical analysis. *P* value < 0.05 was considered statistically significant. All data were analyzed using the Statistical Package for the Social Sciences (IBM

**Table 1 Visibility of the coronary veins was classified on the 0-3 point scale**

| Grade | Visibility |
|---|---|
| 0 | Not visible |
| 1 | Visible but with discontinuities |
| 2 | Visible but with irregular borders |
| 3 | Visible with vascular borders perfectly defined |

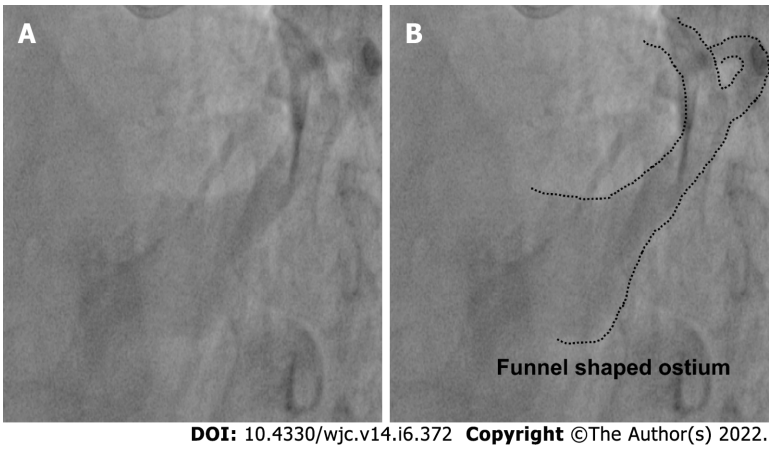


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**Figure 1 Funnel Shaped Ostium as seen in left anterior oblique cranial view.** A: Fluoroscopic image; B: Rendered image with dotted lines outlining coronary sinus morphology.

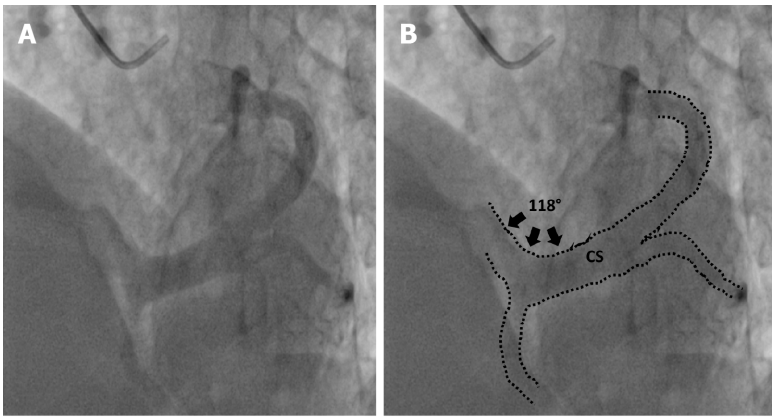


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**Figure 2 Superior angulation made by the proximal portion of the coronary sinus with the body of the coronary sinus in left anterior oblique cranial view.** A: Fluoroscopic image; B: Rendered image with dotted lines outlining coronary sinus anatomy, black arrows represent angle subtended.

SPSS; Chicago, IL, United States) program, version 20.

## RESULTS

A total of 168 patients undergoing coronary angiography for various indications between November 2017 and October 2018 were included in our study. Coronary sinus could not be assessed in four patients due to a suboptimal study (inadequate volume of dye given, too short cine time) and were excluded from analysis. Data of the remaining 164 patients was analysed. 116 (72%) were male and the mean age of the study population was 53.3 years (Figure 4). The various indications for coronary angiography were Chronic Stable Angina in 73 (44.5%) cases, Acute Coronary Syndrome in 65 (39.5%) patients [43 with Non-ST elevation Myocardial infarction, 22 With ST-elevation myocardial infarction], Dilated cardiomyopathy/ischemic cardiomyopathy was present in 11 (7%) patients. Angiography was

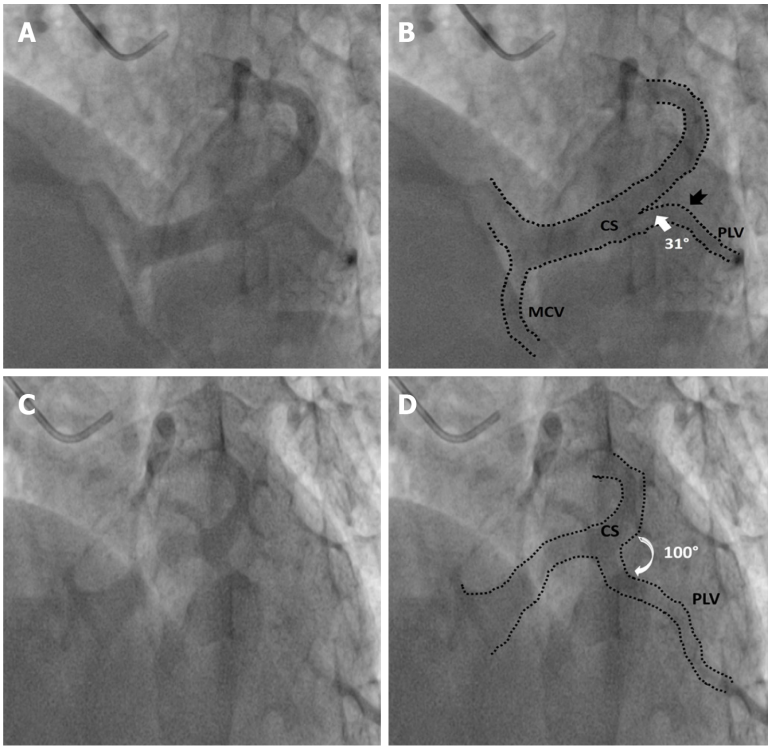


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**Figure 3 Favourable and unfavourable take off angles of posterolateral vein.** A: Example of posterolateral vein (PLV) with favourable angle-fluoroscopic image; B: Corresponding rendered image with dotted lines outlining coronary sinus (CS) morphology, white arrow denoting narrow angle between body of CS and PLV, black notched arrow represents single bend in PLV; C: Example of unfavourable angle PLV-fluoroscopic image; D: Corresponding rendered image with dotted lines outlining CS morphology, white curved arrow denoting wide angle between PLV and CS body.

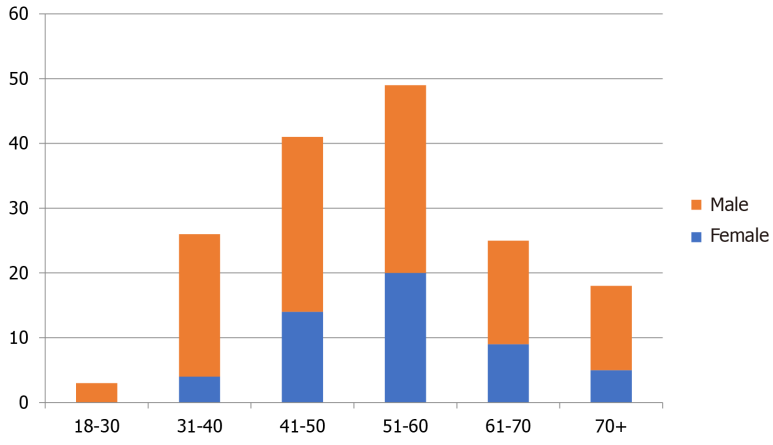


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**Figure 4 Demographic profile of study population.**

performed for the evaluation of atypical chest pain in 09 (5%) patients, 2 patients had VT in a structurally normal heart, 3 patients underwent routine angiography prior to valve replacement, and 1 patient had PSVT with angina. The LVEF of patients ranged from 22%-76%. Eleven patients (7%) had an EF of less than 35%. 93 patients (57%) had an EF of 50% and above. The body mass index (BMI) in 53% of patients ranged from 18-24, 6% had a BMI of 30 or above and 14% had a BMI of less than 18. The visibility of CS did not correlate with BMI ($P = 0.69$). The visibility score was 3 in 121 (74%) cases, 2 in 43 (26%) cases, < 2 in 0 cases. Access was *via* right radial artery in 134 (89%) patients, right femoral artery in 16 (11%) patients. The mean contrast medium volume used was 65.2 ± 26.6 mL. Among complications, two patients developed grade 1 radial hematoma, and none had any complications related to femoral arterial access. No contrast-induced nephropathy was seen in our study.

### *Coronary venous anatomy*

The diameter of CS ostia ranged from 2 mm-18 mm.The diameter was < 10 mm in 80 (48%) of the patients, 10-15 mm in 74 (42%) of patients and > 15 mm in 10% patients. Ostial stenosis (diameter < 2 mm) was present in 1 case with a co-existing left SVC. The shape of proximal portion of CS was tubular in 136 (83%) patients and funnel-shaped in 28 (17%) patients (Figure 1). The superior Angle between body of CS and ostia (take-off angle) in LAO cranial view was 0°-30° (horizontal) in 102 (63%) patients, 31°-60° (intermediate) in 45 (27%) patients and > 60° (sharp angulation) in 16 (10%) patients (Figure 2). Significant posterior indentation in RAO cranial view was seen in 5 patients. Presence of a thebesian valve (directing inferior border of flow into RA superiorly as seen in LAO cranial view) was present in 21 cases. Two or more PLV were present in 8 patients while PLV was absent in 52 (32%) patients. The diameter of the largest PLV was 4.1 mm. Angle of take-off of PLV with body of CS was favourable in 65 (40%) patients (0°-45°). The angle was 45°-90° in 36 patients and difficult take-off angle (> 90°) was seen in 8 patients. Extension or length of largest PLV (from base to apex) was assessed in RAO cranial view. Base to apex length was equally divided into 3 equal parts-proximal, mid and distal one third. It reached distal third in 84 patients, up to mid third in 11 patients and remained in proximal third in 5 patients. No bends were seen in PLV in 79 cases. There was single bend in 29 cases and more than 2 bends in 4 cases. 39 (24%) patients had other veins supplying posterior/lateral wall of LV. There was a single vein supplying lateral/posterior wall in 31 (19%) patients.

Diameter of the middle cardiac vein (MCV) was significantly larger in patients with absent PLV, compared to patients with a PLV. The mean diameter of MCV in patients without a PLV ($n$ = 52) was 4.9 mm (SD 1.7), the mean diameter of patients with a PLV ($n$ = 112) was 3.3 mm (SD 1.5), $P$ = 0.000291. Similarly, diameter of the anterior inter-ventricular vein (AIV) was larger in patients with absent PLV compared to patients with a PLV. Mean diameter of AIV in patients without PLV was 3.3 mm (SD 1.2), the mean diameter of AIV in patients with a PLV was 2.6 mm (SD 1.3). However, the difference did not reach statistical significance ($P$ = 0.076).

Of the 13 cases in which no suitable vein was visible, aberrant origin of left circumflex coronary artery (LCX) *via* the right sinus was detected in retrospect in 1 patient. Five patients had severe CAD involving the LCX, one patient had severe disease involving both the distal right coronary artery (RCA) and the LCX. The MCV was larger than 6 mm in 3 patients, The AIV was > 5 mm in 1 patient. No cause could be found in 2 patients.

Severe CAD involving the arterial supply of the posterior lateral wall of LV was present in 23 out of 50 (46%) patients with an absence of PLV, compared to 18 out of 100 (18%) patients with a PLV (Relative Risk (RR) = 2.55; $P$ value 0.0086). Other findings included separate opening of the PLV into the RA in 1 patient. PLV opening near the ostia of the coronary sinus seen in 6 patients.

## DISCUSSION

In our observational study of levophase of coronary angiograms, we analysed coronary venous anatomy for the purpose of cardiac resynchronization therapy (CRT) LV lead placement. Coronary sinus lead placement for resynchronisation therapy is required at all ages, and younger patients of dilated cardiomyopathy are a common subgroup. There is no sex predilection for dilated cardiomyopathy. In our study the median age was 56 years. Sex ratio was 2.5:1 (male:female). Age and sex distribution of the study is characteristic of the patient population seeking treatment at our tertiary care centre. This phenomenon is known to skew data of studies conducted in developing countries. There is a strong referral bias; female patients are more likely not to reach a tertiary care centre for treatment. The sex ratio in similar studies carried out in the western countries were 0.8:1 in a study of retrograde balloon occlusion venography by Mischke *et al*, and 1.2:1 in a study of levo-phase coronary angiograpy by Gilard *et al*[11,12]. Similarly there was no gender bias in anatomical studies of the coronary venous anatomy on human cadavers.

Nearly all cases in our study underwent coronary angiography for the evaluation and treatment of coronary artery disease. Only 11 patients had severe LV dysfunction which is present in all cases requiring CRT. Although the branching pattern can be assumed to be unaffected by the development of cardiomyopathy, there can be significant change in angle of opening of coronary ostium in cases with significant enlargement of left heart and normal sized RA and RV. Our study had too few cases of cardiomyopathy to be able to detect such a difference. The coronary sinus was adequately visualized in all cases. The borders were sharply delineated in a majority (visibility scale 3 in 74%). In the rest of the cases the borders were hazy but sufficient for the purpose of guiding the planning of LV lead implantation. Surprisingly, obesity (BMI) did not affect visibility. Because we obtained the CS anatomy in levophase in patients undergoing coronary angiography only in two views without any extreme angulation, insignificant amount of additional radiation exposure was anticipated.

The visibility of the venous system in our study was comparable to that attained by 360 slice CT study conducted by Chunjuan Sun *et al*[13]. In our study we identified a separate opening of the PLV into the RA in 1 case, and a suitable PLV opening close to the CS ostia in 6 cases. These are visualized better antegrade than retrograde as selective hooking will cause them not to be opacified. Meisel *et al*[14]

in their study on retrograde CS venography obtained optimum anatomical information in 67% of cases, compared to 92% in our study.

It is believed that retrograde occlusive venography better visualises the CS anatomy but it has its own lacunae. Some physicians use hyperaemic agents to aid visualization of CS in levophase. Arbelo E *et al* [15] compared occlusive retrograde venography with hyperaemic venous return angiography (levophase of coronary angiography). They used 200 µg of intracoronary Nitroglycerine or 60 µg of Adenosine to increase the coronary flow and thus the venous return in coronary sinus. The anatomical information obtained by both methods was adequate (100% *vs* 97.5%, respectively). Although occlusive retrograde venography is the most co mmonly employed technique, it has its own drawbacks. First, in the absence of venous anastamoses, veins with a posterior origin may not be visualized. Sometimes balloon does not provide a completely occlusive barrier, and 2 injections (distal and proximal) are then required to highlight the venous anatomy. In addition, for the opacification of the AIV, contrast medium has to be injected with the balloon inflated more distally in the GCV. This may lead to complications such as dissection of CS and heart blocks[15].

### *Levo-phase radiological anatomy*

We utilized 2 orthogonal views viz. LAO Cranial (40°, 30°), and RAO Cranial (30°, 30°) to view the Coronary Sinus. The LAO Cranial view showed the coronary ostia clearly. This view visualizes the proximal portion of CS without foreshortening and we can also see its angulation with main body of CS. Posterior vein, PLV, lateral vein were also well differentiated in this view along with the take-off angle of the PLV with the body of the CS. However, the distal portion of the Coronary Sinus was foreshortened in this view, making it hard to differentiate an anterolateral vein from an AIV. Presence of a thebesian valve was detected by noting an upward direction of the outflow jet into the RA. The inferior border of the outflow is smooth. We found evidence of a thebesian valve in 21 cases. An obstructive thebesian valve may require an Amplatz guiding catheter to cannulate the CS ostium. Mischke K *et al*[11] in their study of coronary venous anatomy found evidence of a thebesian valve in 11 out of 100 cases. These figures are much less than those found in anatomical studies carried out by Randhawa *et al*[16] (thebesian valves seen in 50 dissections) and by Noheria *et al*[17] (309 valves seen in 643 dissections). Small sized valves visible on direct examination are of little clinical significance[15,16].

RAO cranial view showed the ostia and the proximal portion of the CS end on. The proximal portion was however foreshortened. Posterior indentation of the proximal portion of the CS before joining the main CS body was studied in this view. We found this in 5 (3%) of 164 cases. This view was most useful for showing the length of the vein, from the base of the heart (AV groove) to the apex. In our study, we divided this base to apex distance into 3 equal lengths: Proximal, mid, and distal; 81% of the PLVs extended upto the distal one third.

In some cases, the coronary venous anatomy could also be seen in other views taken during the study. The RAO caudal view was very useful in showing the branches of the MCV, which were not visible in our 2 cranial views. Having more views also helped in showing the PLV in greater detail. More bends could be seen when more views were available.

The optimal site for LV lead placement is the posterior lateral wall of the LV. Of the 164 patients in our study, 151 (92%) had a suitable vein draining the posterior lateral wall of the LV. In 112 cases this was the PLV; in another 39, other veins drained this area. A critically stenosed LCX or a super-dominant RCA were strongly associated with failure to visualize an adequate vein. In one case in which the PLV was not visualized, the patient was found to have an anomalous LCX. If dye had been injected into this anomalous vein (instead of into the LAD) a PLV would probably be seen. The PLV opacifies if dye is injected into the region (posterior lateral wall of the LV) that it drains. In most cases the artery supplying the area drained by the PLV is the LCX, in some it is a super-dominant RCA. If the LCX has flow limiting stenosis, an anomalous origin, or if there is a super-dominant RCA, the posterior lateral part of the LV does not recieve enough dye and likely remains hidden.

We found 4 cases with a very large MCV or AIV (6 mm). Patients without a PLV were found to have on an average 1.5 mm larger MCV than patients with a visible PLV ($P > 0.05$). The AIV was found to be on an average 0.7 mm larger in cases without a PLV, compared to cases with a PLV; but this did not reach statistical significance. An absent PLV was found in 52 cases in our study. In 39 of these cases, there was another vein supplying the posterior-lateral wall of the LV. The number of cases in which the PLV is absent is far greater in our study than in a similar study using levo-phase coronary angiography by Gilard *et al*[12] or in the anatomical studies on human cadavers by Randhawa *et al*[16] and by Noheria *et al*[17]. We did not count small veins (unsuited for CRT LV lead placement) in our study. Veins with a diameter of > 2 mm measured 2cms distal to its ostium were considered favourable. The larger number of cases with no PLV seen in our study, is explained when this is considered. When a PLV was present, it was generally straight with 62% having no bends. The take-off angle was generally favourable, with an unfavourable take-off seen in only 7% patients.

Non availability of a suitable branch draining the lateral or posterior LV wall is an indication for epicardial lead placement by thoracotomy. In our study, we were unable to visualize an adequate vein in 13/164 cases, although the number of cases in which it is truly absent may be lower.

We evaluated only 2 levo-phase views of left coronary angiograms in our study. Use of more views may better identify the venous anatomy. We did not study the venous tree in right coronary angiograms. Although this is not required in most cases, our study shows that visualization from left injections is poor when circumflex territory is not perfused by the left coronary artery. The technique increases total quantity of dye, and radiation during coronary angiogram, and this may be significant in very sick patients in poor general condition. We excluded such patients from our study.

We did not compare our results with retrograde occlusive venography because it may increase the contrast and radiation dose. We also did not use a hyperaemic agent (*e.g.*, nitroglycerine or adenosine) to increase coronary flow and resultant venous return in CS as used in some studies because it might cause hypotension and/or bradycardia in some patients. In addition, adenosine use may not be feasible in patients with bronchial asthma and severe obstructive pulmonary disease.

## CONCLUSION

Levo-phase study of left coronary injection is effective in visualization of the coronary sinus in almost all patients undergoing coronary angiography. Visualization of postero-lateral veins is usually adequate in LAO cranial view, but the veins of interest are not well visualized in patients with occluded left circumflex artery and also in cases with very large right coronary and small left coronary artery. These patients may require levo-phase study of RCA or selective coronary sinus ostium cannulation. But broadly talking, levo-phase study of left coronary angiogram in LAO cranial view may be an useful extension of the standard coronary angiogram protocol, especially in patients with LV dysfunction or LBBB.

## ARTICLE HIGHLIGHTS

### *Research background*

Coronary sinus imaging is gaining importance due to improvement in electrophysiology techniques and wide spread use of left ventricular lead as a part of Cardiac resynchronization therapy.

### *Research motivation*

Although standard technique is retrograde venogram, it has its own challenges.

### *Research objectives*

To evaluate the feasibility of levophase of routine coronary angiography for studying coronary anatomy.

### *Research methods*

We conducted a prospective observational in patients undergoing routine coronary angiography. In two angiographic views (left anterior oblique & right anterior oblique with cranial angulation), we evaluated the levophase for coronary sinus anatomy including ostial uptake, size, branches and angulation.

### *Research results*

The levophase coronary angiography achieved good visibility in almost all patients. Most patients had a tubular coronary sinus ostia with size < 10 mm. Sharp take off between ostia and body as well tortuosity were seen only in a minority.

### *Research conclusions*

Levophase coronary angiogram evaluation for coronary sinus anatomy is safe and highly effective.

### *Research perspectives*

Large randomized studies are need to further substantiate the results.

## FOOTNOTES

**Author contributions:** All authors contributed equally regarding the conceptualization of project, data acquisition, data analysis, literature review and manuscript writing.

**Institutional review board statement:** The study was approved by institutional ethics committee.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior

to study enrollment.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**Data sharing statement:** The data is available with corresponding author and can be made available on request.

**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.

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