Background
CVD causes 1/3 of all deaths in Canada more than any other illness. CAD mortality has decreased by 40% in past several decades due to improvements in CVD risk factors.
**What we know:** It is well established that cholesterol is documented as a risk factor for cardiovascular (CV) mortality. High levels of total cholesterol and non-HDL-C and low levels of HDL-C indicate an increased risk of cardiovascular events and related mortality.
**Background:** Conflicting studies exists about the role of cholesterol and noncardiovascular mortality and limited research specifically regarding subfractions of cholesterol has been documented. This inconsistent data about cholesterol and noncardiovascular mortality could result from the influence of age. As the body ages, biomarkers or “risk-factors” that are of importance earlier in life may not be predictive of the same risk later in life. It is therefore necessary to consider the possibility of evolving risk factors as we age, and to reassess these risk factors to better reflect changes across age groups.

Objective
Evaluate the association between cholesterol and noncardiovascular mortality across different age groups specifically in the elderly
- Association between cholesterol in noncardiovascular and cardiovascular mortality
- Association in a patient sample where cholesterol was measured before statins were introduced into the general public.

Design
- Data taken from Rotterdam Study
  - Residents ≥ 55 years old living in Ommoord district of Rotterdam
  - Enrolled during 1990-93 and followed until Jan 1, 2007
- Large prospective population-based cohort

Patients
Complete data on total cholesterol and HDL-C (n=7,009)
**Exclusion:** mean age 75.3± 10.1; 58.8% female “late-life age groups”
- Extreme cholesterol values (TC>12 mmol/L, HDL-C>3.5 mmol/L, TC:HDL-C>14) n=12
- CVD (prior MI, stroke, CABG, PTCA*) n=717
- Missing CVD information at baseline n=433
- Use of lipid-regulating medication n=93
**Inclusion:** n=5,750; 62% female, 55-99 y/o mean 68.8±8.9
*percutaneous transluminal coronary angioplasty

Interventions
1) Venipuncture from nonfasting blood samples. All measurements at single centre.
   Measured baseline TC, HDL-C and subsequently reported non-HDL-C, TC:HDL-C.
2) Cause of death classified according to International Classification of Death, Tenth Revision (ICD-10)

Outcome Measures
1° **Outcome:** clarify the association between cholesterol and noncardiovascular mortality
   - Total sample analysis – TC and its subfractions and risk of noncardiovascular mortality
   - Age group-specific analyses – TC and its subfractions and risk of noncardiovascular / cardiovascular mortality
2° **Outcomes:**
   - Explore the possibility of a nonlinear association between cholesterol and noncardiovascular mortality
**Multiple covariate assessments**
   - Education, BMI, smoking, diabetes mellitus, systolic/diastolic blood pressure, antihypertensive medication use, family history of early-onset CVD, albumin.

Baseline Characteristics
- As expected with increasing age for discussion includes (sample size, female %, education, smoking, diabetes, SBP, antihypertensive medication, albumin, family hx of early-onset CVD)
- Trends of interest include diastolic blood pressure
- Increasing age significantly associated with all measures of cholesterol
Results

1st Outcome: clarify the association between cholesterol and noncardiovascular mortality

- Total sample size
  - Each 1mmol/L increase in TC reduced the risk of noncardiovascular mortality by 12% (HR=0.88, 95% CI:0.84-0.92, P<0.001)
  - Each 1mmol/L increase in non-HDL-C reduced the risk of noncardiovascular mortality by 11% (HR=0.89, 95% CI:0.85-0.93, P<0.001)
  - HDL-C & Total:HDL-C was not significantly associated with noncardiovascular mortality (Total:HDL-C → trending)

- Age group-specific analyses (Figure 1.)
  - TC significant in those aged 65-74, 75-84 and 85+
  - Non-HDL-C significant in those aged 65-74, 75-84 and 85+
  - HDL-C significant in those aged 55-64
  - TC:HDL-C significant in those aged 55-64 and 85+

2nd Outcome: query nonlinear association between cholesterol & noncardiovascular mortality

- Largely demonstrated a stepwise increase in risk from low to moderate and high categories suggesting the association was linear (Table S2)

Multiple covariate assessments

- Fully adjusted covariates only had an effect of TC in those 85+ (HR=0.86, 95% CI:0.74-0.1.00, P.055) (Table S1)
- Age-group specific analyses of association between total cholesterol and cancer mortality found to be significant in those aged 65-74 and 75-84 (Table S4)
- Similar results from primary outcome seen with all-cause mortality (Table S5)
  - HDL-C inversely associated with cardiovascular mortality (Figure 1)

Author’s Conclusion

“higher total cholesterol was associated with a lower risk of noncardiovascular mortality in older adults. This association varied across the late-life span and was stronger in older age groups. Further research is required to examine the mechanisms underlying this association”

Critique

Intervention:

- Baseline cholesterol only (may change over time); Exclusion of LDL-C, TG and ApoB
- Cardiovascular events occurring during the course of the study (not causing death) may not have been identified in the deceased

Sample Size/Design:

- Data taken from Rotterdam Study (prospective population-based cohort), not RCT
- Not enough information describing statin use
- CVD patient excluded (inconclusive definition of CVD)
- Caucasian population recruited from single district (possible generalization)
- Fishing: covariate assessments & secondary analyses
- Definitions of covariates

Results

- 76.6% died of cardiovascular death vs. 35.4% noncardiovascular death
- Mortality status collected from central registry of Rotterdam municipality
- Explanation of HDL-C in 55-64?
- Numerous ‘re-analysis’ in specific age groups may have lead to favourable results
- CV mortality assessed, and in adults ≥ 85 years higher levels of TC and HDL-C lead to decreased risk of CV mortality. Recent meta-analysis show positive association between TC and CV mortality at ages 80-89
- Survivor bias leading to false conclusions
- Possible underpowering in older age groups for secondary analysis

Other:

- Difficult to apply results ethically and in modern medicine
- Possible government funding influence

Application to practice ➔ Round table discussion to explore individual opinions
Writer’s opinion of discussion:

It was agreed that this study was filled with large gaps of information on top of being poorly written. It discussed that it would be difficult to fully implement this study’s findings not only because of its design but also to ethically. It was agreed that as per the editorial the association between low cholesterol and weight loss which has been linked with greater mortality may explain the study’s results. It is the writer’s opinion that elderly patients for practical purposes should only be taking a statin in patients with documented cardiovascular disease where evidence exists in the literature that doing so will reduce the risk of cardiovascular events and mortality.