

Long-Term Outcomes in Patients with Severe Hypertriglyceridemia – Simulation Using the Archimedes Model

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Abstract:

Background: Individuals with elevated triglyceride (TG) levels are at higher risk for coronary heart disease (CHD). However, there is a lack of long-term data to quantitatively demonstrate the risk in patients with severe (≥500 mg/dl) hypertriglyceridemia (SHTG).

Objective: The objective of this study was to simulate health outcomes and associated costs up to 20 years in SHTG individuals using the Archimedes Model.

Methods: The Archimedes Model is a physiologically based mathematical model that is clinically and administratively detailed and has been rigorously validated using clinical trial data. To help simulate outcomes in SHTG individuals, the lipid component of the Archimedes Model was made more robust using data from individuals with TG>500mg/dl from a managed care plan. The risk of a myocardial infarction (MI), stroke, CHD death, cardiovascular disease (CVD) death, and composite major adverse cardiovascular event (MACE) was determined from simulations using the Model.

Results: The simulation randomly selected SHTG individuals from NHANES 1999-2006 and used these individuals as the basis for a simulated population of 5000 individuals. The average age at baseline was 45 years, with 68% males, 27% diabetics, mean BMI of 30.6 kg/m², blood pressure of 129/79 mmHg, total cholesterol of 265 mg/dl, HDL of 36.1 mg/dl, LDL of 85 mg/dl, TG of 881 mg/dl, FPG of 126 mg/dl, and HbA1c of 6.1%. At 10 years and 20 years respectively, the rate per individual at baseline of total MIs was 14.6% and 32.5%, the rate of ischemic stroke was 3.5% and 7.9%, CHD death was 5% and 11.8%, CVD death was 7.1% and 16.7%, and cumulative fraction of people with MACE was 16.2% and 31.5%.

Conclusion: This simulation demonstrates a significant increase in the risk of future MI, stroke, CHD death, CVD death, and MACE associated with SHTG. More precisely, SHTG individuals are more than twice as likely to suffer an adverse cardiac outcome as compared with individuals with normal TG levels as based on published census data. Physicians should be aware of the need to treat SHTG levels to reduce the risk of long-term cardiovascular (CV) events.

Introduction

- Hypertriglyceridemia is commonly prevalent in the US with 33.1% of adults years 20 and above with elevated triglycerides (TG) levels of > 150 mg/dL¹.
- The prevalence of severe hypertriglyceridemia (SHTG), as characterized with TG ≥500 mg/dL, is about 1.7% in the US¹.
- The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) guidelines recommend first lowering TG in individuals with SHTG due to the increased risk of pancreatitis².
- Published studies indicate an increased risk of coronary heart disease (CHD) in individuals with elevated TG levels^{3,4}. However, there is a lack of long-term data to quantitatively demonstrate the risk in patients with SHTG.

Objectives

- The objective of this study was to estimate long-term event rates over a 20-year period in SHTG individuals using the Archimedes Model.

Methods

- The Archimedes Model is a physiologically based mathematical model that is clinically and administratively detailed and has been rigorously validated using clinical trial data⁵⁻⁷. This model uses ordinary and differential equations to represent normal physiology, and a wide range of diseases and disorders related to cardiovascular disease and other chronic diseases. In addition, the model also represents the use of tests, treatments, care processes, health outcomes, visits and hospital admissions, procedures, and related costs.
- To help simulate outcomes in SHTG individuals, the lipid component of the Archimedes Model was made more robust using data from individuals with TG ≥ 500mg/dl from a managed care plan. The lipid model was validated in this region by reproducing the correct changes in TG, HDL and total cholesterol for 34 intervention scenarios drawn from 20 publications.

Methods (Cont'd)

- The simulations randomly selected adults of ages 18-75 years from NHANES 1999-2006 with TG ≥ 500mg/dL (and TG ≤ 2000 mg/dL). These individuals were used as a basis for generating a cohort of individuals (N=5000) with SHTG, thereby capturing the distributions and correlations of risk factors seen in the real SHTG population.
- The simulations were run over a period of 20 years or until death, with outcomes reported annually. Baseline, 10-year and 20-year results are displayed here.
- Outcomes assessed included the risk of myocardial infarction (MI), stroke, CHD death, cardiovascular disease (CVD) death, and composite major adverse cardiovascular event (MACE).

Results

- The average age of an individual in the simulation was 45 years, with a majority of males, an average BMI of 30.6 Kg/m², and about 27% diabetics. Average TG level was 881 mg/dL, with elevated total cholesterol levels (mean 265 mg/dL).
- The baseline characteristics of individuals included in the simulation is provided in Table 1.
- The risk of CV events in individuals with SHTG as simulated using the Archimedes Model is presented in Table 2.
- At 10 years and 20 years respectively, the rate per individual at baseline of total MIs was 14.6% and 32.5%, the rate of ischemic stroke was 3.5% and 7.9%, CHD death was 5% and 11.8%, CVD death was 7.1% and 16.7%, and cumulative fraction of people with MACE was 16.2% and 31.5%.
- SHTG individuals are more than twice as likely to suffer an adverse cardiac outcome as compared with individuals with normal TG levels as based on published census data. For example, according to the American Heart Association Heart Disease and Stroke statistics update, in 2009, there will be an estimated 230,000,000 Americans older than 18 years⁸. Based on the simulation by the Archimedes Model, the rate of MIs in the SHTG group during the early part of the simulation is approximately 1.2% per year. The corresponding incidence rates for CHD mortality are 0.2% per year for the general US adult population⁸ and 0.45% for SHTG individuals.

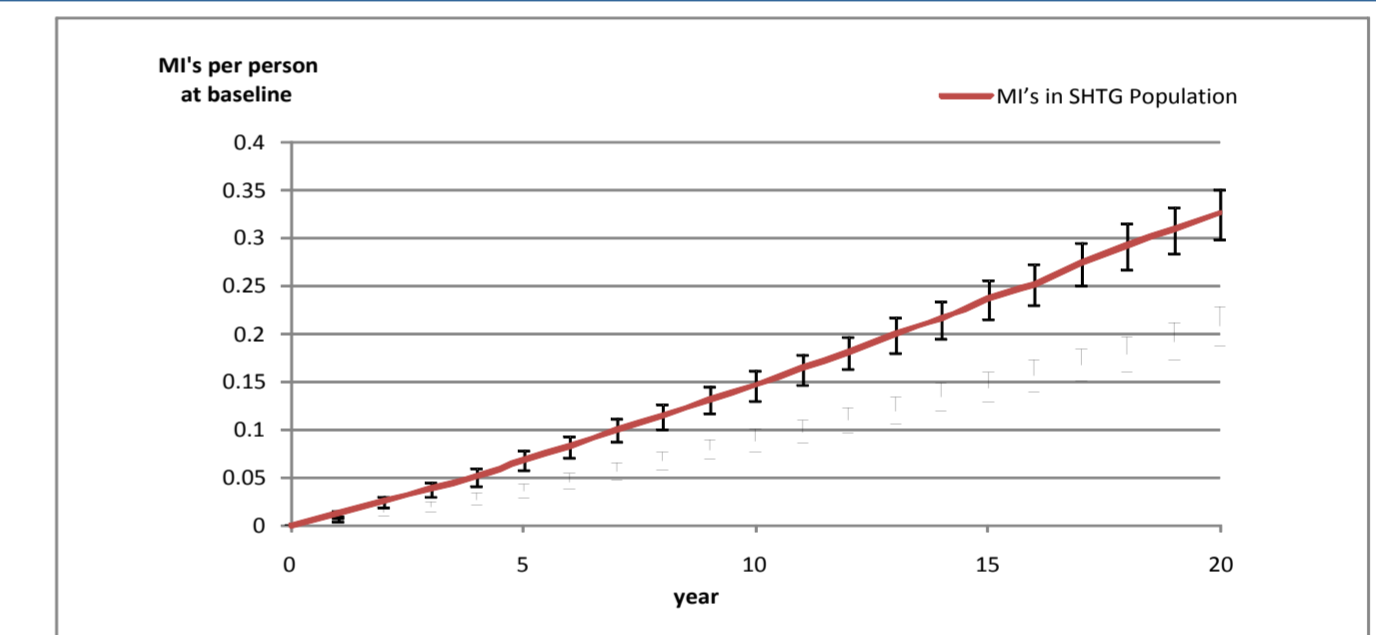
Table 1: Baseline Characteristics of SHTG Population from the Simulation

Baseline Characteristics - SHTG	Mean	Median	SD
Number of People with SHTG	5000		
Age (years)	44.7	44.7	12
Males (%)	68%		
BMI (Kg/m ²)	30.6	30	5.4
SBP (mmHg)	129	126	17
DBP (mmHg)	79	78	12
Total Cholesterol (mg/dL)	265	256	60
HDL (mg/dL)	36.1	35	9.5
LDL (mg/dL)	85	77	37.5
Triglycerides (mg/dL)	881	773	330
FPG (mg/dL)	126	100	67
HbA1c (mg/dL)	6.13	5.45	2
Smokers (%)	35%		
Diagnosed Diabetics (%)	18%		
All Diabetics (%)	27%		

Table 2: Risk of CV Events in SHTG Individuals – Archimedes Simulation

Outcomes	10 Years (%)	10 Years (2SE)	20 Years (%)	20 Years (2SE)
People with MI's per person alive	7.8	0.8	15.4	1.2
First MI (Kaplan Meier event rate)	11	0.9	23.9	1.4
Total MI's per person at baseline	14.6	1.5	32.5	2.6
People with stroke per person alive	2.2	0.4	3.4	0.6
First stroke (Kaplan Meier event rate)	4.1	0.6	9.1	1
Total strokes per person at baseline	4.2	0.8	9.4	1.7
CHD Death per person at baseline	5	0.7	11.8	1.1
Stroke Death per person at baseline	2.1	0.4	4.9	0.7
CVD death per person at baseline	7.1	0.8	16.7	1.3
Cumulative people with MACE	16.2	1.1	31.5	1.6
Any death per person at baseline	13.5	1	32.5	1.6

Figure 1: MI's Per Person in SHTG Population - Archimedes Simulation



Conclusions

- There is a lack of outcomes data in individuals with SHTG. To the best of our knowledge, this is the first mathematical simulation to quantitatively demonstrate the burden of cardiovascular risk associated with SHTG.
- This simulation demonstrates a substantial increase in the risk of future MI, stroke, CHD death, CVD death, and MACE associated with SHTG. More precisely, SHTG individuals are more than twice as likely to suffer an adverse cardiac outcome as compared with individuals with normal TG levels as based on published census data.
- Physicians should be aware of the need to treat SHTG individuals to reduce the risk of long-term cardiovascular events.
- There is a need to conduct long-term outcomes studies to assess the impact of different treatments in reducing the risk of cardiovascular events associated with SHTG.

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