Title: Preventing Anthracycline Cardiovascular Toxicity With Statins (PREVENT)
NCT: NCT01988571
Date: 2/1/2018

University of Wisconsin-Madison
Consent to Participate in Research

Study Title: PREVENTING ANTHRACYCLINE CARDIOVASCULAR TOXICITY WITH STATINS (PREVENT)

Lead Researcher: Toby Campbell, MD [redacted]

Where Lead Researcher works: University of Wisconsin Carbone Cancer Center

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. This study is being done to find out if a drug called Atorvastatin can decrease the chance of developing heart problems while receiving chemotherapy. You are being invited to take part in this study because you have breast cancer or lymphoma, are 21 years or older, and will be treated with chemotherapy that may cause heart problems. This study involves approximately four to six visits over two years. The main study procedures are MRIs of your heart, blood samples, tests of your memory and thinking abilities, quality of life questionnaires as well as telephone calls and recording when you take the study drug on a medication diary.

Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family. If you decide not to participate, any relationship you have with the University of Wisconsin-Madison (UW-Madison) or the University of Wisconsin Hospitals and Clinics (UWHC) will not be affected in any way.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to see if Atorvastatin (generic for Lipitor) 40 mg by mouth daily decreases the chance of developing heart problems in patients receiving anthracycline based chemotherapy for breast cancer or lymphoma.

Atorvastatin has been approved by the US Food and Drug Administration (FDA), but it has not been approved to lessen the chance of heart problems related to chemotherapy.

In this study Atorvastatin will be compared to placebo. A placebo is a substance, like a sugar pill, that is not thought to have any effect on your disease or condition. In this study you will either receive the active study medication (Atorvastatin) or placebo, which is not active. Placebos are used in research studies to see if the drug being studied really does have an effect.

This study will also include questions related to your thinking process and quality of life.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?
Approximately 278 people will take part in this study nationally. Approximately 20 people will be enrolled at this institution.

WHAT IS INVOLVED IN THE STUDY?
You will be randomized into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance of being placed in any group.

One group will receive Atorvastatin 40mg by mouth once daily. The other group will receive a Placebo by mouth once daily.

In some instances subjects may receive an initial one-time dose of 80 mg Atorvastatin (two tablets by mouth) or placebo (two tablets by mouth). No increase in anticipated side effects is expected if a one-time dose is taken.

Neither you nor the investigator will know which study drug or placebo you are receiving. This is done so that a fair evaluation of results can be made. This information is available to the researchers if needed in an emergency.

If you take part in this study, you will have the following tests and procedures:

- MRI exams of your heart at baseline, 6 months and 24 months
- If you receive a MUGA or ECHO as part of your routine care to look at your heart function prior to receiving chemotherapy, the study will require that heart function measures from either of those studies be incorporated into the database.
- Blood samples and biomarker blood samples drawn at baseline, 6 months and 24 months
- Memory and Thinking Ability Testing completed at baseline, 6 months and 24 months
- Quality of Life Questionnaires completed at baseline, 6 months, 12 months, 18 months and 24 months
- You will be contacted by telephone at 12 and 18 months to evaluate if you are having any problems taking your study medication.
- Medication diaries will be provided for you to record when you take your study medication. Staff personnel will provide instructions on completing and returning the diaries.

The questionnaires will take about 10 minutes to complete. The Memory and Thinking Ability Testing will take about 10 minutes at baseline and 30 minutes at 6 and 24 months to complete.

After 24 months of study medication, you will be followed for an additional 30 days after the last dose of study medication. The research staff will contact you to ask if you have experienced any problems related to the study medication since it was stopped.

You will have approximately 4 tablespoons of blood withdrawn from a vein or currently placed central line (port-a-cath) to test several types of blood cell levels including liver and kidney function. These blood samples and biomarker blood samples will be drawn at baseline, 6 months and 24 months. The total amount of blood withdrawn during the study will be approximately 12 tablespoons. If your blood sugar or cholesterol is above normal, you will be asked to not eat or drink anything except water for 8 hours and return to the clinic. You will have 1 teaspoon of blood drawn to repeat these labs. If your physician decides you should have additional lab work to check your liver and kidney function, you will have one teaspoon of blood drawn at one and three months.

Each MRI exam will take about 1 hour. The MRI exam, or your own clinical MUGA or ECHO, is to evaluate specific parts of your heart. The MRI is for study purposes only, the imaging results will not be reviewed by your local health care team and only alert values pertaining to severely abnormal heart or aorta size will be furnished to your physicians. No other reports of these studies will be furnished to you or your physicians.

HOW LONG WILL I BE IN THE STUDY?
You will be in the study for about 24 months. You will receive one additional contact 30 days after the last dose of study medication.

You can stop participating at any time. If you decide to stop participating in the study, we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

WHAT ARE THE RISKS OF THE STUDY?
Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to the Atorvastatin include:

Most Common:
- Abdominal pain - 7.3%
- Constipation - 6.6%
- Nausea - 5.4%
- Headache – 7.4%
- Upper Respiratory Infection – 9%
- Muscle pain – 6%

Less Common:
- Confusion < 2%

Rare but serious:
- Cholestatic hepatitis (1%)
- Increased liver enzymes (1%)
- Decreased blood supply to the lower leg (1%)
- Abnormal muscle breakdown (1%)
- Endocrine: Diabetes < 0.25% or 1 per 400

You may experience discomfort, bruising and/or bleeding where the needle is inserted during blood draws. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

An MRI is a procedure in which a magnet linked to a computer is used to create detailed pictures of areas inside the body. MRI scans are not associated with any known side effects. Some subjects experience discomfort associated with enclosed spaces during MRI scanning.

If you receive contrast, additional data from your MRI will be collected to examine the development of scar tissue in the heart. If your site has contrast available and it is determined that you may receive the Federal Drug Administration (FDA) approved contrast, ProHance® (Gadoteridol), it will be injected into either a vein or currently placed central line (port-a-cath). The MRI contrast is used to help identify structures within the body on a MRI scan. Serious or life-threatening reactions have been reported in about 1 in 400,000 patients who receive contrast agents. All standard of care, medications and monitoring will be provided during this MRI scan. You may still participate in this study if a) you cannot receive Gadolinium-contrast because you have known allergies to this contrast or have other severe drug allergies or b) you are not allergic to gadolinium-contrast but choose not to receive this contrast due to the risks associated with the procedure or c) the contrast is not available.

Sometimes contrast may leak out of the IV into the fatty tissue around a vein. This happens in one out of every 250 to 500 procedures and is not likely to cause tissue damage.

In very rare circumstances, gadolinium in very high doses has been reported to be associated with nephrogenic systemic fibrosis (NSF), a condition that causes hardening of tissue under the skin and potentially death. To minimize the risk of developing this disorder, this study complies with all FDA criteria for administration of gadolinium. To identify potential risk to study participation an estimation of your kidney function will be obtained within 30 days prior to your MRI scans. Those with decreased kidney function will not receive contrast as part of this study.

Recent medical literature publications have reported that patients receiving gadolinium contrast may accumulate gadolinium in parts of the brain long after the last administration. Currently available information has not identified any adverse health effects resulting from this accumulation of gadolinium-based contrast. You may still participate in this study if you do not choose to receive the gadolinium-based contrast. You will be notified of new information related to gadolinium as it becomes available. If you receive contrast (gadolinium**)** the risks and side effects include:

Most Common Events (may occur in about 2% of patients)

- headache,
- nausea,
- vomiting,
- itching,
- watery eyes,
- skin rash,
- facial and/or tongue swelling,
- wheezing,
- chest tightness, or troubled breathing,
- hypotension (a decrease in blood pressure)

Less Common (<0.2 to 0.4%):

- extravasation happens in one out of every 250 to 500 procedures.

Rare but Serious Events (<1%):

- renal failure
- nephrogenic systemic fibrosis (NSF) (a condition that causes hardening of tissue under the skin)
- confusion

If contrast is available at your site and you are eligible to receive contrast, please circle your answer and initial on the line provided to show whether or not you choose to receive contrast.

YES NO Subject Initials _____

Participants will be required to wear earplugs or a headset during their MRI scan, to protect their hearing against the noise generated by the MRI scanner.

There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks. The risk of harm or discomfort that may happen as a result of taking part in this research study is not expected to be more than in daily life or from routine physical or psychological examinations or tests. You should discuss the risk of being in this study with the study staff.

In addition, there is a risk of a breach of confidentiality. We will do our best to protect your confidential information. Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

We may request your email address so we can stay in touch with you throughout the study. This may include setting up clinic visits, sending study-related reminders, or answering any general questions you may have. Email is generally not a secure way to communicate about your health as there are many ways for unauthorized users to access email. You should avoid sending sensitive, detailed personal information by email. Email should also not be used to convey information of an urgent nature. If you need to talk to someone immediately, please contact the nurse triage line at [redacted]. You do not have to provide your email address to participate in this study.

A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study.

REPRODUCTIVE RISKS AND OTHER ISSUES TO PARTICIPATING IN RESEARCH
Women who are currently breast-feeding and pregnant women are excluded from participation in this study. If you become pregnant while on this study you must notify your physician and study staff immediately.

Due to unknown risks and potential harm to the unborn fetus, women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

Because some methods of birth control are not 100% reliable, a negative pregnancy test is required at least 10 days prior to study registration for women of childbearing potential and a negative pregnancy test may be required at least 10 days prior to each MRI exam.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future.

WHAT OTHER CHOICES ARE THERE?
You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have.

Currently, there is not a standard treatment for possible heart problems that may occur from your standard cancer treatment. Your alternative is to not participate in this study.

If your primary care physician determines you need to be on Atorvastatin or a similar medication used to decrease your cholesterol and/or triglycerides your study drug should be stopped before starting the new medication. You should notify study personnel

immediately.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study may be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer. Only the following people or organizations will be granted access to your Protected Health Information:

1) The study investigator and his/her staff, or others at The Comprehensive Cancer Center of Wake Forest University (CCCWFU) and Wake Forest University Health Sciences who oversee research
2) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences and Wake Forest University Baptist Medical Center
3) The National Cancer Institute and the National Heart, Lung and Blood Institute (NHLBI)
4) FDA (Food and Drug Administration)
5) LabCorp (Bio-repository facility specifically for storing of specimens)
6) University of Wisconsin Carbone Cancer Center
7) University of Wisconsin Hospital and Clinics Health Information Systems including billing
8) University of Wisconsin Hospital and Clinics and your local providers
9) UW Investigators for the research study and their staff
10) UW-Madison regulatory and research oversight boards and offices
11) Research support services staff at the UW-Madison and its affiliates
12) The Alliance for Clinical Trials in Oncology
13) Wake Forest NCORP Research Base Data Management Center
14) Biologics – the company who supplies the study drug and bottles
15) Greenstone – the company who manufactures the study drug

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups, it may no longer be protected by federal or state law.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization

does not expire and/or any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center.

You can tell Dr. Toby Campbell that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Toby Campbell, MD
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

WILL MY CONFIDENTIALITY BE PROTECTED?

The researchers might use information learned from this study in scientific journal articles or in presentations. None of this information will identify you personally. The US Food and Drug Administration may look at study records. Your information will be protected by coding research records, keeping research records secure in a cabinet in a locked office, on password protected computers, and allowing only authorized people to have access to research records.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS?
There are no costs to you for taking part in this study. All study costs, including Atorvastatin or placebo and procedures, MRI, and blood draws that are related directly to the study will be paid for by the study. Costs for your regular medical care, including chemotherapy treatment and associated tests/procedures which are not related to this study, will be your own responsibility.

WILL YOU BE PAID FOR PARTICIPATING?
You will receive no payment or other compensation for taking part in this study

WHO IS SPONSORING THIS STUDY?
This study is being sponsored by the National Cancer Institute and the National Heart, Lung and Blood Institute. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?
If you are injured or get sick because of this study, medical care is available to you through UW Health, your local provider, or emergency services, as it is to all sick or injured people.

- If it is an emergency, call 911 right away or go to the emergency room.
- For non-emergency medical problems, contact your regular health care provider or the nurse triage line at [redacted].
- Call the Lead Researcher, Dr. Toby Campbell at [redacted], to report your sickness or injury.

Here are some things you need to know if you get sick or are injured because of this research:

- If the sickness or injury requires medical care, the costs for the care will be billed to you or your insurance, just like any other medical costs.
- Your health insurance company may or may not pay for this care.
- No other compensation (such as lost wages or damages) is usually available.
- UW-Madison and UW Health do not have a program to pay you if you get sick or are injured because of this study.
- By signing this consent form and taking part in this study, you are not giving up any legal rights you may have. You keep your legal rights to seek payment for care required because of a sickness or injury resulting from this study.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?
Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any

penalty or loss of benefits to which you are entitled. Your decision of whether or not to participate in this study will not affect the quality of your medical care at this institution. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. Toby Campbell at [redacted].

If you have any questions about your rights as a research subject or have complaints about the research study or study team, contact UW Health Patient Relations at [redacted]. The Patient Relations Representatives work with research subjects to address concerns about research participation and assist in resolving problems.

You will be given a copy of this signed consent form.

OPTIONAL BLOOD COLLECTIONS AND BIOBANKING FOR POSSIBLE FUTURE STUDIES
Researchers are trying to learn more about other health problems. Much of this research is done using samples from your blood. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Blood samples are being drawn for biomarker testing at baseline, 6 months and 24 months for the main study.

If you choose to take part in this study, the main study doctor would like to collect an additional 1 Tablespoon of blood at baseline, 6 months and 24 months.

We would like this additional blood to be banked for future testing. Any future testing may include new blood tests to look for changes in your heart related to chemotherapy. Future testing may also include problems related to other heart diseases or other diseases in general.
The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called “biobanking”. Your sample will be obtained at the University of Wisconsin. The sample will be stored in a LabCorp bio-repository (a facility specifically for storing of specimens), Covance Biorepository, [redacted]. It

will be given only to researchers approved by Dr. W. Greg Hundley, the primary investigator of this study. An Institutional Review Board (IRB) must also approve any future research study using your blood sample.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) If you agree to participate in the storing of blood for future research you will have approximately 1 additional tablespoon of blood drawn at baseline, 6 months and 24 months for a total of 3 additional tablespoons of blood drawn during the study.
2) Your sample and some related health information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom Wake Forest NCORP Research Base sends your sample

and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.

4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?
You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?
There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?
If you decide you no longer want your samples to be used, you can call the study doctor, Toby Campbell at [redacted] who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?
If you have questions about the use of your samples for research, contact the study doctor, Toby Campbell at [redacted].

BLOOD FOR FUTURE RESEARCH STUDIES:
My blood and related information may be kept in a Biobank for use in future health research. If I do not choose for my blood to be saved for future research, I am still eligible to participate in the study.

Please circle your answer and initial on the line provided to show whether or not you would like to take part in biobanking for future research.

YES NO Subject Initials _____

Authorization to participate in the research study:

I have read the information in this consent form. I voluntarily agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing

this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed): _____

Subject Signature: _____

Date: _____ Time:_____ am pm

Person Obtaining Consent:_____

Date: _____ Time:_____ am pm

****You will receive a copy of this form****