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# Cholesterol Drugs Improve Breast Cancer Prognosis in Women with Diabetes Mellitus

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## Abstract

**Study objective:** To evaluate the impact of Cholesterol management on breast cancer recurrence and survival (CHOLBRES) in diabetic women with breast cancer.

**Design:** Cholbres study included all incident breast cancer cases with pre-existing diabetes mellitus diagnosed with cancer between 01/01/2003-12/31/2007. Clinical characteristics, outcomes, and pharmacotherapy were abstracted from medical records or hospital-developed databases. The follow-up, with a median of 31 months, began at breast cancer diagnosis and ended at first recurrence, death, or date of last contact.

**Patients:** All diabetes mellitus women with incident breast cancer were identified (n=269); of these 208 met the inclusion criteria and were used for analysis.

**Methods:** The association between self-reported cholesterol-lowering medications and breast cancer outcomes was evaluated with multivariate Cox proportional hazards models.

**Main results:** Women taking cholesterol-lowering drugs were found to have fewer recurrences (HR=0.54, 95% CI: 0.24 to 1.18, p=0.12), improved overall survival (HR=0.48, 95% CI: 0.27 to 0.86, p=0.01), and better disease-free survival (HR=0.65, 95% CI: 0.35 to 1.21, p=0.17) than women who did not take any cholesterol-lowering medication. Cholesterol management employing statins as a mono-therapy was associated with better overall survival (HR=0.42, 95% CI: 0.21 to 0.84, p=0.08) and slightly improved disease-free survival (HR=0.49, 95% CI: 0.23 to 1.04, p=0.24).

**Conclusion:** Our findings demonstrate that cholesterol-lowering therapy significantly improves breast cancer prognosis in women with diabetes mellitus. Though larger studies are needed to confirm this potential added benefit, efforts to ensure that women with breast cancer and diabetes receive guideline-appropriate cholesterol-lowering medications should have significant impact on breast cancer outcomes.

**Keywords:** Cholesterol; Statins; Breast cancer; Prognosis; Diabetes

## Introduction

Diabetes mellitus's hallmarks, insulin resistance, dyslipidemia and inflammation, are all associated with increased breast cancer risk and poorer prognosis in diabetic women [1-11]. According to American Diabetes Association guidelines, statins (3-hydroxy-3-methylglutaryl Coenzyme A reductase inhibitors) should be initiated regardless of lipid levels in 98.5% of diabetes mellitus patients, however, over one-third of eligible patients do not receive a prescription for statins in US clinical practices [12]. Statins exhibit pleiotropic effects that can affect carcinogenesis and cancer outcomes through several pathways, including inflammation, immune response, cell migration, and apoptosis [13-17]. While dyslipidemia management recommended by the American Diabetes Association targets prevention of cardiovascular disease events [18], addition of statins may also improve cancer outcomes in diabetic women with breast cancer. Currently, the association between statin use and breast cancer risk is unclear, with some data suggesting that statin use may reduce the risk of breast cancer recurrence [19-21]. Since statin therapy can positively influence several key risk factors related to breast cancer prognosis that are more prevalent among women with diabetes mellitus, we hypothesize that diabetic women will derive greater breast cancer-outcome related benefits from statin therapy compared to the general population of breast cancer patients [20,22-24]. This study examined whether cholesterol-lowering therapy improves breast cancer outcomes in a hospital-based retrospective cohort of women with pre-existing diabetes mellitus.

## Methods

### Patient population and data collection

This study was approved by the Institutional Review Board of Roswell Park Cancer Institute and State University of New York at Buffalo. All women with incident breast cancer treated at RPCI with a diagnosis date from 01/01/2003-12/31/2007 were reviewed (n=2,149). Eligible cases were those >18 years of age with pre-existing diabetes and no previous history of cancer. Presence of diabetes was determined by cancer-center coding of the International Classification of Diseases, Ninth Revision (ICD-9), and by self-reported pharmacotherapy and/

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or medical history. Based on the ICD-9 codes, 170 cases with diabetes were identified. Of the remaining 1,979 cases, chart review identified 99 additional diabetes mellitus patients, for a total of 269 cases. Of these, 61 were excluded due to: male gender (n=3), unknown or type 1 diabetes (n=19), gestational diabetes or diabetes mellitus diagnosed post- breast cancer diagnosis (n=9), unclear date of breast cancer diagnosis (n=5), personal history of prior breast cancer (n=8), and incomplete data (n=16). A total of 208 individuals were included in the final analyses.

Date of breast cancer diagnosis, age, race, body mass index (BMI), patient- and tumor-related clinical parameters were obtained from a hospital-developed prospective database of the Roswell Park Cancer Institute Breast Program; medical history and pharmacotherapy at diagnosis were documented by individual chart review. Data collection accuracy was ensured by comparison of at least two independent review reports for each patient. Any discrepancies were resolved on a case-by-case basis by a third reviewer in consultation with ACC. The

| | | | | | Type of Cholesterol-lowering Medication | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Non-Users** | | **Users** | | ***P*[1]** | **Non-statin Only** | | **Statin Only** | | **Non-statin + Statin** | | ***P*[2]** |
| | No. | % | No. | % | | No. | % | No. | % | No. | % | |
| All Patients | 69 (33.2) | | 139 (66.8) | | | 26 | 18.7 | 75 | 54.0 | 38 | 27.3 | |
| Age, years | | | | | | | | | | | | |
| <50 | 14 | 20.3 | 13 | 9.4 | 0.09 | 3 | 23.1 | 7 | 53.9 | 3 | 23.1 | 0.97 |
| 50 to 59 | 21 | 30.4 | 37 | 26.6 | | 5 | 13.5 | 20 | 54.1 | 12 | 32.4 | |
| 60 to 69 | 19 | 27.5 | 44 | 31.7 | | 9 | 20.5 | 23 | 52.3 | 12 | 27.3 | |
| ≥ 70 | 15 | 21.7 | 45 | 32.4 | | 9 | 20.0 | 25 | 55.6 | 11 | 24.4 | |
| Race/ethnicity | | | | | | | | | | | | |
| White | 49 | 71.0 | 103 | 74.1 | 0.78 | 23 | 22.3 | 50 | 48.5 | 30 | 29.1 | 0.20 |
| African American | 18 | 26.1 | 33 | 23.7 | | 3 | 9.1 | 23 | 69.7 | 7 | 21.2 | |
| Other | 2 | 2.9 | 3 | 2.2 | | 0 | 0 | 2 | 66.7 | 1 | 33.3 | |
| Menopausal Status | | | | | | | | | | | | |
| Premenopausal | 14 | 20.3 | 12 | 8.6 | 0.04 | 2 | 16.7 | 7 | 58.3 | 3 | 25.0 | 0.02 |
| Postmenopausal | 53 | 76.8 | 125 | 89.9 | | 23 | 18.4 | 67 | 53.6 | 35 | 28.0 | |
| Unknown | 2 | 2.9 | 2 | 1.4 | | 1 | 50.0 | 1 | 50.0 | 0 | 0 | |
| BMI, Kg/m$^2$ | | | | | | | | | | | | |
| <25 | 7 | 10.1 | 6 | 4.3 | 0.39 | 1 | 16.7 | 4 | 66.7 | 1 | 16.7 | 0.90 |
| 25 to <30 | 13 | 18.8 | 26 | 18.7 | | 2 | 7.7 | 16 | 61.5 | 8 | 30.8 | |
| 30 to <40 | 23 | 33.3 | 61 | 43.9 | | 12 | 19.7 | 32 | 52.5 | 17 | 27.9 | |
| 40+ | 16 | 23.2 | 28 | 20.1 | | 7 | 25.0 | 13 | 46.4 | 8 | 28.6 | |
| Unknown | 10 | 14.5 | 18 | 13.0 | | 4 | 22.2 | 10 | 55.6 | 4 | 22.2 | |
| Tumor Stage | | | | | | | | | | | | |
| 0 | 3 | 4.4 | 19 | 13.7 | 0.08 | 0 | 0.0 | 13 | 68.4 | 6 | 31.6 | 0.21 |
| I | 27 | 39.1 | 54 | 38.9 | | 12 | 22.2 | 25 | 46.3 | 17 | 31.5 | |
| II | 22 | 31.9 | 33 | 23.7 | | 6 | 18.2 | 19 | 57.6 | 8 | 24.2 | |
| III | 13 | 18.8 | 20 | 14.4 | | 3 | 15.0 | 13 | 65.0 | 4 | 20.0 | |
| IV | 2 | 2.9 | 12 | 8.6 | | 4 | 33.3 | 5 | 41.7 | 3 | 25.0 | |
| X (Unknown) | 2 | 2.9 | 1 | 0.7 | | 1 | 100.0 | 0 | 0 | 0 | 0 | |
| Tumor Grade | | | | | | | | | | | | |
| 1 | 10 | 14.5 | 12 | 8.6 | 0.61 | 0 | 0 | 6 | 50.0 | 6 | 50.0 | 0.19 |
| 2 | 29 | 42.0 | 59 | 42.5 | | 14 | 23.7 | 27 | 45.8 | 18 | 30.5 | |
| 3 | 21 | 30.4 | 46 | 33.1 | | 7 | 15.2 | 29 | 63.0 | 10 | 21.7 | |
| Unknown | 9 | 13.0 | 22 | 15.8 | | 5 | 22.7 | 13 | 59.1 | 4 | 18.2 | |
| Tumor Size, cm | | | | | | | | | | | | |
| 0–2.0 | 37 | 53.6 | 81 | 58.3 | 0.79 | 19 | 23.5 | 40 | 49.4 | 22 | 27.2 | 0.38 |
| >2.0 to 5.0 | 14 | 20.3 | 24 | 17.3 | | 1 | 4.2 | 16 | 66.7 | 7 | 29.2 | |
| > 5 | 4 | 5.8 | 5 | 3.6 | | 1 | 20.0 | 2 | 40.0 | 2 | 40.0 | |
| Unknown | 14 | 20.3 | 29 | 20.9 | | 5 | 17.2 | 17 | 58.6 | 7 | 24.1 | |
| ER Status | | | | | | | | | | | | |
| ER+ | 51 | 73.9 | 90 | 64.8 | 0.12 | 23 | 25.6 | 46 | 51.1 | 21 | 23.3 | 0.03 |
| ER- | 15 | 21.7 | 30 | 21.6 | | 3 | 10.0 | 16 | 53.3 | 11 | 36.7 | |
| Unknown | 3 | 4.4 | 19 | 13.7 | | 0 | 0.0 | 13 | 68.4 | 6 | 31.6 | |
| ACE-27 Comorbidity Scores | | | | | | | | | | | | |
| Mild | 10 | 14.5 | 11 | 7.9 | 0.23 | 2 | 18.2 | 5 | 45.5 | 4 | 36.4 | 0.57 |
| Moderate | 13 | 18.8 | 36 | 25.9 | | 4 | 11.1 | 23 | 63.9 | 9 | 25.0 | |
| Severe | 46 | 66.7 | 92 | 66.2 | | 20 | 21.7 | 47 | 51.1 | 25 | 27.2 | |

**Abbreviations:** BMI, body mass index.[1]P-value associated with Fisher's exact test comparing women taking any cholesterol management medication versus women who do not take any. [2]P-value associated with Fisher's exact test comparing 3 groups of medication users: non-statin only, statin only, and both statins and non-statins.

**Table 1:** Use of cholesterol therapy according to patient- and tumor-related variables (n=208).

| | Breast Cancer Recurrence[1] | | | | | | Overall Mortality | | | | | | Disease Free Survival | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Age-adjusted | | Multivariate[2] | | | | Age-adjusted | | Multivariate[2] | | | | Age-adjusted | | Multivariate[2] | |
| **Cholesterol Management** | **No.** | **No of Events** | **HR** | **95% CI** | **HR** | **95% CI** | **No** | **No of Events** | **HR** | **95% CI** | **HR** | **95% CI** | **No** | **No of Events** | **HR** | **95% CI** | **HR** | **95% CI** |
| No Medication (group 1) | 64 | 13 | Ref | - | Ref | | 69 | 22 | Ref | - | Ref | | 64 | 19 | Ref | | Ref | |
| Non-statin only (group 2) | 26 | 5 | 1.29 | 0.44 to 3.78 | 0.71 | 0.24 to 2.12 | 26 | 8 | 0.50 | 0.21 to 1.18 | 0.50 | 0.21 to 1.18 | 26 | 11 | 1.48 | 0.67 to 3.24 | 0.96 | 0.43 to 2.16 |
| Statin only (group 3) | 71 | 8 | 0.66 | 0.27 to 1.63 | 0.51 | 0.20 to 1.32 | 75 | 17 | 0.42 | 0.21 to 0.84 | 0.42 | 0.21 to 0.84 | 71 | 14 | 0.59 | 0.29 to 1.22 | 0.49 | 0.23 to 1.04 |
| Both Non-statin & Statin (group 4) | 36 | 2 | 0.33 | 0.07 to 1.47 | 0.38 | 0.08 to 1.81 | 38 | 7 | 0.61 | 0.26 to 1.45 | 0.61 | 0.26 to 1.45 | 36 | 6 | 0.59 | 0.23 to 1.49 | 0.73 | 0.28 to 1.88 |
| *P* | | | 0.31 | | 0.43 | | | | 0.08 | | 0.08 | | | | 0.09 | | 0.24 | |
| Any cholesterol medication (groups 2+3+4 vs. 1) | 133 | 15 | 0.67 | 0.31 to 1.45 | 0.54 | 0.24 to 1.18 | 139 | 32 | 0.59 | 0.34 to 1.03 | 0.48 | 0.27 to 0.86 | 133 | 31 | 0.74 | 0.40 to 1.34 | 0.65 | 0.35 to 1.21 |
| *P* | | | 0.30 | | 0.12 | | | | 0.06 | | 0.01 | | | | 0.32 | | 0.17 | |

**Abbreviations:** HR, hazard ratio; 95% CI, 95% confidence interval.1Disease recurrence and disease free survival analysis limited to N=197 women, excluding 11 women who were never disease free. 2All multivariate analyses are adjusted for cancer stage (0, 1 to IIIa, IIIB+, unknown), ER status (positive, negative, unknown), age at breast cancer diagnosis (continuous variable), race (Caucasian, African American, other), and ACE-27 comorbidity score (1-2, 3).

**Table 2:** Associations of Cholesterol Medicatiom with Breast Cancer Outcomes: Proportional Hazards model.

grade of cogent comorbid ailments at diagnosis was estimated using the Adult Comorbidity Evaluation 27 (ACE-27) score (http://oto2.wustl.edu/clinepi/calc.html) [25].

### Ascertainment of vital status and cancer outcome variables

Information on vital status and breast cancer recurrences were obtained from the National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes Database at Roswell Park Cancer Institute, with ≥ 92% complete follow-up. NCCN-coordinated linking with the National Death Index for all patients who were defined as "lost to follow-up" was completed 12/08/2011. Outcomes of interest were breast cancer recurrence, disease free survival, and overall mortality. Disease-free survival was defined as the time from initial diagnosis to breast cancer recurrence, death from any cause, or end of follow-up. If alive, individuals were followed through their last day of contact or vital status update, whichever was more recent. Follow-up began at diagnosis and ended at first confirmed recurrence and/or death depending on the analysis. Women lost to follow-up were censored at the date of last contact. Events documentation was limited to data collected through to 02/14/2012.

### Statistical analysis

Baseline cohort characteristics in cholesterol therapy users versus non-users and, respectively, users of statins, non-statins, and statin-nonstatin combined regimens were compared using Fisher's exact tests. Kaplan-Meier (KM) log-rank tests were used to evaluate differences in breast cancer outcomes by type of cholesterol medications used. Two sets of analyses were performed for each outcome: 1) comparison of non-users versus users of any cholesterol-lowering pharmacotherapy; and 2) comparison of non-users, non-statin users, statin users, and users of combined statin and nonstatin regimens. Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) for univariate and multivariate analyses examining associations between a defined event and use of statins and/or non-statins. Multivariate models were adjusted for cancer stage, ER status, age-at-diagnosis, race, BMI, and ACE-27 score as *a priori* adjustment factors (Table 1). SAS for Windows, version 9.2 or 9.3 were used for all statistical analyses.

## Results

The mean age at breast cancer diagnosis was 63.0 ± 11.3 years, with 86% of women being postmenopausal; mean BMI was 35.3 ± 8.3 Kg/m$^2$. Unknown ER status was noted in approximately 10% of women and this was attributed to the information not being required to guide treatment. Two-thirds (66.8%) of the study population received cholesterol-lowering medications, with 54.3% receiving statin therapy. Older and postmenopausal women were more likely to receive cholesterol-lowering drugs, although only menopausal status was statistically significant, p=0.04. Cases with unknown ER status (86% stage 0) were more likely to have received a statin alone or in combination, p=0.03 (Table 1). Type of cholesterol-lowering medication did not vary with ACE-27 scores or with any other variable analyzed.

After a median follow-up of 59.7 months (ranging from 3 to 105 months), fewer recurrences (15/133 versus 13/64), overall deaths (32/139 versus 22/69) and disease-free survival events (31/133 versus 19/64) were reported in cholesterol-lowering medication users versus non-users, with a trend towards higher 5-year recurrence-free (0.89 versus 0.78), overall (0.82 versus 0.75), and disease-free survival (0.81 versus 0.71) (Figure 1). In fully adjusted multivariate Cox proportional hazards models, cholesterol-lowering medications were associated with approximately 2-fold reduced mortality (HR=0.48, 95% CI, 0.27 to 0.86, p=0.01) and recurrences (HR=0.54, 95% CI, 0.24 to1.18, p=0.12), and approximately 50% longer disease-free survival (HR=0.65, 95% CI, 0.35 to 1.21, p=0.17) as compared to non-users (Table 2). Statin monotherapy had the most beneficial effect on overall mortality (HR=0.42, 95% CI,0.21 to 0.84, p=0.01) and disease-free survival (HR=0.49, 95% CI,0.23 to 1.04, p=0.06), while addition of non-statins to statin regimens attenuated the benefit of statins alone increasing HR for overall mortality and disease-free survival to HR=0.61 (95% CI, 0.26 to 1.45, p=0.26) and HR=0.73 (95% CI,0.28 to 1.88, p=0.51), respectively.

## Discussion

Our data demonstrates a strong association between use of cholesterol-lowering drugs and improved breast cancer prognosis in type 2 diabetic women, resulting in approximately 2-fold reduced mortality and breast cancer recurrences, and 54% improved disease-free survival. The benefit appeared to be stronger among women

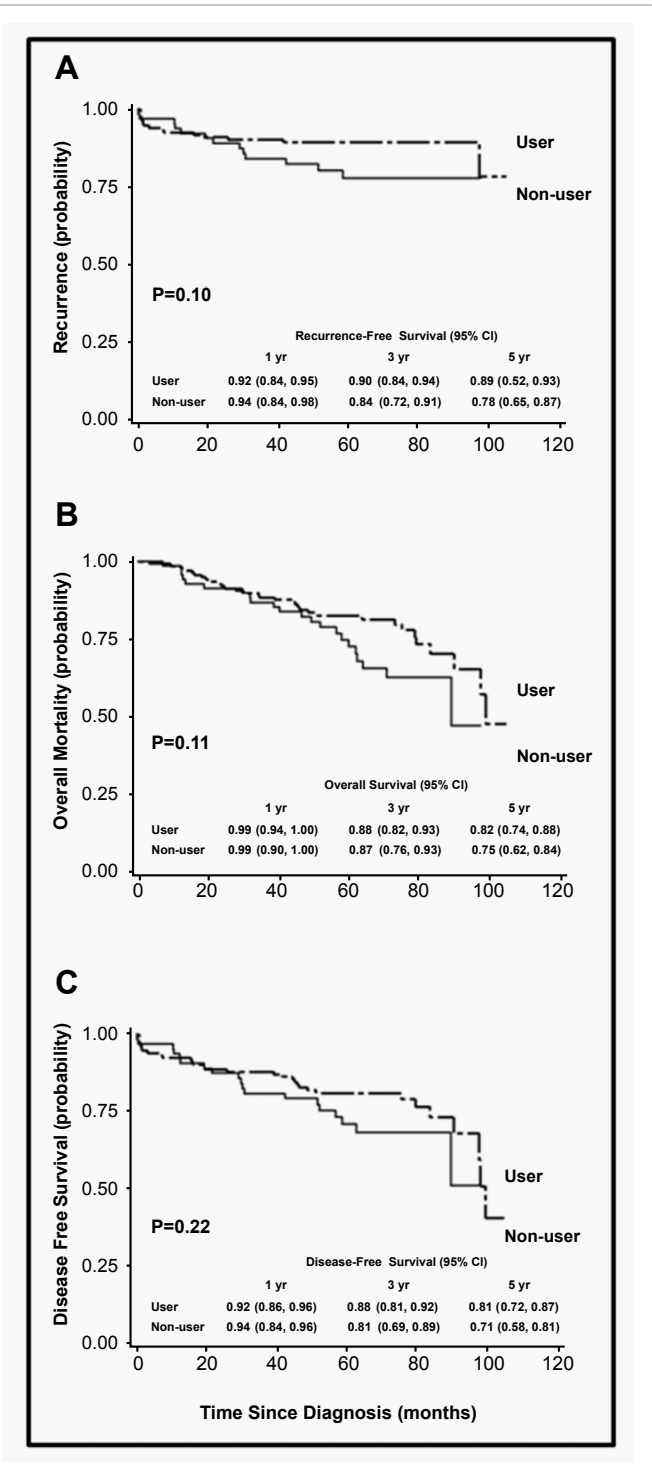


**Figure 1:** Kaplan-Meier plots indicating a trend towards fewer breast cancer recurrences (A), lower overall mortality (B), and better disease free survival (C) in cholesterol-lowering drug users as compared to non-users. Disease recurrence and disease free survival analysis limited to N=197 women, excluding 11 women who were never disease free.

receiving statins alone and support recent findings that statin use may be linked to better breast cancer prognosis [19-21]. Similar to previous observations [23], one-third of our eligible patients were not receiving any form of cholesterol-lowering medication at the time of breast cancer diagnosis.

To date, only a few studies examined the prognostic significance of cholesterol-lowering medications with most providing some evidence for improved breast cancer outcomes [17-19]. The largest population-based study thus far (18,800 women) reported HR estimates similar to those reported in smaller studies [19-21] and found lipophilic statins to be associated with 43% lower 5-year breast cancer recurrence rates (HR= 0.70, 95% CI, 0.53 to 0.92)[17]. Given that cholesterol-lowering drugs users may have more cogent ailments than non-users, the magnitude of protective effects observed among users may be underestimated [25]. Such considerations merit attention as recent studies have associated statin use with increased risk for diabetes mellitus [26-28] and could contribute to underutilization of statins in specific patient populations who are most likely to benefit from statin therapy.

From a mechanistic stand-point, diabetes mellitus hallmarks are also risk factors for breast cancer and are positively impacted by statin pharmacotherapy [9]. Potentially, mevalonate pathway inhibition [29,30], down-regulation of proteins responsible for breast cancer invasiveness [29-32], or prevention of insulin receptor inactivation may each reduce breast cancer recurrence [33,34]. Further evidence is, however, needed to verify whether observed statins benefits occur through any of these mechanisms.

The primary limitation of our study was small sample size, which prevented us from exploring subclasses of cholesterol-lowering medication in relationship with breast cancer outcomes and also precluded us from exploring associations stratified by tumor stage. Larger studies may clarify whether the statin benefits identified by us are a class effect or could potentially differ between lipophilic and hydrophilic members [19,35]. Unfortunately, no studies evaluating statin use and breast cancer prognosis have been able to address this question due to limited sample size [20,21]. Another limitation was that our study could not account for new prescriptions or drug changes occurring post-diagnosis. Such misclassifications are expected to underestimate the magnitude of protective effects.

In summary, this study shows that cholesterol-lowering medications, particularly statins, are significantly associated with improved breast cancer prognosis in women with diabetes mellitus. Although larger prospective studies are needed to confirm this benefit, efforts to assure that women with breast cancer and diabetes mellitus receive guideline-appropriate dyslipidemia management should have a significant positive impact on breast cancer outcomes.

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