# The effect of prophylactic carvedilol on subclinical left ventricular dysfunction after 1 cycle FAC chemotherapy in breast cancer patients

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ABSTRACT

*Background:* Despite its efficacy, FAC regimen may cause fatal cardiotoxicity. Carvedilol may also exert additional antioxidant effects. This study aimed to assess the effect of carvedilol in preventing decline of left ventricular function in breast cancer patients receiving FAC regimen chemotherapy.
*Methods:* The study was a quasi-experimental study. The study subjects were consisted of breast cancer patients currently receiving post-first cycle FAC chemotherapy regimen in period of March – May 2019. The study subjects were divided into 2 groups: control and intervention group. In intervention groups, the patients consumed up titrated carvedilol with initial dose of $2 \times 6.25$ mg daily, follow-up echocardiography was performed for the patients in order to assess GLS score of left ventricle.
*Result:* Eighty patients were enrolled to the study, with each group consisted of 40 patients. Patient baseline characteristics were not significantly different between both groups. Left ventricular function was assessed using speckle tracking echocardiography and assessing the change of GLS score. Decrease of GLS score was higher in the intervention group compared to the control group, although the decrease was not statistically significant ($0.767 \pm 0.355$ vs. $0.897 \pm 0.526$; p = 0.838). Percentage wise, similar findings were reported, albeit no significant ($3.34 \pm 1.65$ vs. 3.46 vs. 2.58; p = 0.968).
*Conclusions:* Carvedilol was not able to prevent the decline of subclinical left ventricular function after such chemotherapy cycle. However, it maybe more likely that the benefits appear in patients whose given larger cumulative dose of anthracycline and have multiple risk factors.

## 1. Introduction

Global incidence of cancers are increasing. According to Global Cancer Incidence, Mortality, and Prevalence (GLOBOCAN) study, there were estimated 18.1 million new cancer cases. Breast cancer is one of the most frequently occurring cancer on women, approximately occurring in 24.2% of cancer cases worldwide. Breast cancers are the second most commonly found malignancy cases in women before cervical cancer in Indonesia, with incidence rate reaching 40 cases/100,000 women. The incidence rate has increased, compared with previous incidence rate in 2002 of 26 cases/100,000 women [1,2]. Numerous treatment options for breast cancer have appeared, namely with systemic chemotherapy, with one of the most frequently given regimen is 5-fluorouracil, Adriamycin, and cyclophosphamide (FAC). FAC regimen, approximately given in 80–90% of breast cancer patients in Indonesia, is commonly used as the first line chemotherapy in breast cancer patients. The regimen is given in 6–8 cycles in order to achieve therapeutic effects with acceptable adverse effects. FAC is known as chemotherapy drug that has the best efficacy for solid cell cancer and hematologic cancer. Its cardiotoxicity effects depends on cumulative doses. The regimen is efficacious in reducing rate of progression and size of the lesion [3].

Despite its efficacy, FAC regimen may cause fatal cardiotoxicity. Chemotherapy-associated cardiotoxicity was reported as high as 5.1 – 48% in FAC regimens with cumulative dose-responsive incidence. The morbidity and mortality rates were even higher in patients with previous cardiological problems [4,5]. In a single center study in Jakarta, there were about 36.6% of patients undergoing the regimen whom had suffered from cardiotoxicity [6]. Type I (or irreversible) cardiotoxicity may occur in FAC usage, mainly caused by anthracycline in the regimen, with up to 5 times the risk of left ventricular failure compared to other regimens without anthracycline [7,8].

The proposed mechanism of anthracycline-induced cardiotoxicity was suggested to be an accumulation of free radicals; increase of pro-inflammatory cytokines; inhibition of tyrosine kinase enzymes; damaging the DNA of myocytes; and titin degradation. Damage and/or necrosis may be widespread in the cardiac tissue. Decreased left ventricular function was noted in doses as low as 60 – 98 mg/m$^2$ [9,10]. As such, prophylactic treatments were administered in patients receiving FAC chemotherapy regimen, such as beta-blockers, angiotensin-converting enzyme inhibitors, and statins [11,12].

Carvedilol is a third-generation non-selective beta blockers. The drug works by non-selective inhibition of beta-1 and beta-2 receptors, with additional alpha-1 receptor inhibition, causing peripheral vasodilation. Carvedilol, compared to other non-selective beta blockers, has higher efficacy compared to similar drugs. Carvedilol may also exert additional antioxidant effects by inhibiting lipid peroxidase release and maintaining the physiological concentration of natural antioxidants [13,14]. Carvedilol can increase other chemotherapy drug concentration such as afatinib, which often considered as alternative chemotherapy drug if possible. When carvedilol is combined with anthracycline, drug-drug interaction involving QT-prolongation can occur. Therefore appropriate electrocardiographic (ECG) and electrolyte monitoring are needed [14].

To the knowledge of the author, administration of beta-blockers have yet to be used in guidelines in prophylaxis of left-ventricular function decline in breast cancer patients receiving FAC chemotherapy regimen. This study aimed to assess the effect of carvedilol in preventing decline of left ventricular function, assessed by global longitudinal strain (GLS) in breast cancer patients receiving FAC regimen chemotherapy.

## 2. Materials and methods

This was a quasi-experimental study. The study design was chosen due to unparalleled/non-equivalent data collection between control and intervention group, so randomized controlled trial cannot be conducted. The study subjects were collected from Dr. Hasan Sadikin General Hospital Bandung, consisted of breast cancer patients currently receiving FAC chemotherapy regimen in period of March – May 2019. The study subjects were further specified into breast cancer patients with post-first cycle with FAC chemotherapy regimen. The inclusion criteria was as following: Female patients diagnosed with breast cancer at any stage; older than 19 years old; received FAC chemotherapy regiment (as an adjuvant or neoadjuvant therapy); and sinus heart rhythm. The pre-chemotherapy exclusion criteria was as following: diagnosed with acute or chronic heart failure; poor echocardiography window; history of valvular heart disease or congenital heart disease; systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg; PR interval $\geq$ 240 ms; second or third degree AV block; history of bronchial asthma, chronic obstructive pulmonary disease (COPD); history of Adriamycin administration with dose of 50 mg/m$^2$ or more; and previous medical history of cardioprotective drugs (such as ACE-inhibitors, statins, or dexrazoxane). The post-chemotherapy (after single cycle) exclusion criteria were as following: history of acute coronary syndrome (ACS), emergency hypertension, hypersensitivity to carvedilol, and/or did not attend evaluation in 3 weeks after first FAC chemotherapy regimen. Sample size was calculated using unpaired numerical comparison formula. The minimum sample size in this study were 32 patients for each group.

The study subjects were divided into 2 groups: control group (not receiving carvedilol) and intervention group (receiving carvedilol). Data from the control group was collected from *Registri Kardiomiopati Kardiotoksisitas pada Penderita Kanker Payudara Pascakemoterapi* from patients visiting the Oncological Surgery clinic in Dr. Hasan Sadikin General Hospital Bandung. Data from the intervention group was performed twice, before and after carvedilol therapy consecutively in subjects that had fulfilled the criteria for the study. Independent variables were administration of carvedilol and dependent variables were GLS changes. Transthoracic 2D echocardiography (GE Medical System, Horten, Norway with a 3.5-MHz multifrequency transducer) was performed on both groups. Subclinical decline of left ventricular function was defined as change of GLS score after and before one cycle of chemotherapy regimen without signs of heart failure. The GLS score was assessed using Speckle tracking echocardiography method. The echocardiography results were analysed by two independent cardiologists subspecializing in echocardiography. Intravariability and intra-observer reliability were assessed.

The most valued parameter of left ventricular systolic function is left ventricle ejection fraction (LVEF). The current guidelines regarding cardiotoxicity are based on LVEF and defined as a reduction of LVEF > 10%, to a value of <53%. The current LVEF assessment has several important limitations: (i) geometrical assumptions; (ii) foreshortening; and (iii) did not account for all left ventricular walls. However, Global longitudinal strain (GLS) is superior to LVEF due to declined regional function in early stage of cardiotoxicity. The declined regional function can still be compensated by other myocardial regions, so the LVEF still tends to be normal in the initial stages. Decreased ejection fraction occurs at advanced stage. GLS examination using STE technique has higher sensitivity than LVEF due to its average assessment of the function of several segments, whereas LVEF measure assessment on one segment [15]. The patients in both groups had received intravenous FAC chemotherapy regimen, consisted of 5-fluorouracil 600 mg/m$^2$, Adriamycin 60 mg/m$^2$, and cyclophosphamide 600 mg/m$^2$. Signed informed consent from the patients were received before enrolment to the study. Various doses of carvedilol were used in previous studies, and this is still a controversial issue. The recommended dosage in the "MOCHA" (Multicenter Oral Carvedilol Heart Failure Assessment) study is 12.5 to 50 mg. Most previous heart failure studies regarding carvedilol, due to issue of patient tolerance, recommended an initial dose of carvedilol at 3.125 mg twice daily. However, in other studies, carvedilol is used once or twice daily, and it shows that even low-dose carvedilol at 6.25 mg has a potential antioxidant effect to prevent cardiotoxicity [13,14]. In intervention groups, the patients consumed carvedilol with initial dose of 2 × 6.25 mg daily, 1 week before the administration of FAC chemotherapy regimen. Three weeks after the chemotherapy, follow-up *trans*-thoracic echocardiography was performed for the patients in order to assess GLS score of left ventricle. Signed and written informed consent had been received from the patients prior to the study.

Statistical analysis of the study was performed using descriptive statistics and normality tests of the variables, using Shapiro-Wilks tests (sample size of less than 50). Normally distributed data would be presented in means and standard deviation; non-normally distributed data would be presented in median and range. Unpaired t-test was performed to compare the GLS scores between control and intervention group after the a cycle of FAC chemotherapy regimen. Mann-Whitney test was performed as an alternative test. Linear regression statistics was performed in order to control for the confounding variables. The data was analyzed using R software version 3.2.0 for Windows. The data was deemed significant with p value of $\leq$ 0.05.

## 3. Results

Eighty patients were enrolled to the study, with each group consisted of 40 patients. Patient characteristics (age, body mass

index, risk factors of cardiotoxicity, and pre-chemotherapy GLS) were not significantly different between both groups (Table 1). Mean age of intervention group was 48 ± 8 years; mean age of control group was 48 ± 8 years; both groups were not significantly different in age (p = 0.930). Mean GLS score before chemotherapy was 20.16 ± 2.23% and 19.73 ± 1.82% in intervention and control groups, respectively. The GLS score between both groups was not significantly different (p = 0.350). There were 52% and 57.5% patients with obesity in intervention and control groups, respectively; no significant difference in obesity rates were found in the study (p = 0.843). There were 37.5% and 27.5% patients with hypertension in intervention and control groups, respectively; no significant difference between both groups in hypertension rates were noted (p = 0.340). There were 2.5% and 5% patients with diabetes in the intervention and control group, respectively; without significant differences between both groups (p = 1.000). Previous medical history of ACS in the intervention group and control group were 5%. None of the patients had history of smoking.

Left ventricular function was assessed using speckle tracking echocardiography and assessing the change of GLS score. Decrease of GLS score was higher in the intervention group compared to the control group (Table 2), although the decrease was not statistically significant (0.767 ± 0.355 vs. 0.897 ± 0.526; p = 0.838). Percentage wise, similar findings were reported, albeit no significant (3.34 ± 1.65 vs. 3.46 vs. 2.58; p = 0.968). Cut-off point using GLS score of 19% had resulted in a significant difference in both groups (Table 3). Previous study by Sawaya, et al reported that in addition to decreased GLS by ≥ 10%, the absolute value of GLS to < 19% was a predictor for cardiotoxicity within 1 year after chemotherapy regimens containing anthracycline. A decrease in GLS to an absolute value of < 19% has a sensitivity value of 74%, a specificity of 73%, a positive prediction of 53%, and a negative prediction of 87% in predicting cardiotoxicity at 1 year post-chemotherapy [16]. In the control group, there were 8 patients (33.3%) with GLS score ≥ 19 and 16 patients (66.7%) with GLS score < 19. In the intervention group, there were 17 patients (60.7%) with GLS

**Table 1**
Baseline characteristics of the study subjects.

| Baseline Characteristics | Groups | | P value |
| --- | --- | --- | --- |
| | Intervention n = 40 | Control n = 40 | |
| Age (years), mean ± SD | 48 ± 10 | 48 ± 8 | 0,930[a] |
| Body mass index, n (%) | | | |
| 18,5–22,9 kg/m$^2$ | 10 (25%) | 10 (25%) | 0,843[b] |
| 23,0–24,9 kg/m$^2$ | 9 (22%) | 7 (17,5%) | |
| 25,0–29,9 kg/m$^2$ | 21 (52%) | 23 (57,5%) | |
| Risk factors, n (%) | | | |
| Hypertension | 15 (37,5%) | 11 (27,5%) | 0,340[b] |
| Diabetes | 1 (2,5) | 2 (5%) | 1,000[c] |
| Family history of ACS | 2 (5%) | 2 (5%) | 1,000[c] |
| Smoking | 0 (0%) | 0 (0%) | 1,000[c] |
| Baseline GLS score, mean ± SD | 20,16 ± 2,23 | 19,73 ± 1,82 | 0,350[a] |

Analyzed using t-test[a], chi-square[b], and Fisher exact test[c].

**Table 2**
Changes in GLS score in intervention and control groups.

| Variables | Groups | | P value |
| --- | --- | --- | --- |
| | Intervention Mean ± SE | Control Mean ± SE | |
| Change in GLS score | 0,767 ± 0,355 | 0,897 ± 0,526 | 0,838 |
| Change in GLS score (%) | 3,34 ± 1,65 | 3,46 ± 2,58 | 0,968 |

*Analysis using unpaired *t*-test.

**Table 3**
Subjects with GLS score change (cutoff point 19%) in intervention and control groups.

| Variables | Intervention | Control | P value |
| --- | --- | --- | --- |
| Post-chemotherapy GLS score ≥ 19 | 17 (60,7%) | 8 (33,3%) | 0.049 |
| Post-chemotherapy GLS score < 19 | 11 (39,3%) | 16 (66,7%) | |
| Total | 28 (100%) | 24 (100%) | |

OR 3.091 ; CI 95% 0.99–9.65.

score ≥ 19 and 11 patients (39.3%) with GLS score < 19. Significant differences were noted between both groups with the cutoff point. Therefore, it may be concluded that carvedilol administration may significantly (p = 0.049) decrease the rate of GLS score decline with the cutoff point of 19%. At the end of the study, no adverse effects of carvedilol such as symptomatic hypotension, dizziness, nausea etc are observed in intervention group.

## 4. Discussion

Chemotherapy using FAC regimen remains one of the first-line therapy in breast cancer treatment, given either as an adjuvant or neoadjuvant treatment [3,17,18]. Decrease of mortality in breast cancer patients may, consequently, increase the risk of mortality due to cardiotoxicity, associated with anthracycline-containing regiments. The incidence of cardiotoxicity in breast cancer patients had a dose–response relationship, with cumulative doses of 400 mg/m$^2$ associated with incidence rate of 3 – 5% and with cumulative doses of 700 mg/m$^2$, the incidence increased up to 18 – 48% [4,19,20]. Myocardial deformation associated with anthracycline usage may be assessed using speckle tracking echocardiography, particularly the function of left ventricle, even on lower doses (≤240 mg/m$^2$) [21]. Similar results were found regarding the decrease of GLS score in the study due to FAC regimen, although the decrease in the present study was smaller compared to other study. Motoki et al. had reported > 1% decrease of GLS score in patients receiving anthracycline-containing regimens. Smaller decrease of GLS score in the present study may related to smaller anthracycline dose used in the FAC regimen (60 mg/m$^2$). Biltagi et al. and Ganame et al. had reported that GLS decrease may occur as early after one cycle of chemotherapy with anthracycline-containing regimen, occurring with rates of 2.4% and 4% on the respective studies. Another factor on larger and much earlier decrease of GLS score in both studies, however, may be related to the study subjects; both groups had enrolled younger participants (<15 years old) with leukemia [22,23].

Subclinical left ventricular function decline in this study were reduced with carvedilol administration. The difference between the control group, however, was not significant. Higher doses of carvedilol can provide better protection against cardiotoxicity. Prevention of decreased GLS in the intervention group was not significant. This result was probably due to the small cumulative dose of anthracycline, minimum accompanying risk factors, and the relatively small dose of carvedilol. The study results presented contradicts other study results regarding carvedilol administration on decline of left ventricular function. Kalay et al. had used carvedilol as a prophylaxis in preventing decline of left ventricular ejection fraction. The study had found significantly lower decrease (p = 0.001) of left ventricular ejection fraction after 6 months post-chemotherapy according to the assessment using echocardiography [24]. Zamani et al. had found that administration of carvedilol with dose of 1 × 1.25 mg daily had successfully prevented decline of systolic and diastolic function after receiving anthracycline-containing chemotherapy regimen in 14.7% and 27.8% patients respectively [25]. Abousa et al. had reported significant effects on decrease left ventricular ejection fraction after

6 months receiving anthracycline-containing chemotherapy, with scores of 62.0 ± 4.6% to 58.2 ± 6.6% (p = 0.002) [26]. The aforementioned studies had shown that variety of carvedilol doses (6.25 mg, 12.5 mg, and 25 mg daily) may be effective in preventing decrease of left ventricular function 6 months after receiving anthracycline-containing chemotherapy regimen.

The rationale of using cut-off GLS score was due to earlier occurrence of GLS score decrease compared to left ventricular function during anthracycline-containing chemotherapy regimen. The score has an adequate value in predicting mortality and morbidity in such groups of patients, with both relative and absolute decrease of the score were predictive of cardiotoxicity in such regimens. Sawaya et al. had reported that decrease of GLS ≥ 10% from baseline measurement before the chemotherapy were strongly associated with cardiotoxicity after 6 months of chemotherapy; with the sensitivity, specificity, positive predictive value, and negative predictive value of 78%, 79%, 50%, and 93% respectively [16]. In the present study, 2 subjects were found with decrease of GLS ≥ 10% on control groups while in the intervention group, no patients had decrease of GLS ≥ 10%. In contrast with result from this study, previous studies reported that patients with GLS score ≥ 19 with multiple risk factors and chemotherapy with larger cumulative dose is known to have benefit from carvedilol administration.

## 5. Conclusion

Carvedilol was not able to demonstrate prevention of the decline of subclinical left ventricular function (subclinical) after such chemotherapy cycle. However, it maybe more likely that the benefits appear in patients whose given larger cumulative dose of anthracycline and have multiple risk factors. Further study with larger sample size with randomization are required to asses the efficacy of carvedilol in preventing cardiotoxicity. To our knowledge, this was the first study that were conducted in South-East asia population and using STE technique to assessed GLS.

## CRediT authorship contribution statement

**Januar W. Martha:** Conceptualization, Methodology, Investigation, Writing - original draft, Visualization, Data curation, Software, Writing - review & editing. **Dery A. Soedarsono:** Conceptualization, Methodology, Visualization, Writing - original draft, Investigation, Writing - review & editing. **Mohammad Iqbal:** Conceptualization, Methodology, Investigation, Writing - review & editing. **Astri Astuti:** Conceptualization, Methodology, Visualization, Writing - original draft, Investigation, Writing - review & editing. **Erwan Martanto:** Conceptualization, Methodology, Investigation, Writing - review & editing. **M. Rizki Akbar:** Supervision, Validation, Writing - review & editing. **I. Gede Sumantra:** Visualization, Software, Writing - review & editing.

## Declaration of Competing Interest

The authors declare no conflicts of interest.

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