Dear Reader,

We are honoured to present you the 5th issue of "The State of the Heart", which explores the clinical evidence supporting the new understandings and happenings in the field of cardiology.

In India, the epidemiological transition from predominantly infectious disease conditions to non-communicable diseases has occurred over a rather succinct period of time. Despite wide heterogeneity in the prevalence of cardiovascular risk factors across different regions, CVD has emerged as the leading cause of death in all parts of India, including poorer states and rural areas. In this research driven time, management of these disorders is also constantly evolving towards the betterment whether it's pharmacological or non-pharmacological.

Being a healthcare custodian of the society, clinicians are constantly thriving to be abreast with the novel understandings of disease and its management. In this context, this is our initiative to provide you a compiled and to the point information.

Present booklet comprises of recent and latest deeds in the field of cardiovascular diseases like dyslipidemia, coronary artery disease, heart failure and its management. We hope that it will facilitate increased cooperation and innovation, and enthuse commitment to prevent these life-threatening and disabling disorders and providing the best possible care for people who suffer from these conditions.

Editor in chief

Dr. Dixit Patel (MBBS, MD)

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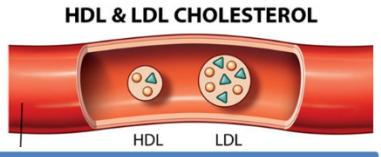
1. Novel Equation Gives More Precise LDL-C, Even Without Fasting

Novel Equation Gives More Precise LDL-C, Even Without Fasting

Triglycerides (mg/dL)	Non-HDL Cholesterol		
	<100 mg/dL	130–159 mg/dL	>220 mg/dL
7–49	3.5	3.3	3.1
101–105	5.5	5.0	4.5
147–154	6.5	5.7	4.8
202–220	7.6	6.4	5.3
293–399	9.3	7.5	5.9

Table: Partial Table of Factors to Calculate Novel Estimated LDL Cholesterol



Earlier: LDL cholesterol (mg/dL) = total cholesterol – HDL cholesterol – triglycerides/5, where triglycerides/5 represents triglycerides/VLDL cholesterol

Novel estimated LDL cholesterol (mg/dL) = total cholesterol – HDL cholesterol – triglycerides/ factor, where factor = value from table cells.

Ref. Circulation. 2018;137:10-19.

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Background—Recent recommendations favoring non-fasting lipid assessment may impact low-density lipoprotein-cholesterol (LDL-C) estimation. The novel method of LDL-C estimation (LDL-CN) uses a flexible approach to derive patient-specific triglyceride (TG) to very low-density lipoprotein-cholesterol ratios.

Methods— They used a US cross-sectional sample of 1,545,634 patients (959,153 fasting ≥10-12 hours; 586,481 non-fasting) from the second harvest of the Very Large Database of Lipids study to assess for the first time the impact of fasting status on novel LDL-C accuracy. Rapid ultracentrifugation was used to directly measure LDL cholesterol content (LDL-CD). Accuracy was defined as the percentage of LDL-CD falling within an estimated LDL-C (LDL-CN or LDL-CF) category by clinical cut points. For low estimated LDL-C (<70 mg/dL),

Results—In both fasting and non-fasting samples, accuracy was higher with the novel method across all clinical LDL-C categories (range: 87-94%) compared to Friedewald estimation (range: 71-93%) ($p \leq 0.001$). With LDL-C <70 mg/dL, non-fasting LDL-CN accuracy (92%) was superior to LDL-CF (71%) ($p<0.001$). In this LDL-C range, 19% of fasting and 30% of non-fasting patients had differences ≥10 mg/dL between LDL-CF and LDL-CD, whereas only 2% and 3% of patients respectively had similar differences with novel estimation. Accuracy of LDL-C <70 mg/dL further decreased as TG increased, particularly for Friedewald estimation (range: 37-96%) versus the novel method (range: 82-94%). With TG 200-399 mg/dL in non-fasting patients, LDL-CN <70 mg/dL accuracy (82%) was superior to LDL-CF (37%) ($p<0.001$). In this TG range, 73% of fasting and 81% of non-fasting patients had ≥10 mg/dL differences between LDL-CF and LDL-CD, compared to 25% and 20% of patients respectively with LDL-CN.

Conclusions—Novel adaptable LDL-C estimation performs better in non-fasting samples than the fixed Friedewald estimation, with a particular accuracy advantage in settings of low LDL-C and high TG.

2. Flu Virus Linked to Imminent Risk for Acute MI

Flu Virus Linked to Imminent Risk for Acute MI

Table: Incidence Ratios for Acute MI Hospitalization by Specific Infections within 7 days

Infection	Incidence Ratio (95% CI)
Influenza A	5.17 (3.02–8.84)
Influenza B	10.11 (4.37–23.38)
RSV	3.51 (1.11–11.12)
Noninfluenza virus, non-RSV	2.77 (1.23–6.24)
Illness, no respiratory virus identified[a]	3.30 (1.90–5.73)

RSV = respiratory syncytial virus.[a]From among influenza A, influenza B, RSV, parainfluenza virus, adenovirus, human metapneumovirus, coronavirus, or enterovirus.

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This study found significant association between respiratory infections, especially influenza, and acute myocardial infarction. Incidence ratios for acute myocardial infarction within 7 days was increased by multifold when compared with control

Ref. N Engl J Med 2018; 378:345-353

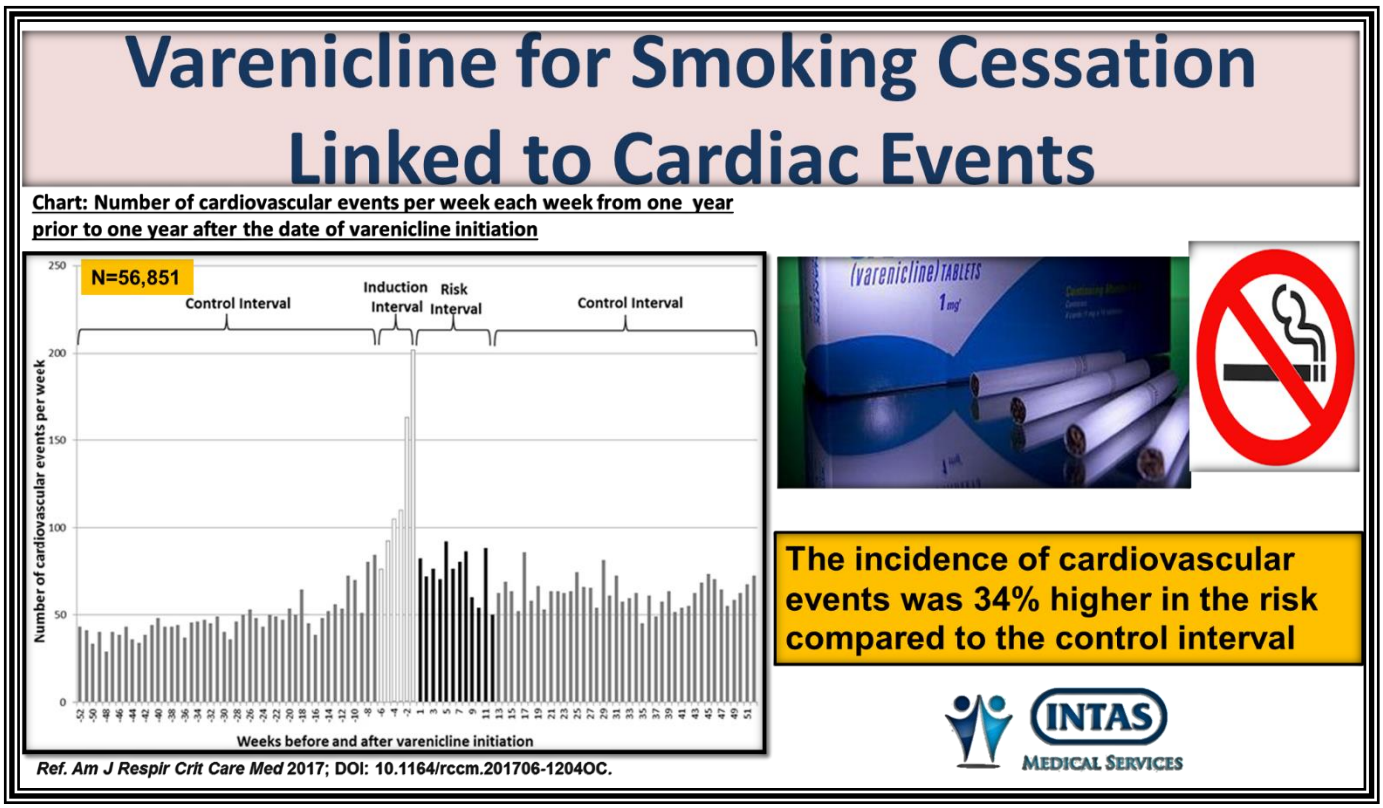
BACKGROUND: Acute myocardial infarction can be triggered by acute respiratory infections. They have evaluated the association between laboratory-confirmed influenza infection and acute myocardial infarction.

METHODS: They used the self-controlled case-series design to evaluate the association between laboratory-confirmed influenza infection and hospitalization for acute myocardial infarction. They defined the "risk interval" as the first 7 days after respiratory specimen collection and the "control interval" as 1 year before and 1 year after the risk interval.

RESULTS: They identified 364 hospitalizations for acute myocardial infarction that occurred within 1 year before and 1 year after a positive test result for influenza. Of these, 20 (20.0 admissions per week) occurred during the risk interval and 344 (3.3 admissions per week) occurred during the control interval. The incidence ratio of an admission for acute myocardial infarction during the risk interval as compared with the control interval was 6.05 (95% confidence interval [CI], 3.86 to 9.50). No increased incidence was observed after day 7. Incidence ratios for acute myocardial infarction within 7 days after detection of influenza B, influenza A, respiratory syncytial virus, and other viruses were 10.11 (95% CI, 4.37 to 23.38), 5.17 (95% CI, 3.02 to 8.84), 3.51 (95% CI, 1.11 to 11.12), and 2.77 (95% CI, 1.23 to 6.24), respectively.

CONCLUSIONS: They found a significant association between respiratory infections, especially influenza, and acute myocardial infarction.

3. Varenicline for Smoking Cessation Linked to Cardiac Events



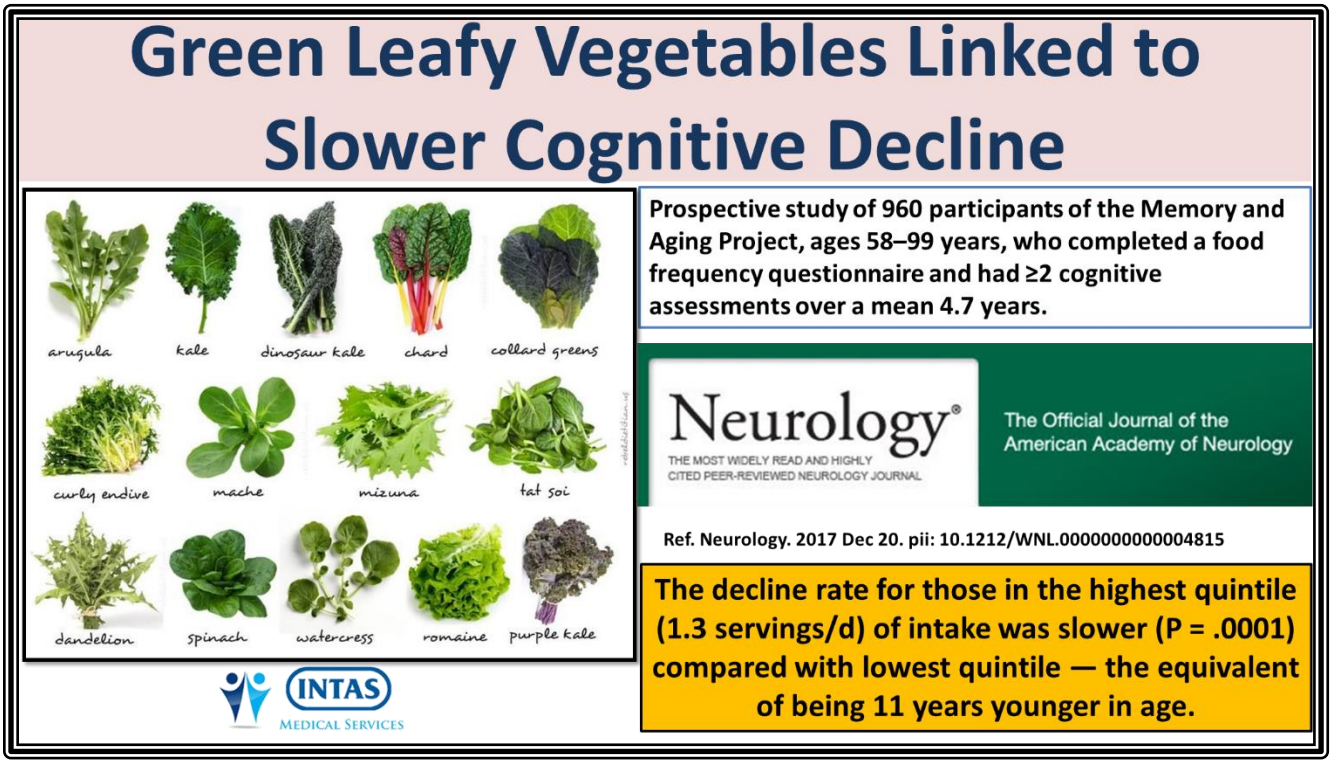
Background: Varenicline aids in smoking cessation but has also been associated with serious adverse events. The aim of this study was to determine the risks of cardiovascular and neuropsychiatric events following varenicline receipt in a real-world setting.

Methods: A population-based, self-controlled risk interval study using linked universal health administrative data from the diverse, multicultural population of Ontario, Canada was conducted. In two separate analyses, new varenicline users between September 1, 2011 and February 15, 2014 were observed from one year before to one year after varenicline receipt. The relative incidences of cardiovascular and neuropsychiatric hospitalizations and emergency department visits in the 12 weeks following varenicline receipt (the risk interval) compared with the remaining observation period (the control interval) were estimated in two separate fixed-effect conditional Poisson regressions. Sensitivity analyses tested the robustness of the results.

Measurement and Main Results: Among 56,851 new users of varenicline, 6317 cardiovascular and 10,041 neuropsychiatric hospitalizations and emergency department visits occurred from one year before to one year after receipt. The incidence of cardiovascular events was 34% higher in the risk compared to the control interval (Relative Incidence [RI] 1·34; 95% CI 1·25-1·44). Findings were consistent in sensitivity analyses, most notably in those without any history of previous cardiovascular disease. The relative incidence of neuropsychiatric events was marginally significant in the primary (Relative Incidence 1·06; 95% CI 1·00-1·13) but not all sensitivity analyses.

Conclusions: Varenicline appears to be associated with an increased risk of cardiovascular but not neuropsychiatric events.

4. Green Leafy Vegetables Linked to Slower Cognitive Decline



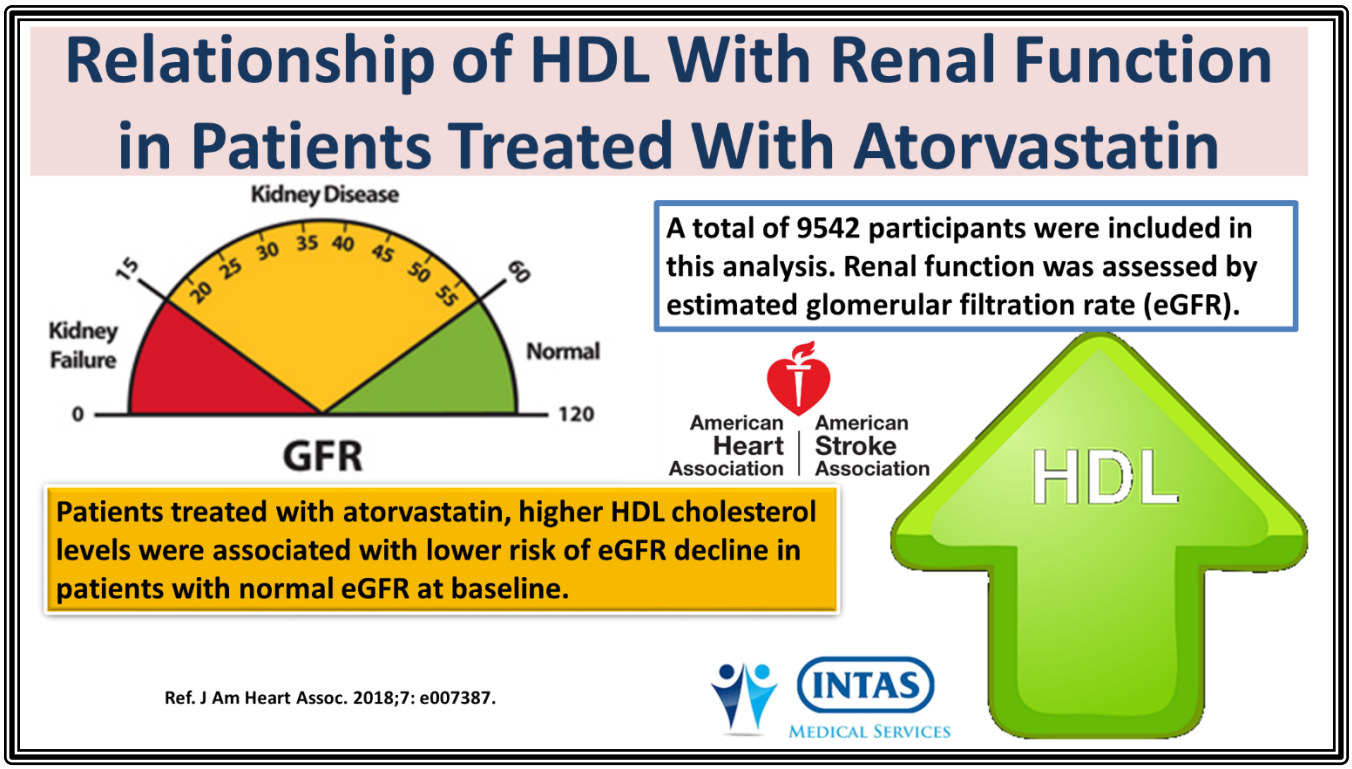
Objective: To increase understanding of the biological mechanisms underlying the association, They investigated the individual relations to cognitive decline of the primary nutrients and bioactives in green leafy vegetables, including vitamin K (phylloquinone), lutein, β-carotene, nitrate, folate, kaempferol, and α-tocopherol.

Methods: This was a prospective study of 960 participants of the Memory and Aging Project, ages 58–99 years, who completed a food frequency questionnaire and had ≥2 cognitive assessments over a mean 4.7 years.

Results: In a linear mixed model adjusted for age, sex, education, participation in cognitive activities, physical activities, smoking, and seafood and alcohol consumption, consumption of green leafy vegetables was associated with slower cognitive decline; the decline rate for those in the highest quintile of intake (median 1.3 servings/d) was slower by β = 0.05 standardized units (p = 0.0001) or the equivalent of being 11 years younger in age. Higher intakes of each of the nutrients and bioactives except β-carotene were individually associated with slower cognitive decline. In the adjusted models, the rates for the highest vs the lowest quintiles of intake were β = 0.02, p = 0.002 for phylloquinone; β = 0.04, p = 0.002 for lutein; β = 0.05, p < 0.001 for folate; β = 0.03, p = 0.02 for α-tocopherol; β = 0.04, p = 0.002 for nitrate; β = 0.04, p = 0.003 for kaempferol; and β = 0.02, p = 0.08 for β-carotene.

Conclusions: Consumption of approximately 1 serving per day of green leafy vegetables and foods rich in phylloquinone, lutein, nitrate, folate, α-tocopherol, and kaempferol may help to slow cognitive decline with aging.

5. Relationship of HDL With Renal Function in Patients Treated With Atorvastatin

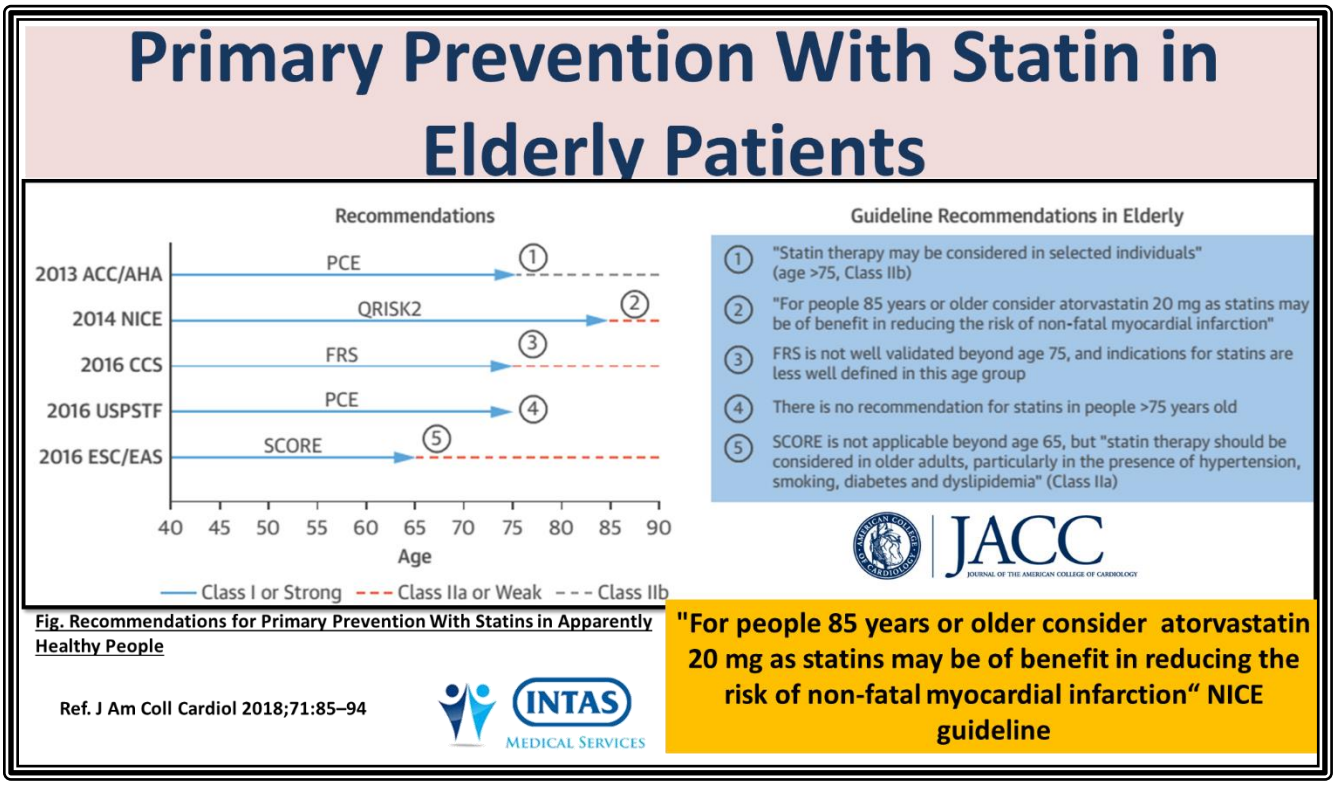


Background: It is not known whether the concentration of high-density lipoprotein (HDL) cholesterol is related to renal function in statin-treated patients. They therefore investigated whether HDL cholesterol levels predicted renal function in atorvastatin-treated patients in the TNT (Treating to New Targets) trial.

Methods and Results: A total of 9542 participants were included in this analysis. Renal function was assessed by estimated glomerular filtration rate (eGFR). HDL cholesterol levels at month 3 were used as this is the time point at which on-treatment HDL cholesterol levels became stable. Among 6319 participants with a normal eGFR (≥60 mL/min per 1.73 m^2) at baseline, higher HDL cholesterol levels at month 3 were significantly associated with lower risk of decline in eGFR (ie, having eGFR <60 mL/min per 1.73 m^2) during follow-up (HR of 1.04, 0.88, 0.85, and 0.77 for HDL cholesterol quintiles 2, 3, 4, and 5, respectively, relative to quintile 1, *P* for trend=0.006). Among 3223 participants with an eGFR (<60 mL/min per 1.73 m^2) at baseline, higher HDL cholesterol levels at month 3 had less impact on eGFR during follow-up, with statistical significance observed only when analyzing HDL cholesterol levels as a continuous variable (*P*=0.043), but not as a categorical quintile variable (*P* for trend=0.27).

Conclusions: In patients treated with atorvastatin, higher HDL cholesterol levels were associated with lower risk of eGFR decline in patients with normal eGFR at baseline. However, further study is needed to establish whether there is any causal relationship between HDLs and renal function.

6. Primary Prevention with Statin in Elderly Patients



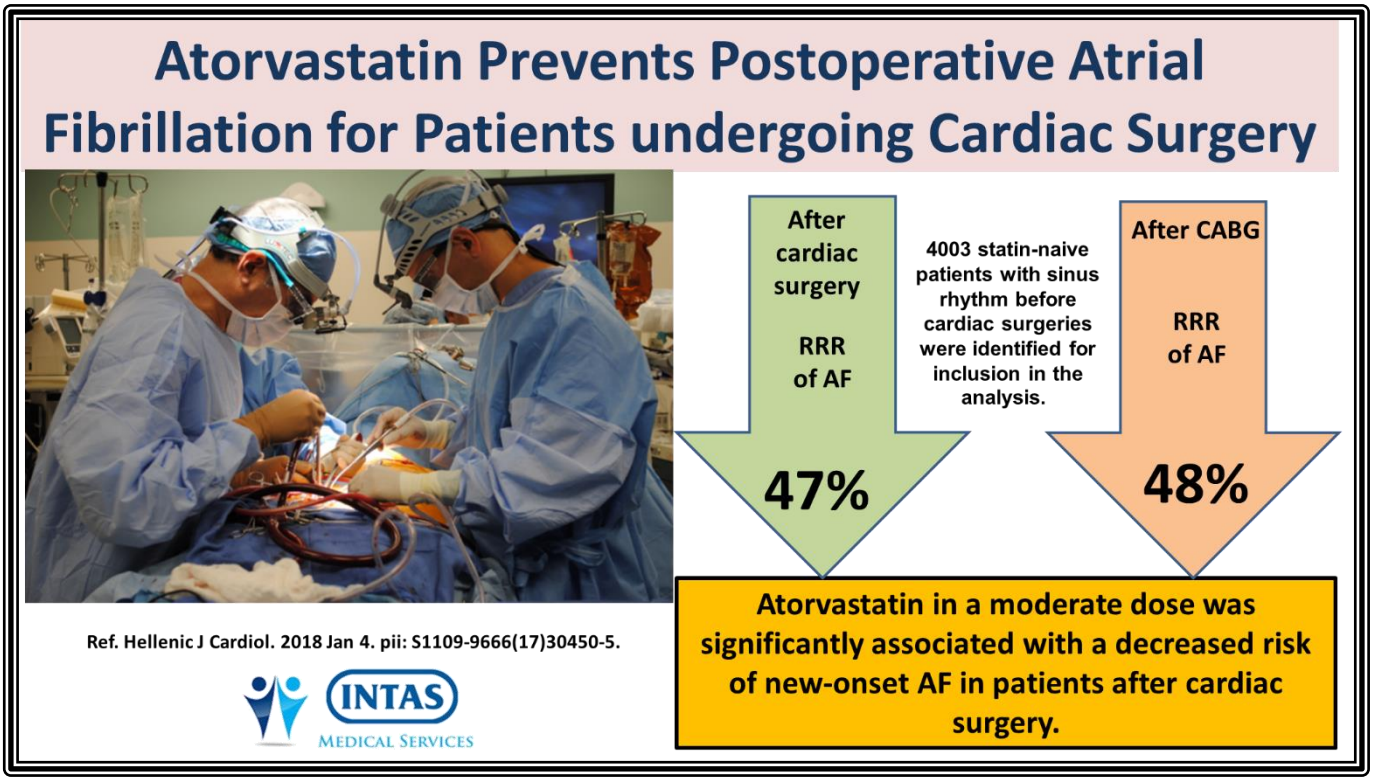
Overview:

The burden of atherosclerotic cardiovascular disease (ASCVD) in high-income countries is mostly borne by the elderly. With increasing life expectancy, clear guidance on sensible use of statin therapy to prevent a first and potentially devastating ASCVD event is critically important to ensure a healthy aging population.

Since 2013, 5 major North American and European guidelines on statin use in primary prevention of ASCVD have been released by the American College of Cardiology/American Heart Association, the UK National Institute for Health and Care Excellence, the Canadian Cardiovascular Society, U.S. Preventive Services Task Force, and the European Society of Cardiology/European Atherosclerosis Society. Guidance on using statin therapy in primary ASCVD prevention in the growing elderly population (>65 years of age) differs markedly.

The authors discuss the discrepant recommendations, place them into the context of available evidence, and identify circumstances in which uncertainty may hamper the appropriate use of statins in the elderly. Indeed, there are reasons to believe that the benefit of statin treatment in elderly people may be substantial for both the individual patient and for the society.

7. Atorvastatin Prevents Postoperative Atrial Fibrillation for Patients undergoing Cardiac Surgery



AIM AND METHODS: They aimed to evaluate whether different statins can reduce risk of AF in different doses. A random effects model was used when there was substantial heterogeneity.

RESULTS: Eighteen published studies including 4003(2009 receiving satins, 1994 receiving regime) statin-naive patients with sinus rhythm before cardiac surgeries were identified for inclusion in the analysis. Thirteen studies investigated prevention of AF by atorvastatin, two studies investigated prevention of AF by rosuvastatin, two studies investigated prevention of AF by simvastatin, and one study investigated prevention of AF by pravastatin. The rest two studies compared effects of different doses of atorvastatin on prevention of AF for patients undergoing coronary artery bypass grafting (CABG). Overall, statin therapy was associated with a significant decreased risk of AF (relative risk (RR) 0.57, 95% confidence interval (CI) 0.45-0.73, P = 0.000). However, subgroup analyses showed that only atorvastatin reduced the risk of new-onset AF in patients after cardiac surgery (RR 0.53, 95% CI 0.41-0.69, P = 0.000). Patients undergoing CABG possibly received more benefits from statin therapy (RR 0.52, 95% CI 0.39-0.68).Statin therapy in a moderate dose may be optimal(RR 0.42,95% CI 0.28-0.64).

CONCLUSIONS: This meta-analysis suggests that statin therapy has an overall protective effect against postoperative AF, among which, atorvastatin in a moderate dose was significantly associated with a decreased risk of new-onset AF in patients after coronary surgery. Moreover, simvastatin may also exert significant protective effect against the AF recurrences in patients undergoing cardiac surgeries, thus further prospective studies are warranted.

8. Benefit of Adding Ezetimibe to Statin Therapy on CV Outcomes in With vs. Without Diabetics: IMPROVE-IT

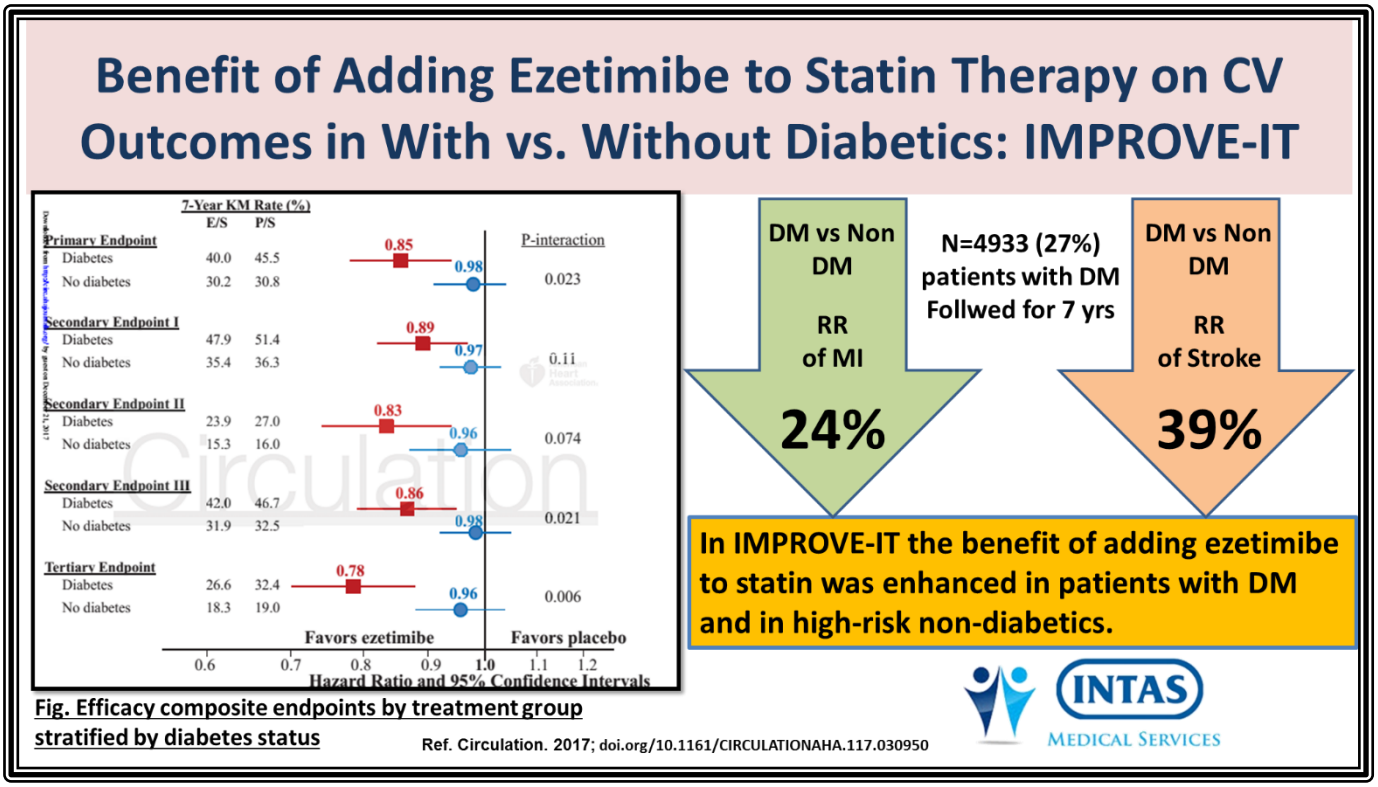


Fig. Efficacy composite endpoints by treatment group stratified by diabetes status

Ref. Circulation. 2017; doi.org/10.1161/CIRCULATIONAHA.117.030950

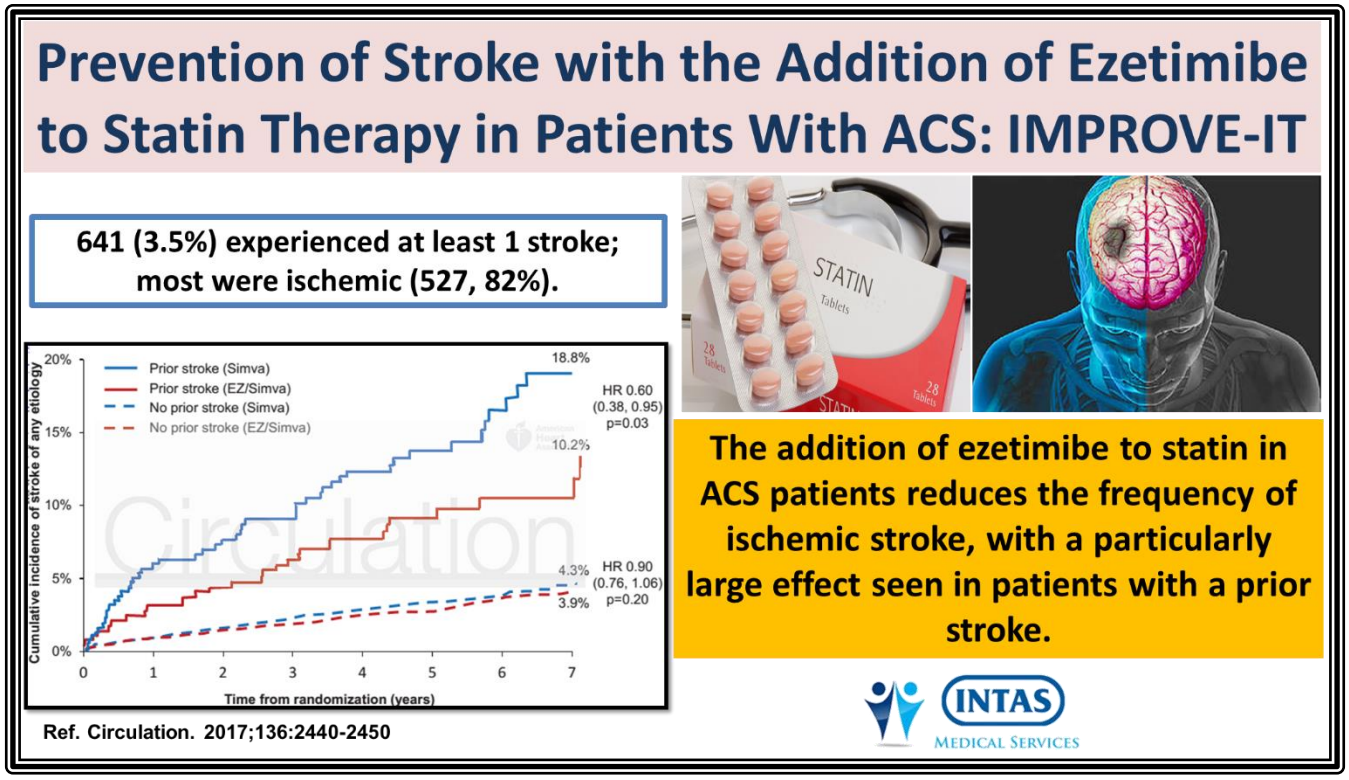
Background: Ezetimibe, when added to simvastatin, reduces cardiovascular events following acute coronary syndrome (ACS); They explored outcomes stratified by diabetes mellitus (DM).

Methods: In IMPROVE-IT, 18,144 patients post ACS with LDL-C 50-125 mg/dL were randomized to ezetimibe/simvastatin-40mg (E/S) or placebo/simvastatin-40mg (P/S). The primary composite endpoint was cardiovascular death, major coronary events, and stroke. DM was a prespecified subgroup.

Results: The 4933 (27%) patients with DM were more often older, female, with prior MI and revascularization, and presented more frequently with non-ST segment elevation ACS compared to non-DM (each p<0.001). The median admission LDL-C was lower among patients with DM (89 vs. 97 mg/dL, p<0.001). E/S achieved a significantly lower median time-weighted average LDL-C compared to P/S, irrespective of DM (DM: 49 vs. 67 mg/dL; No DM: 55 vs. 71 mg/dL, both P<0.001). In DM patients, E/S reduced the 7-year Kaplan-Meier primary endpoint event rate by 5.5% absolute (HR 0.85; 95% CI, 0.78-0.94); in non-DM patients the absolute difference was 0.7% (HR 0.98; 95% CI, 0.91-1.04; Pinteraction=0.02). The largest relative reductions in DM patients were in MI (24%) and ischemic stroke (39%). No differences in safety outcomes by treatment were present regardless of DM.

Conclusions: In IMPROVE-IT the benefit of adding ezetimibe to statin was enhanced in patients with DM and in high-risk non-diabetics.

9. Prevention of Stroke with the Addition of Ezetimibe to Statin Therapy in Patients With ACS: IMPROVE-IT



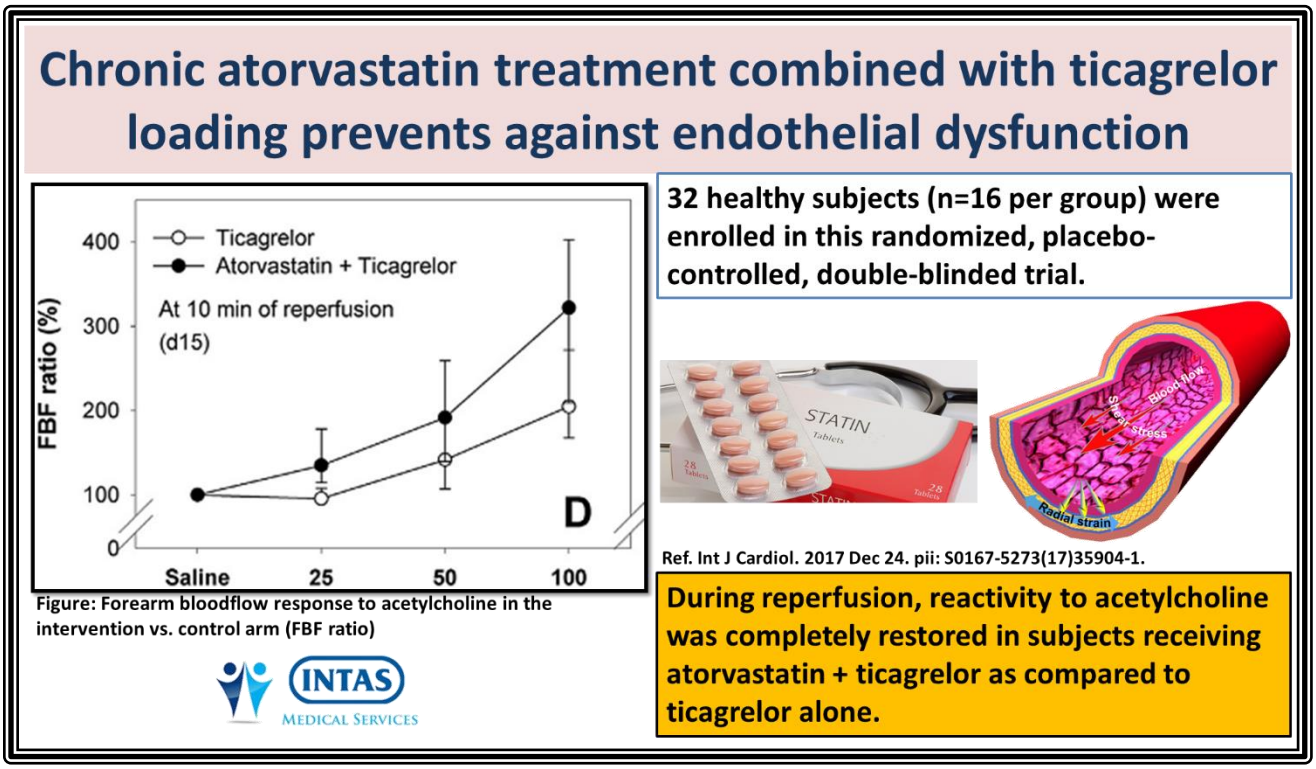
Background: Ezetimibe improved cardiovascular outcomes when added to statin therapy in patients stabilized after acute coronary syndrome. They investigated the efficacy of the addition of ezetimibe to simvastatin for the prevention of stroke and other adverse cardiovascular events in IMPROVE-IT

Methods: Treatment efficacy was assessed for the entire population and by subgroups for the first and total (first and subsequent) events for the end points of stroke of any etiology, stroke subtypes, and the primary trial end point at 7 years.

Results: Of 18 144 patients, 641 (3.5%) experienced at least 1 stroke; most were ischemic (527, 82%). Independent predictors of stroke included prior stroke, older age, atrial fibrillation, congestive heart failure, diabetes mellitus, myocardial infarction, and renal dysfunction. There was a nonsignificant reduction in the first event of stroke of any etiology (4.2% versus 4.8%; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.73–1.00; P=0.052) with ezetimibe/simvastatin versus placebo/simvastatin, driven by a significant 21% reduction in ischemic stroke (3.4% versus 4.1%; HR, 0.79; 95% CI, 0.67–0.94; P=0.008) and a nonsignificant increase in hemorrhagic stroke (0.8% versus 0.6%; HR, 1.38; 95% CI, 0.93–2.04; P=0.11).

Conclusions: The addition of ezetimibe to simvastatin in patients stabilized after acute coronary syndrome reduces the frequency of ischemic stroke, with a particularly large effect seen in patients with a prior stroke.

10. Chronic atorvastatin treatment combined with ticagrelor loading prevents against endothelial dysfunction



BACKGROUND: They studied the effect of high-dose atorvastatin combined with ticagrelor loading on endothelial dysfunction in a model of forearm vascular ischemia-reperfusion (IR) injury.

METHODS: 32 healthy subjects (n=16 per group) were enrolled in this randomized, placebo-controlled, double-blinded trial. Forearm blood flow (FBF) measurements in response to increasing intra-arterial doses of the vasodilator acetylcholine (ACh; endothelium-dependent agonist) and glyceryltrinitrate (GTN; endothelium-independent) were performed before and after a cuff-induced 20min forearm ischemia, respectively.

RESULTS: Ticagrelor loading mitigated ischemia-induced endothelial dysfunction and in combination with repeated atorvastatin dosing the response to ACh during reperfusion was completely normalized (FBF AChAUC ratio post- vs. pre-ischemia: 0.81 [ticagrelor] vs. 1.04 [atorvastatin+ticagrelor]; P=0.001). As expected, GTN-induced vasodilation was not affected by IR injury. Atorvastatin significantly reduced total and low density lipoprotein cholesterol concentrations, while high density lipoprotein cholesterol and triglyceride levels remained unchanged.

CONCLUSION: Chronic atorvastatin treatment combined with ticagrelor loading prevents against endothelial dysfunction after acute forearm ischemia. Ticagrelor alone mitigated the impaired endothelium-dependent FBF response as compared to no pharmacological intervention.

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