



The Cardiovascular Benefits of the Virta Treatment

James P McCarter MD PhD

Head of Research, *Virta Health*

Adjunct Professor of Genetics, *Washington University School of Medicine*

Ethan J Weiss MD

Science Advisor, *Virta Health*

Associate Professor of Medicine and Member of the Cardiovascular Research Institute,
University of California San Francisco School of Medicine

Summary

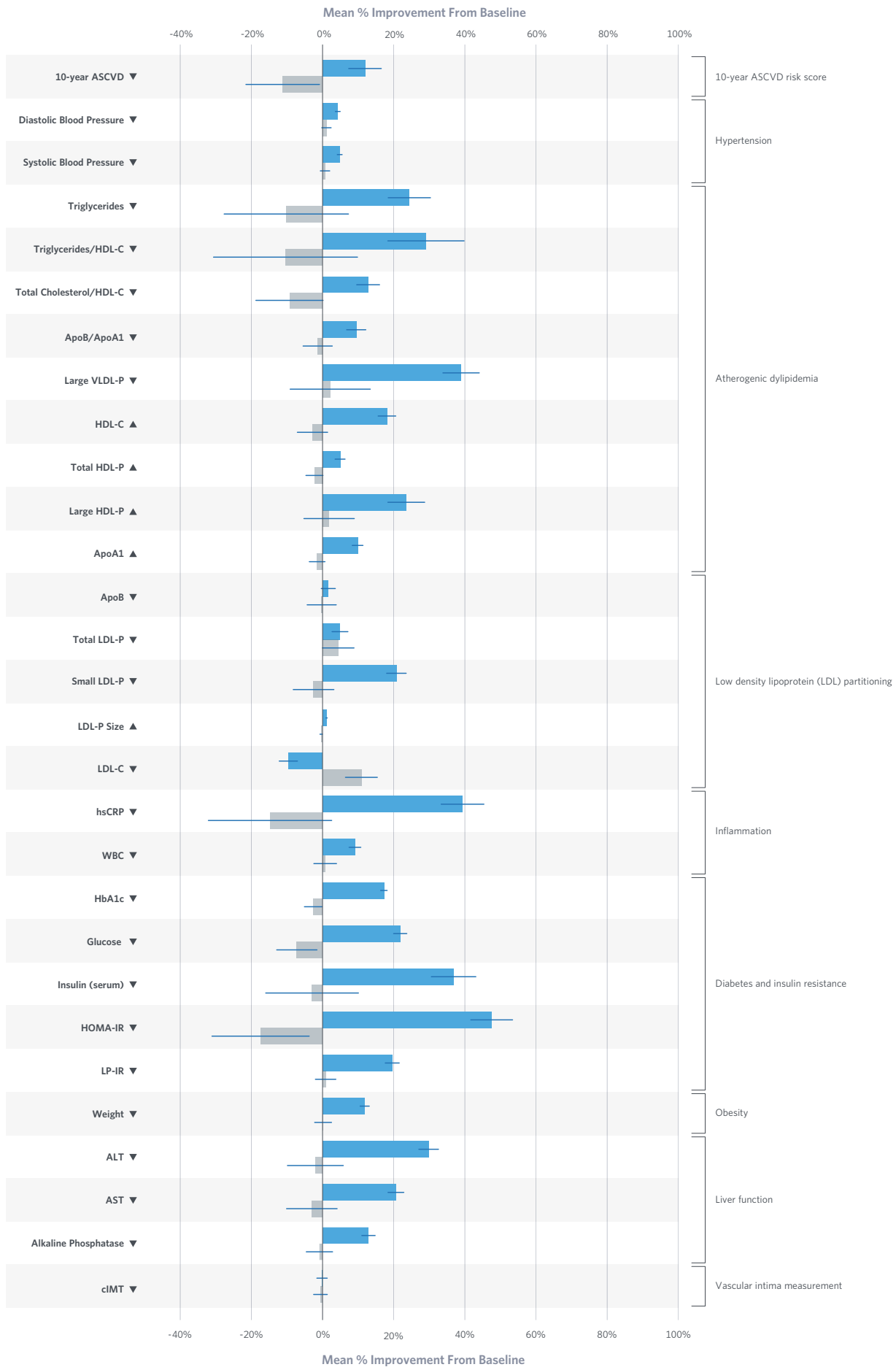
Cardiovascular disease (CVD) is the number one cause of morbidity and mortality in patients with type 2 diabetes (T2D) (Gregg et al., 2007). Virta Health provides the first clinically-proven treatment to reverse type 2 diabetes and other chronic metabolic diseases without the use of added medications or surgery. At one year, 60% of patients in the Virta clinical trial achieved diabetes reversal, defined as hemoglobin A1c (HbA1c) <6.5% without medication other than metformin. 94% of insulin users reduced or eliminated usage altogether and 83% of patients remained active in the trial (Hallberg et al., 2018; McKenzie et al., 2017). In addition to T2D improvements, patients demonstrate dramatic improvement in many cardiovascular risk factors indicating an opportunity to substantially reduce CVD complications in T2D populations (Bhanpuri et al., 2018).

Here, we systematically review 29 parameters associated with CVD which were tracked in the clinical trial, 25 of which show statistically significant improvement following 1-yr of Virta treatment. A usual care group by contrast saw no significant improvement in the 29 parameters.

These parameters can be grouped into the following categories:

1. 10-year ASCVD risk score (which improved by 11.9% following Virta treatment)
2. hypertension
3. atherogenic dyslipidemia
4. low density lipoprotein (LDL) partitioning
5. inflammation
6. diabetes and insulin resistance
7. obesity
8. liver function
9. vascular intima measurement
10. Medication usage for hypertension, cholesterol and diabetes was also tracked and substantial prescription reduction was demonstrated following Virta treatment

Together these findings provide a robust case for both near-term and projected long-term improvement in CVD outcomes in T2D patients with the Virta treatment.



Introduction

In August of 2015, Virta Health and Indiana University Health (IUH) began a 2-yr prospective longitudinal non-randomized controlled clinical trial (n=465) to determine efficacy, safety and sustainability of the Virta treatment for 262 T2D patients and 116 pre-diabetes patients with an additional 87 T2D patients receiving usual care. Virta treatment patients received online continuous remote care support including telemedicine, health coaching, individualized education for nutrition and behavior change (including nutritional ketosis), biometric feedback and peer support. Usual care patients were seen by an endocrinologist and met with a registered dietitian and diabetes educator. A description of the trial is provided by Bhanpuri et al., 2018; Hallberg et al., 2018; McKenzie et al., 2017 including 70-day and 1-yr outcomes for T2D patients. (Outcomes for pre-diabetes patients will be described in a future publication.) The trial is registered at Clinicaltrials.gov, Identifier NCT02519309.

Methods

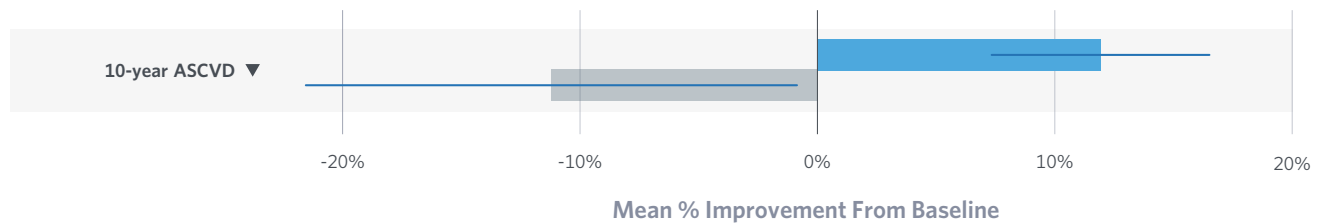
The statistical significance of biomarker changes for T2D patients following Virta treatment (n=262) or usual care (n=87) was determined by comparing baseline and 1-yr values. Two-sample t-tests were used for comparisons between groups and ANCOVA and paired t-tests were used for comparisons within groups. Both intent-to-treat with multiple imputation (provided here) and completers analysis were conducted with Bonferroni adjustment for the number of variables examined ($p < 0.0017$) (Hallberg et al., 2018) ($p < 0.0019$) (Bhanpuri et al., 2018). Most of the improvements in CVD risk observed in the Virta Health trial have precedence in the published literature describing the application of dietary changes including nutritional ketosis under medical supervision for T2D, pre-diabetes and metabolic syndrome patients. Examples are cited below with more extensive citations available in reviews by Feinman et al., 2015; Noakes and Windt, 2017. It should be noted that the biomarkers described here have varying degrees of validation from changes correlated with mortality in clinical trials, to correlations with mortality in epidemiological studies, to experimental support. Some are tightly correlated with one another whereas others are independent. Together, they provide a global picture of cardiometabolic change.

Results

A review of all scores, biomarkers, and medication use shows statistically significant improvement in 25 of 29 factors along with decreased medication use during the first year of the Virta treatment. For each measure, the forest plot shows the Virta treatment first in blue followed by the usual care in gray. Position of the bar indicates population mean and the black line indicates standard error. Movement to the right is considered favorable (i.e. improved biomarker status, decreased medication use) and movement to the left is considered unfavorable. Results are from the intention-to-treat analysis with missing values imputed. Next, we present these changes in ten sections.

1. Aggregate Cardiovascular Disease Risk Score Improves

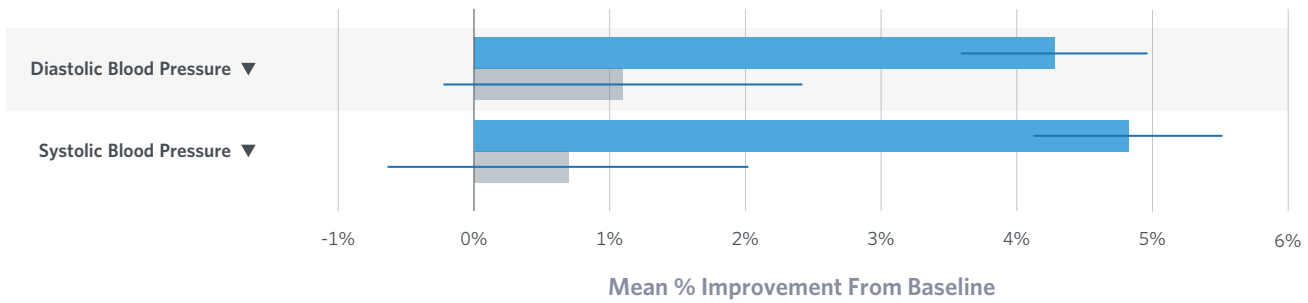
The aggregate atherosclerotic cardiovascular disease (ASCVD) risk score was developed by the American Heart Association and American College of Cardiology to estimate the 10-year and lifetime risks for atherosclerotic cardiovascular disease (ASCVD), defined as coronary death, nonfatal myocardial infarction, or fatal or nonfatal stroke based on the aggregation of systolic blood pressure, total, LDL and HDL cholesterol, along with diabetes history, medication use, age, sex, and race (Goff et al., 2014). Following 1-yr of the Virta treatment, the mean patient 10-year ASCVD risk score decreased 11.9% ($P=4.9 \times 10^{-5}$) indicating a potential reduced risk of myocardial infarction or stroke. Usual care mean ASCVD risk increased 10.4% ($P=0.17$). Therefore, relative to the usual care group, the Virta treatment showed a trend toward greater risk reduction (net percent change of -22.3%, $P=0.008$) (Bhanpuri et al., 2018). (Note that taking a conservative approach, diabetes status was scored as unchanged in the calculation despite improvements observed in the Virta treatment group.)



A meta-analysis of 17 trials comparing low carbohydrate versus low fat diets showed a greater 10-yr ASCVD risk score improvement with the low carbohydrate groups (Sackner-Bernstein et al., 2015).

2. Hypertension Improves

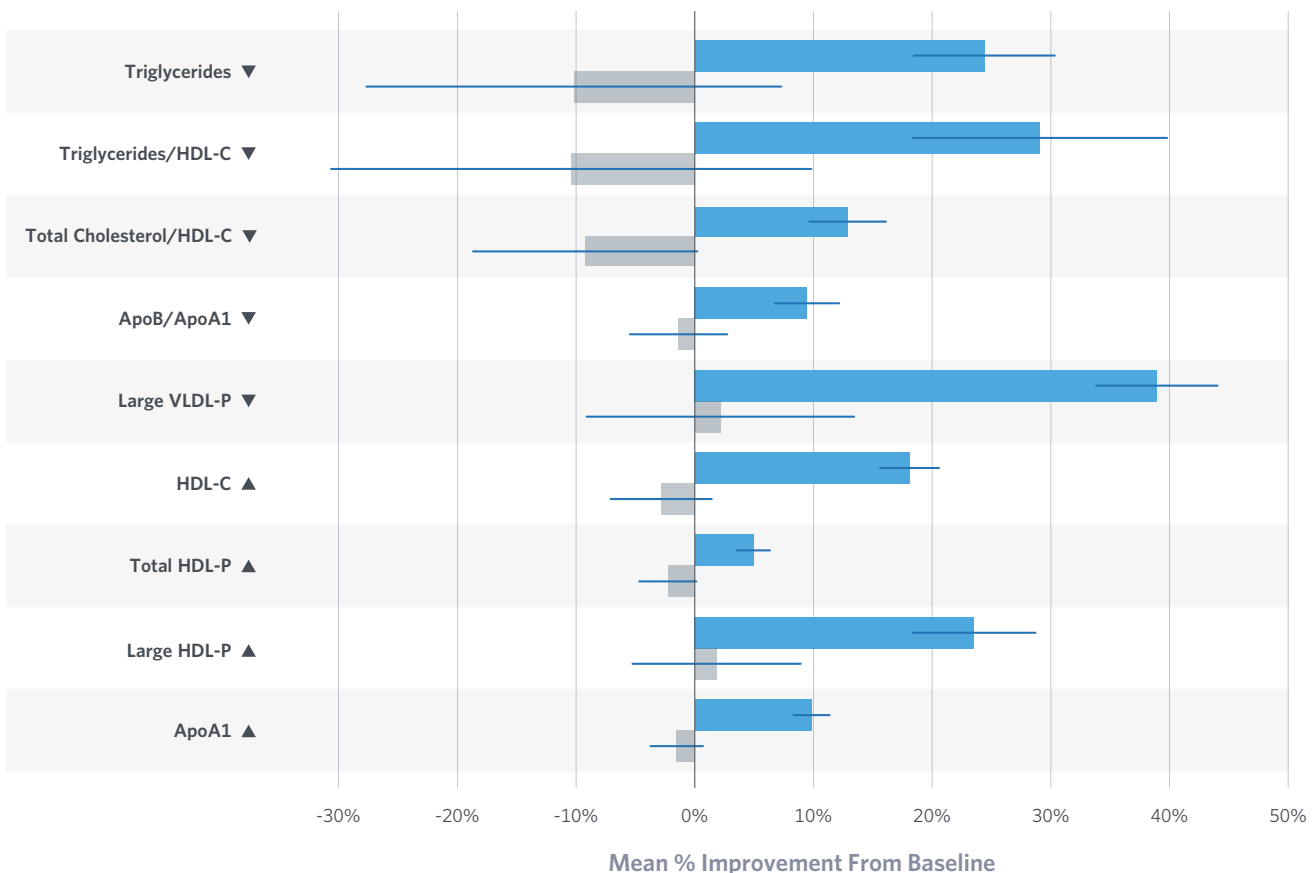
Strong evidence exists that hypertension is a primary cardiovascular risk factor; reduction in blood pressure (BP) is therefore a major target for medical therapy (Ettehad et al., 2016). Revised 2017 guidelines from the ACC/AHA task force recommend treatment, through lifestyle modification and/or medication, should begin at 130/80 mm Hg rather than 140/90 (Whelton et al., 2017). Following 1-yr of the Virta treatment, the mean patient systolic BP decreased 4.8% from 132 to 126 ($P=1.3 \times 10^{-8}$) while mean patient diastolic BP decreased 4.3% from 83 to 79 ($P=7.2 \times 10^{-8}$) (Bhanpuri et al., 2018). Blood pressure reductions in the Virta treatment group occurred simultaneous with reduced overall use of antihypertensive medication (-17.0%) and especially diuretics (-24.8%) as described in detail below (section 10). The usual care group showed no statistically significant change in BP at one year; 130/82 to 129/81 ($P=0.67$ and 0.45 , respectively), and no reduction in use of antihypertensive medication.



Blood pressure reductions following carbohydrate restriction and/or nutritional ketosis have been demonstrated in several trials (Ballard et al., 2013; Shai et al., 2010; Tay et al., 2014).

3. Atherogenic Dyslipidemia Improves

Atherogenic dyslipidemia, a known risk factor for CVD (Fruchart et al., 2008) is highly prevalent in patients with T2D (Arca et al., 2012). The condition is characterized by lipid profile abnormalities including increased triglycerides and decreased high-density lipoprotein cholesterol (HDL-C). Furthermore, evidence suggests that elevated large very low-density lipoprotein particles (large VLDL-P) may be one of the key underlying abnormalities in atherogenic dyslipidemia (Adiels et al., 2008). In addition to impacting the eight factors shown here, atherogenic dyslipidemia also results in increased small LDL-P described below (section 4). Following 1-yr of the Virta treatment, mean fasting triglyceride was reduced 24.4% ($P < 10^{-16}$), triglyceride/HDL-C ratio was reduced 29.1% ($P < 10^{-16}$), total cholesterol/HDL-C ratio was reduced 11.2% ($P = 1.7 \times 10^{-5}$), ApoB/ApoA1 ratio was reduced 9.5% ($P = 1.9 \times 10^{-7}$),

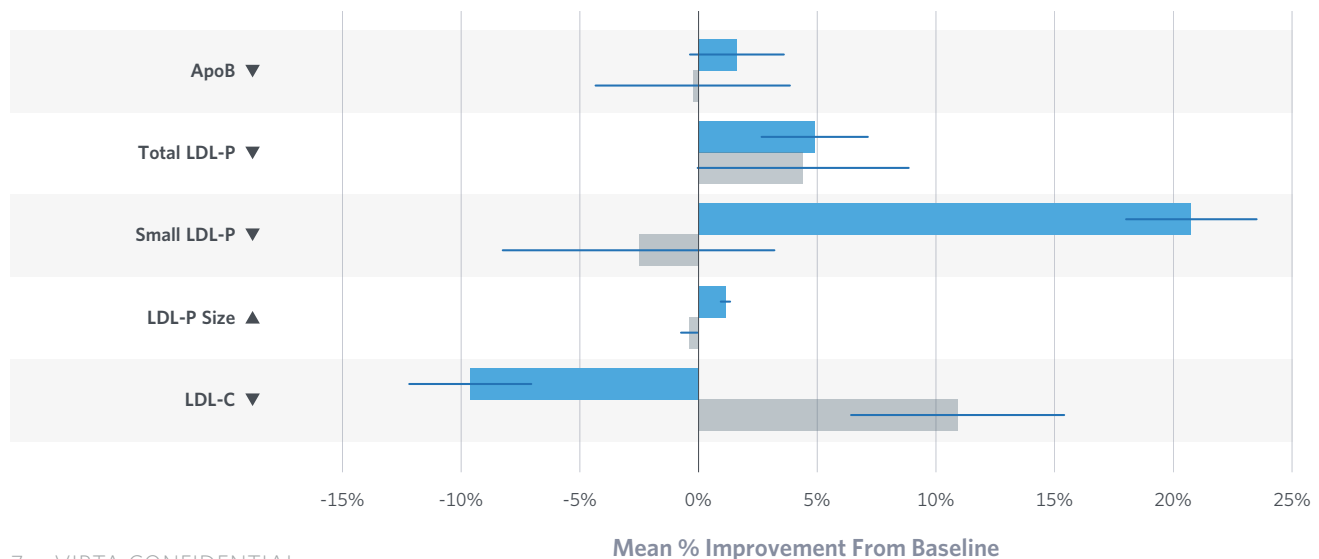


large VLDL-P was reduced 38.9% ($P=4.2 \times 10^{-15}$), HDL-C increased 18.1% ($P < 10^{-16}$), total HDL particles (HDL-P) increased 4.9% ($P=5.6 \times 10^{-6}$), and large HDL-P increased 23.5% ($P=1.2 \times 10^{-11}$). Apolipoprotein A1 (Apo A1), a marker of HDL particles, also increased 9.9% ($P < 10^{-16}$) (Bhanpuri et al., 2018; Hallberg et al., 2018). All of these changes are favorable and together indicate an improvement of atherogenic dyslipidemia following the Virta treatment. The usual care group showed no statistically significant change in these parameters; triglyceride +10.1% ($P=0.43$), triglyceride/HDL-C ratio +9.8% ($P=0.24$), total cholesterol/HDL-C ratio +7.9% ($P=0.24$), ApoB/ApoA1 ratio +2.8% ($P=0.58$), large VLDL-P +0% ($P=0.77$), HDL-C -2.6% ($P=0.41$), total HDL-P -2.3% ($P=0.23$), large HDL-P +2.6% ($P=0.74$), and Apo A1 -1.4% ($P=0.37$).

Greater improvement of atherogenic dyslipidemia in low carbohydrate versus low fat diets have been reproduced in many trials measuring triglycerides and HDL-C including Westman et al., 2008 (T2D), Volek et al., 2008 (metabolic syndrome), Hussain et al., 2012 (T2D), Tay et al., 2014 (T2D), and Bazzano et al., 2014 (obesity) and confirmed in a meta-analysis of eleven trials (Mansoor et al., 2016).

4. LDL Particles Shift Toward the Non-atherogenic Fraction

While higher calculated low-density lipoprotein cholesterol (LDL-C) has traditionally been associated with increased CVD risk (Giugliano et al., 2017; Law et al., 2003), LDL-C has recently been correlated with improved survival in two large prospective studies and a systematic review (Orozco-Beltran et al., 2017; Ravnskov et al., 2016; Zuliani et al., 2017). The pattern is especially apparent in elderly cohorts. Studies also indicate tracking Apolipoprotein B (ApoB) (Barter et al., 2006) or LDL-P particle number (Otvos et al., 2011) provides a better CVD risk measure. Further, the subfraction distribution of LDL particles is likely more important with small, dense LDL particles (small LDL-P) associated with atherogenesis while large, buoyant LDL particles appear relatively neutral in their effect on CVD risk (Gardner et al., 1996; Rizzo and Berneis, 2007; Superko, 2001). Following 1-yr of the Virta treatment, while mean LDL-C rises (+9.6%, $P=4.9 \times 10^{-5}$), overall LDL particle number is unchanged as measured by both Apo B (-1.9%, $P=0.37$) and LDL-P (-4.9%, $P=0.02$). The distribution of LDL particles shifts

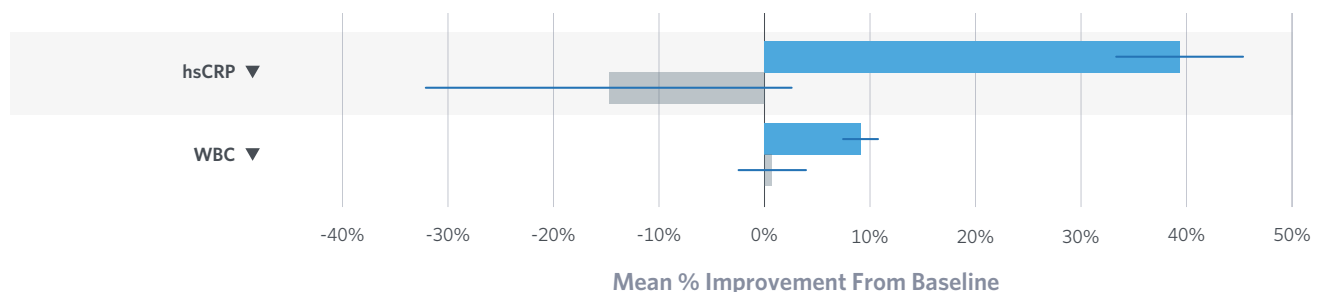


significantly away from small LDL-P (-20.8% , $P=1.2 \times 10^{-12}$) and the mean LDL particle size rises ($+1.1\%$, $P=6.0 \times 10^{-10}$) (Bhanpuri et al., 2018). While counter to the traditional metric, the overall picture is of a potentially beneficial change in the LDL profile. The usual care group showed no statistically significant change in LDL parameters; LDL-C (-11.0% , $P=0.02$), Apo B ($+0\%$, $P=0.95$), LDL-P (-4.4% , $P=0.31$), small LDL-P ($+2.5\%$, $P=0.67$) and mean LDL-P size (-0.3% , $P=0.25$).

While higher saturated fat consumption can result in an LDL-C rise, it does not result in an increase in CVD risk (Chowdhury et al., 2014; Mente et al., 2017; Ramsden et al., 2016; Siri-Tarino et al., 2010a), contradicting the diet-heart hypothesis (Noakes and Windt, 2017; Siri-Tarino et al., 2010b). Low carbohydrate and nutritional ketosis trials often show a rise in LDL-C (Mansoor et al., 2016; Nordmann et al., 2006), but trials also show a consistent reduction in the small, dense LDL particles and a corresponding increase in large, buoyant LDL particles relative to low fat diets (Aude et al., 2004; Forsythe et al., 2010; Volek et al., 2008; R. J. Wood et al., 2006). A reasonable interpretation of the evidence is that LDL-C is not a useful marker of CVD risk in the context of a ketogenic diet where fat is the primary fuel source, the LDL profile is dominated by large non-atherogenic LDL particles (T. R. Wood et al., 2016), and other CVD risk factors are showing favorable changes.

5. Inflammation Improves

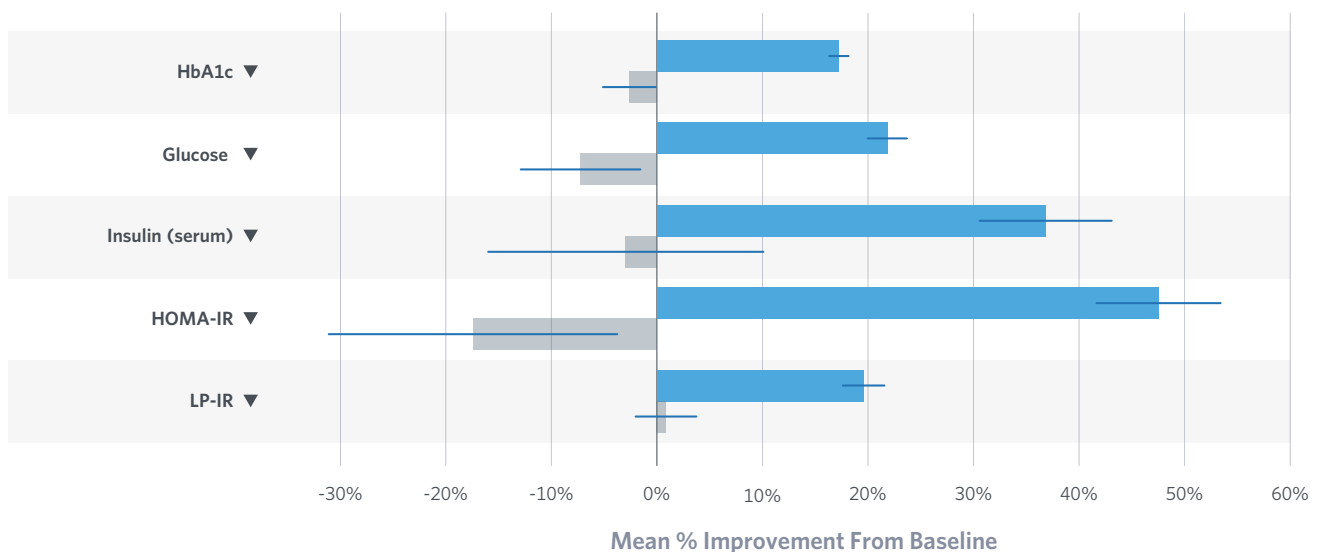
Inflammation is an independent CVD risk factor involved in all stages of atherogenesis (Libby et al., 2009). High-sensitivity C-reactive protein (hsCRP) and white blood cell count (WBC) are widely accepted markers of inflammation and risk factors for CVD (Folsom et al., 2002; Kannel et al., 1992). Following 1-yr of the Virta treatment, hsCRP was reduced 39.3% ($P < 10^{-16}$) and WBC was reduced 9.1% ($P < 3.2 \times 10^{-11}$) indicating a substantial reduction in inflammation (Bhanpuri et al., 2018). The usual care group showed no statistically significant change in hsCRP ($+14.4\%$, $P=0.93$) or WBC (-1.2% , $P=0.76$).



Reductions in inflammation through carbohydrate restriction and/or nutritional ketosis have been demonstrated in several prior clinical trials. Forsythe found significant decreases in inflammatory markers following twelve weeks of a low carbohydrate diet in overweight adults including hsCRP (-23%) and significantly larger decreases than a low fat diet for TNF- α , IL-8, MCP-1, E-selectin and I-CAM (Forsythe et al., 2007). Shai observed a significant decrease in hsCRP (-29%) following a 2-yr low carbohydrate diet (Shai et al., 2008).

6. Type 2 Diabetes Status Improves

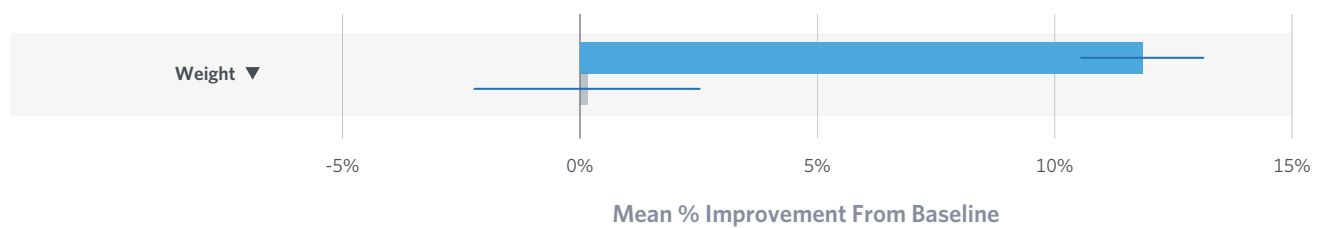
Diabetes itself is a major CVD risk factor. CVD risk increases two to four-fold with a diagnosis of T2D (Martín-Timón et al., 2014) and risk is reduced with lowered HbA1c (Eeg-Olofsson et al., 2016). T2D status following one year of Virta treatment improves based on mean HbA1c decrease of 17% ($P < 1.0 \times 10^{-16}$) (from 7.6% to 6.3%), fasting glucose decrease of 22% ($P < 1.0 \times 10^{-16}$), fasting insulin decrease of 43% ($P = 6.7 \times 10^{-16}$), homeostatic model assessment of insulin resistance (HOMA-IR) decrease of 55% ($P = 73.2 \times 10^{-5}$) (Hallberg et al., 2018) and NMR-derived lipoprotein insulin resistance score (LP-IR) decrease of 19.6% ($P < 10^{-16}$) (Bhanpuri et al., 2018). Additionally, 69.8% of Virta patients achieved a 1-yr HbA1c below the diabetes threshold of 6.5%. Diabetes status improvements in the Virta treatment group occurred simultaneous with reduced use of diabetes medications other than metformin (-47.8% of all prescriptions discontinued) and especially insulin (94% of prescriptions reduced or discontinued) as described in detail below (section 10). 60% of patients had a 1-yr HbA1c $< 6.5\%$ while taking no diabetes medications or metformin only, a metric used by Virta for “diabetes reversal”. Virta manages toward long-term reversal through continued nutritional and behavior change. The usual care group showed no improvement in diabetes status; mean changes included HbA1c +2.6% ($P = 0.18$), fasting glucose +7.3% ($P = 0.2$), fasting insulin +3.0% ($P = 0.81$), HOMA-IR +17.5% ($P = 0.22$), and LP-IR -1.4% ($P = 0.74$). Aggregate scores are described by Matthews et al., 1985 for HOMA-IR and by Shalaurava et al., 2014 for LP-IR, a combination of six lipoprotein measures.



Improvements in T2D status through nutritional ketosis under medical supervision have been demonstrated previously in short-term randomized in-patient experiments (Boden et al., 2005), in randomized out-patient trials of up to one year (Goday et al., 2016; Saslow, 2017; Saslow et al., 2017; 2014; Westman et al., 2008) in trial follow-up of over 3 years (Nielsen and Joensson, 2008), in non-randomized trials (Hussain et al., 2012), and in clinical case series (Dashti et al., 2007).

7. Obesity Improves

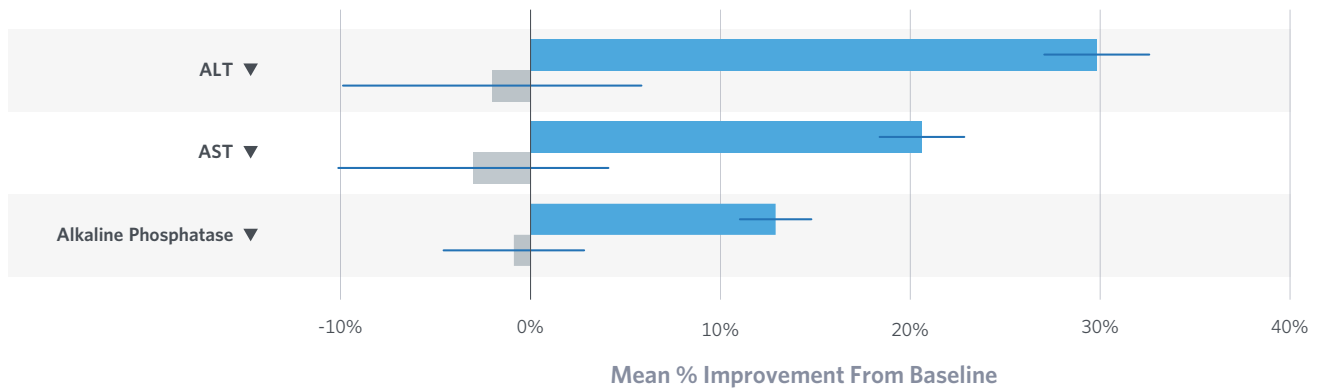
Obesity is an important independent CVD risk factor (GBD 2015 Obesity Collaborators et al., 2017; Hubert et al., 1983). Virta intervention trial participants had a mean starting weight of 116.5 kg (256.9 lbs.), mean body mass index (BMI) of 40.4 kg/m², 93% were obese and 45.6% had class III (high risk) obesity. Following 1-yr of the Virta treatment, the mean patient weight declined 12% ($P < 1.0 \times 10^{-16}$) or 30.8 lbs, mean BMI declined 4.8 to 35.6 kg/m², and class III obesity was reduced to 19.6% of the cohort (Hallberg et al., 2018). The usual care group had a mean starting weight of 105.6 kg (232.9 lbs), mean BMI of 36.7, and 82% were obese; no improvement in mean weight was observed at 1-yr (-0.15% , $P = 0.85$), and BMI and obesity class distribution were also unchanged.



Improvements in obesity through carbohydrate restriction or nutritional ketosis have been demonstrated in numerous clinical trials including Bazzano et al., 2014; Gardner et al., 2007; Moreno et al., 2014; Shai et al., 2008; Yancy et al., 2005. It should be noted that few trials have obtained the degree of weight loss achieved by the Virta treatment at one year possibly because expectations around dietary changes were less intensive (e.g. mild carbohydrate restriction versus monitored nutritional ketosis) or support for behavior change was less effective (e.g. group instruction versus individualized online health coaching and telemedicine) (Gardner et al., 2018).

8. Liver Function Improves

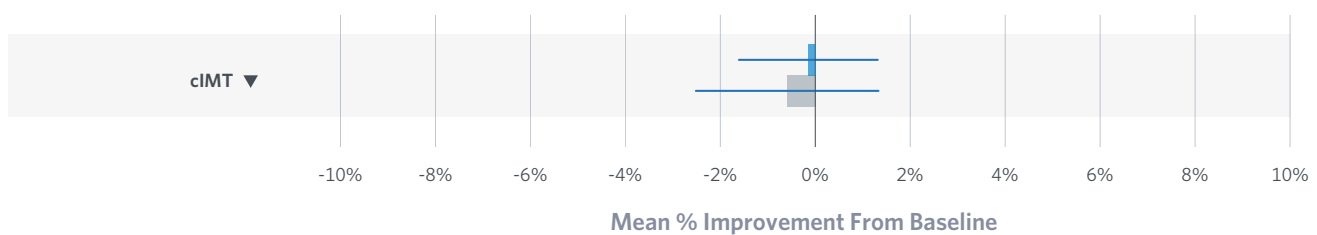
Non-alcoholic fatty liver disease (NAFLD) is highly prevalent among obese and T2D patients (Portillo-Sanchez et al., 2015) and is associated with increased CVD risk (Adams et al., 2017). NAFLD can progress to non-alcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Elevated serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) are often observed in NAFLD; elevated ALT and ALP are CVD risk factors (Targher and Byrne, 2015). ALT and AST are used in calculating NAFLD liver fat score (NAFLD-LFS) and NAFLD fibrosis score (NFS) (Angulo et al., 2007; Kotronen et al., 2009). Following 1-yr of the Virta treatment, mean patient ALT declined 29.4% ($P = 2.4 \times 10^{-10}$), AST declined 20.0% ($P = 5.1 \times 10^{-7}$) and ALP declined 12.9% ($P < 1.0 \times 10^{-16}$) (Hallberg et al., 2018). The usual care group showed no significant change in enzymes; ALT +2.2% ($P = 0.77$), AST +2.5% ($P = 0.72$) and ALP +1.0% ($P = 0.67$).



Few studies have examined liver enzymes and liver fat in long-term ketogenic diets. A two-year study of a low carbohydrate diet with weight loss resulted in statistically significant reduction in ALT (-9.2%) (Shai et al., 2008). A caloric restriction diet resulting in weight loss with or without mild carbohydrate restriction (38% or 53% carbohydrate) reduced ALT from elevated levels (de Luis et al., 2010). Short-term (two week) carbohydrate restriction (<20 g/day) resulted in sharp reduction in liver fat (Browning et al., 2011) and improved cardiometabolic risk factors in NAFLD patients (Mardinoglu et al., 2018).

9. Carotid Intima Media Thickness is Unchanged

Carotid intima media thickness (cIMT) is a non-invasive measure of atherosclerosis that is significantly associated with CVD morbidity (Doneen and Bale, 2013). However, a recent meta-analysis found that cIMT progression over an average of 3.6 years in 3,902 T2D patients did not correlate with increased CVD events (Lorenz et al., 2015). Following 1-yr of the Virta treatment or usual care there was no significant change in cIMT from baseline (P=0.65 and 0.87, respectively) (Bhanpuri et al., 2018).



Change in cIMT following long-term use of a ketogenic diet for epilepsy control has been examined in small cohorts. In 13 patients over two years (Kapetanakis et al., 2014) and 10 patients over a decade (Heussinger et al., 2017), no significant change in cIMT was observed. Progression or regression of cIMT may take many years to manifest and may require a larger cohort to achieve statistical significance. In summary, there is currently no cIMT evidence of vascular harm or benefit from long-term nutritional ketosis.

10. Medication use for Hypertension and Diabetes is Decreased

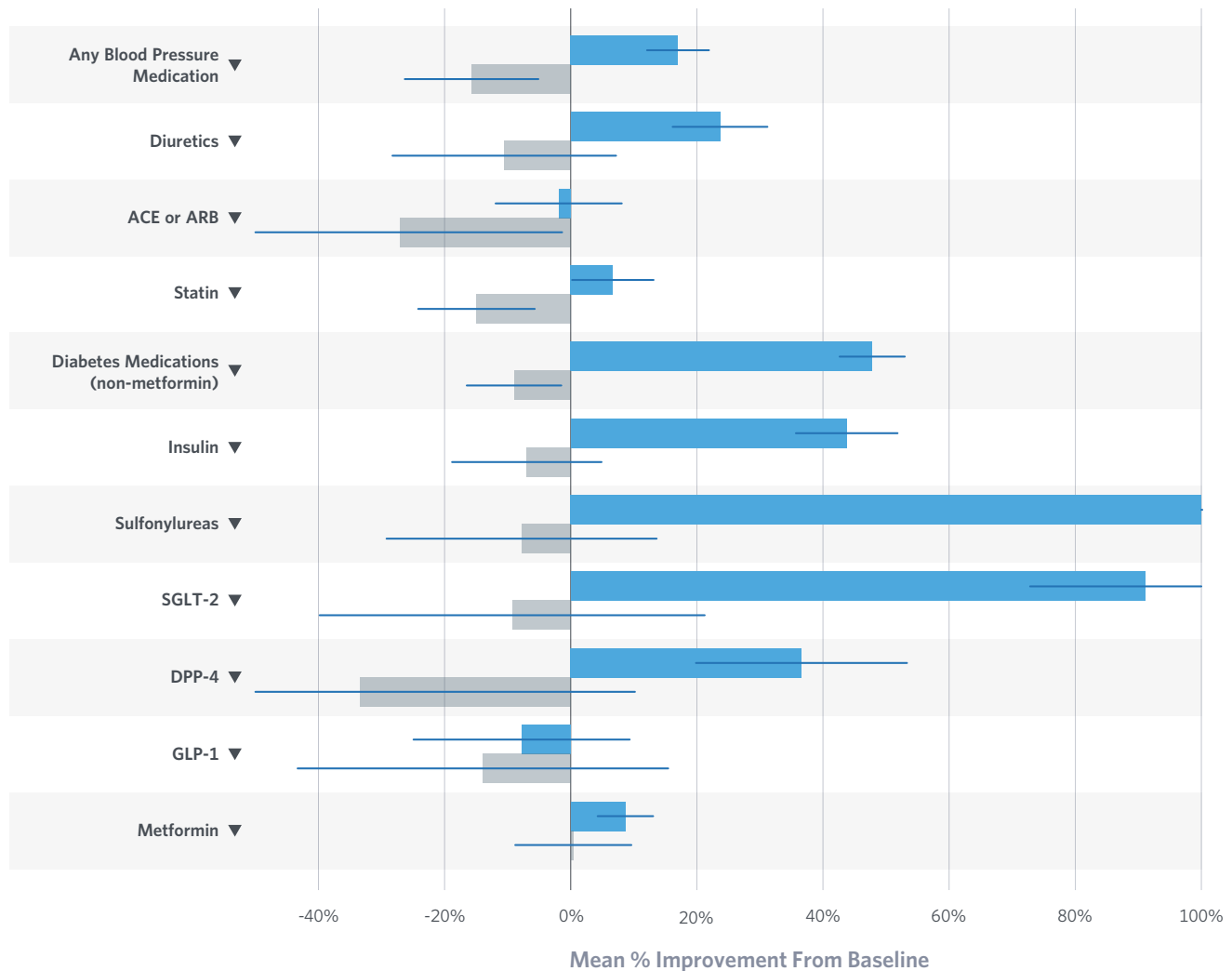
Prescription medications have powerful physiological impacts that come with substantial risk of iatrogenic effect so that reduced medication use when pharmaceutical treatment is no longer required can be beneficial (Gnjidic et al., 2012; Iyer et al., 2008). Negative effects of medications can result from side effects, allergic reactions, incorrect doses and timing, missed doses, overdose, drug-drug interactions (polypharmacy), physician and pharmacy mistakes, and product quality control issues (Classen et al., 2011; Ernst and Grizzle, 2001; Garfinkel et al., 2015; Poudel et al., 2017). Medications for hypertension can be problematic for hypotension and syncope especially in elderly patients (Williamson et al., 2016). Diabetes medications, especially insulin and sulfonylureas, can cause hypoglycemia and syncope (Abdelhafiz and Sinclair, 2017; Action to Control Cardiovascular Risk in Diabetes Study Group et al., 2008; McCoy et al., 2016). Insulin use also results in weight gain (Henry et al., 1993) and tight glycemic control achieved with pharmaceuticals is associated with a paradoxical increase in cardiovascular mortality (the ACCORD Study Group, 2011). Therefore, in both hypertension and diabetes care, an excellent rationale exists for removing medications when the health conditions can be managed effectively with individualized nutrition and behavior change.

Virta has developed physician-directed guidance for patient medication reductions and eliminations as blood pressure and blood glucose measurements and symptoms allow (Bhanpuri et al., 2018; Hallberg et al., 2018). Following resolution of hypertension, diuretics and beta blockers are often discontinued first. Angiotensin-converting-enzyme inhibitors (ACEs) and angiotensin II receptor blockers (ARBs) are generally continued due to known renal protection with diabetes (Jafar et al., 2001; Schmieder et al., 2011). Glycemic medications are reduced or eliminated to safely adjust for targeted decreases in glucose concentrations with a primary focus on preventing episodes of symptomatic hypoglycemia. Medication eliminations typically occur by first discontinuing sulfonylureas and SGLT-2 inhibitors, followed by short-acting, and then long-acting insulin. Thiazolidinediones, DPP-4 inhibitors, and GLP-1 are discontinued later. Metformin, given its effectiveness, low cost, tolerability and recommendation for use in pre-diabetes (American Diabetes Association, 2018), is often continued.

Following 1-yr of the Virta treatment, antihypertensive medication use declined 17.0% (from 67.2 to 55.8% of the population prescribed any BP medication, $P=5.3 \times 10^{-5}$) and diuretic use declined 24.8% (from 40.8 to 31.2%, $P=0.0004$). Changes in ACE or ARB use (+2.0%, from 29.4 to 30.0%, $P=0.76$) were not significant. Statin use did not change significantly (-6.6%, from 50.0 to 46.7%, $P=0.15$) (Bhanpuri et al., 2018). The use of any diabetes medication other than metformin declined 47.8% (from 56.9 to 29.7%, $P<1.0 \times 10^{-16}$). Use of individual diabetes prescriptions changed as follows: sulfonylureas, -100% (from 23.7% to 0%, $P<1.0 \times 10^{-16}$), SGLT-2 inhibitors -91.3% (10.3% to 0.9%, $P=9 \times 10^{-7}$), thiazolidinediones -73.3% (from 1.5%

to 0.4%, $P=.23$), insulin -44.0% (from 29.8% to 16.7%, $P=4.3 \times 10^{-9}$), DPP-4 -36.4% (from 9.9 to 6.3%, $P=.11$), metformin -9.0% (71.4% to 65.0%, $P=.04$) and GLP-1 +7.5% (from 13.4% to 14.4%, $P=.67$). Reductions in sulfonylureas, SGLT-2 inhibitors and insulin use were statistically significant. Patients who continued to use insulin reduced daily dosage significantly (-48.9%, from 105.2 to 53.8 units, $P<0.0001$) (Hallberg et al., 2018). The usual care group showed a trend toward increased medication use at 1-yr; any antihypertensive (+15.7%, $P=0.09$), diuretics (+10.4%, $P=0.44$), ACE/ARBs (+27.2%, $P=0.13$), statins (+15.0%, $P=0.04$), any diabetes medication other than metformin (+9.0%, $P=0.09$), sulfonylureas (+7.9%, $P=0.65$), SGLT-2 inhibitors (+6.1%, $P=0.78$), thiazolidinediones (+21.0%, $P=0.67$), insulin (+6.9%, $P=0.39$), DPP-4 (+32.6%, $P=0.37$), metformin (+0.1%, $P=0.99$), and GLP-1 (+20.9%, $P=0.44$). For the usual care participants who continued using insulin, the average daily dose increased significantly (+16.6% from 96.0 to 111.9 units, $P<0.0001$).

Medication eliminations following initiation of a ketogenic nutrition plan in T2D patients has been previously demonstrated for sulfonylureas and DPP-4 inhibitors at three months and one year (Saslow et al., 2017; 2014). Hussain et al., 2012 also report medication reductions and eliminations upon initiation of a ketogenic diet in T2D patients.



Conclusions

In published 1-yr results of a prospective longitudinal clinical trial comparing 262 intervention subjects and 87 usual care subjects with type 2 diabetes, the Virta treatment has demonstrated substantial and sustained beneficial impact on cardiovascular risk factors including improvement in the 10-year ASCVD risk score, hypertension, atherogenic dyslipidemia, LDL partitioning, inflammation, diabetes and insulin resistance, obesity and liver function. Simultaneously, medication usage for hypertension and diabetes was significantly reduced. Usual care subjects showed no improvements in CVD risk factors and no medication reductions. Numerous published studies of nutritional ketosis and carbohydrate restriction provide precedence for the observed CVD risk factor improvements. Together these findings provide a robust case for both near-term and projected long-term improved CVD outcomes in Virta's T2D patients.

References

- Abdelhafiz, A.H., Sinclair, A.J., 2017. Deintensification of hypoglycaemic medications-use of a systematic review approach to highlight safety concerns in older people with type 2 diabetes. *Journal of Diabetes and its Complications*. doi:10.1016/j.jdiacomp.2017.11.011
- Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein, H.C., Miller, M.E., Byington, R.P., Goff, D.C., Bigger, J.T., Buse, J.B., Cushman, W.C., Genuth, S., Ismail-Beigi, F., Grimm, R.H., Probstfield, J.L., Simons-Morton, D.G., Friedewald, W.T., 2008. Effects of intensive glucose lowering in type 2 diabetes. *N. Engl. J. Med.* 358, 2545-2559. doi:10.1056/NEJMoa0802743
- Adams, L.A., Anstee, Q.M., Tilg, H., Targher, G., 2017. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. *Gut* 66, 1138-1153. doi:10.1136/gutjnl-2017-313884
- Adiels, M., Olofsson, S.-O., Taskinen, M.-R., Borén, J., 2008. Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. *Arteriosclerosis, Thrombosis, and Vascular Biology* 28, 1225-1236. doi:10.1161/ATVBAHA.107.160192
- American Diabetes Association, 2018. 5. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 41, S51-S54. doi:10.2337/dc18-S005
- Angulo, P., Hui, J.M., Marchesini, G., Bugianesi, E., George, J., Farrell, G.C., Enders, F., Saksena, S., Burt, A.D., Bida, J.P., Lindor, K., Sanderson, S.O., Lenzi, M., Adams, L.A., Kench, J., Therneau, T.M., Day, C.P., 2007. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology* 45, 846-854. doi:10.1002/hep.21496
- Arca, M., Pigna, G., Favocchia, C., 2012. Mechanisms of diabetic dyslipidemia: relevance for atherogenesis. *Curr Vasc Pharmacol* 10, 684-686.
- Aude, Y.W., Agatston, A.S., Lopez-Jimenez, F., Lieberman, E.H., Marie Almon, Hansen, M., Rojas, G., Lamas, G.A., Hennekens, C.H., 2004. The national cholesterol education program diet vs a diet lower in carbohydrates and higher in protein and monounsaturated fat: a randomized trial. *Arch. Intern. Med.* 164, 2141-2146. doi:10.1001/archinte.164.19.2141
- Ballard, K.D., Quann, E.E., Kupchak, B.R., Volk, B.M., Kawiecki, D.M., Fernandez, M.L., Seip, R.L., Maresh, C.M., Kraemer, W.J., Volek, J.S., 2013. Dietary carbohydrate restriction improves insulin sensitivity, blood pressure, microvascular function, and cellular adhesion markers in individuals taking statins. *Nutrition Research* 33, 905-912. doi:10.1016/j.nutres.2013.07.022
- Barter, P.J., Ballantyne, C.M., Carmena, R., Castro Cabezas, M., Chapman, M.J., Couture, P., de Graaf, J., Durrington, P.N., Faergeman, O., Frohlich, J., Furberg, C.D., Gagne, C., Haffner, S.M., Humphries, S.E., Jungner, I., Krauss, R.M., Kwiterovich, P., Marcovina, S., Packard, C.J., Pearson, T.A., Reddy, K.S., Rosenson, R., Sarrafzadegan, N., Sniderman, A.D., Stalenhoef, A.F., Stein, E., Talmud, P.J., Tonkin, A.M., Walldius, G., Williams, K.M.S., 2006. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel., in: Presented at the Journal of internal medicine, Blackwell Publishing Ltd, pp. 247-258. doi:10.1111/j.1365-2796.2006.01616.x
- Bazzano, L.A., Hu, T., Reynolds, K., Yao, L., Bunol, C., Liu, Y., Chen, C.-S., Klag, M.J., Whelton, P.K., He, J., 2014. Effects of Low-Carbohydrate and Low-Fat Diets. *Ann Intern Med* 161, 309-318. doi:10.7326/M14-0180
- Bhanpuri, N.H., Hallberg, S.J., Williams, P.T., McKenzie, A.L., Ballard, K.D., Campbell, W.W., McCarter, J.P., Phinney, S.D., Volek, J.S., 2018. Cardiovascular Disease Risk Factor Responses to a Type 2 Diabetes Care Model Including Nutritional Ketosis at One Year: An Open Label, Non-Randomized, Controlled Study. doi:10.1101/262709
- Boden, G., Sargrad, K., Homko, C., Mozzoli, M., Stein, T.P., 2005. Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Ann Intern Med* 142, 403-411.
- Browning, J.D., Baker, J.A., Rogers, T., Davis, J., Satapati, S., Burgess, S.C., 2011. Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction. *American Journal of Clinical Nutrition* 93, 1048-1052. doi:10.3945/ajcn.110.007674
- Chowdhury, R., Warnakula, S., Kunutsor, S., Crowe, F., Ward, H.A., Johnson, L., Franco, O.H., Butterworth, A.S., Forouhi, N.G., Thompson, S.G., Khaw, K.-T., Mozaffarian, D., Danesh, J., Di Angelantonio, E., 2014. Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk. *Ann Intern Med* 160, 398-406. doi:10.7326/M13-1788
- Classen, D.C., Phansalkar, S., Bates, D.W., 2011. Critical drug-drug interactions for use in electronic health records systems with computerized physician order entry: review of leading approaches. *J Patient Saf* 7, 61-65. doi:10.1097/PTS.0b013e31821d6f6e
- Dashti, H.M., Mathew, T.C., Khadada, M., Al-Mousawi, M., Talib, H., Asfar, S.K., Behbahani, A.I., Al-Zaid, N.S., 2007. Beneficial effects of ketogenic diet in obese diabetic subjects. *Mol. Cell. Biochem.* 302, 249-256. doi:10.1007/s11010-007-9448-z
- de Luis, D.A., Aller, R., Izaola, O., Gonzalez Sagrado, M., Conde, R., 2010. Effect of two different hypocaloric diets in transaminases and insulin resistance in nonalcoholic fatty liver disease and obese patients. *Nutr Hosp* 25, 730-735.
- Doneen, A.L., Bale, B.F., 2013. Carotid intima-media thickness testing as an asymptomatic cardiovascular disease identifier and method for making therapeutic decisions. *Postgrad Med* 125, 108-123. doi:10.3810/pgm.2013.03.2645

- Eeg-Olofsson, K., Zethelius, B., Gudbjörnsdottir, S., Eliasson, B., Svensson, A.-M., Cederholm, J., 2016. Considerably decreased risk of cardiovascular disease with combined reductions in HbA1c, blood pressure and blood lipids in type 2 diabetes: Report from the Swedish National Diabetes Register. *Diab Vasc Dis Res* 13, 268–277. doi:10.1177/14791641166637311
- Ernst, F.R., Grizzle, A.J., 2001. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc (Wash)* 41, 192–199.
- Ettehad, D., Emdin, C.A., Kiran, A., Anderson, S.G., Callender, T., Emberson, J., Chalmers, J., Rodgers, A., Rahimi, K., 2016. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 387, 957–967. doi:10.1016/S0140-6736(15)01225-8
- Feinman, R.D., Pogozelski, W.K., Astrup, A., Bernstein, R.K., Fine, E.J., Westman, E.C., Accurso, A., Frassetto, L., Gower, B.A., McFarlane, S.I., Nielsen, J.V., Krarup, T., Saslow, L., Roth, K.S., Vernon, M.C., Volek, J.S., Wilshire, G.B., Dahlqvist, A., Sundberg, R., Childers, A., Morrison, K., Manninen, A.H., Dashti, H.M., Wood, R.J., Wortman, J., Worm, N., 2015. Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. *Nutrition* 31, 1–13. doi:10.1016/j.nut.2014.06.011
- Folsom, A.R., Aleksic, N., Catellier, D., Juneja, H.S., Wu, K.K., 2002. C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk In Communities (ARIC) study. *American Heart Journal* 144, 233–238.
- Forsythe, C.E., Phinney, S.D., Feinman, R.D., Volk, B.M., Freidenreich, D., Quann, E., Ballard, K., Puglisi, M.J., Maresh, C.M., Kraemer, W.J., Bibus, D.M., Fernandez, M.L., Volek, J.S., 2010. Limited Effect of Dietary Saturated Fat on Plasma Saturated Fat in the Context of a Low Carbohydrate Diet. *Lipids* 45, 947–962. doi:10.1007/s11745-010-3467-3
- Forsythe, C.E., Phinney, S.D., Fernandez, M.L., Quann, E.E., Wood, R.J., Bibus, D.M., Kraemer, W.J., Feinman, R.D., Volek, J.S., 2007. Comparison of Low Fat and Low Carbohydrate Diets on Circulating Fatty Acid Composition and Markers of Inflammation. *Lipids* 43, 65–77. doi:10.1007/s11745-007-3132-7
- Fruchart, J.-C., Sacks, F., Hermans, M.P., Assmann, G., Brown, W.V., Ceska, R., Chapman, M.J., Dodson, P.M., Fioretto, P., Ginsberg, H.N., Kadowaki, T., Lablanche, J.-M., Marx, N., Plutzky, J., Reiner, Z., Rosenson, R.S., Staels, B., Stock, J.K., Sy, R., Wanner, C., Zambon, A., Zimmet, P., 2008. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. *The American Journal of Cardiology* 102, 1K–34K. doi:10.1016/S0002-9149(08)01833-X
- Gardner, C.D., Fortmann, S.P., Krauss, R.M., 1996. Association of Small Low-Density Lipoprotein Particles With the Incidence of Coronary Artery Disease in Men and Women. *JAMA* 276, 875–881. doi:10.1001/jama.1996.03540110029028
- Gardner, C.D., Kiazand, A., Alhassan, S., Kim, S., Stafford, R.S., Balise, R.R., Kraemer, H.C., King, A.C., 2007. Comparison of the Atkins, Zone, Ornish, and LEARN Diets for Change in Weight and Related Risk Factors Among Overweight Premenopausal Women. *JAMA* 297, 969–977. doi:10.1001/jama.297.9.969
- Gardner, C.D., Trepanowski, J.F., Del Gobbo, L.C., Hauser, M.E., Rigdon, J., Ioannidis, J.P.A., Desai, M., King, A.C., 2018. Effect of Low-Fat vs Low-Carbohydrate Diet on 12-Month Weight Loss in Overweight Adults and the Association With Genotype Pattern or Insulin Secretion: The DIETFITS Randomized Clinical Trial. *JAMA*. 319:667–679. doi:10.1001/jama.2018.0245
- Garfinkel, D., Ilhan, B., Bahat, G., 2015. Routine deprescribing of chronic medications to combat polypharmacy. *Ther Adv Drug Saf* 6, 212–233. doi:10.1177/2042098615613984
- GBD 2015 Obesity Collaborators, Afshin, A., Forouzanfar, M.H., Reitsma, M.B., Sur, P., Estep, K., Lee, A., Marczak, L., Mokdad, A.H., Moradi-Lakeh, M., Naghavi, M., Salama, J.S., Vos, T., Abate, K.H., Abbafati, C., Ahmed, M.B., Al-Aly, Z., Alkerwi, A., Al-Raddadi, R., Amare, A.T., Amberbir, A., Amegah, A.K., Amini, E., Amrock, S.M., Anjana, R.M., Ärnlöv, J., Asayesh, H., Banerjee, A., Barac, A., Baye, E., Bennett, D.A., Beyene, A.S., Biadgilign, S., Biryukov, S., Bjertness, E., Boneya, D.J., Campos-Nonato, I., Carrero, J.J., Cecilio, P., Cercy, K., Ciobanu, L.G., Cornaby, L., Damtew, S.A., Dandona, L., Dandona, R., Dharmaratne, S.D., Duncan, B.B., Eshrati, B., Esteghamati, A., Feigin, V.L., Fernandes, J.C., Fürst, T., Gebrehiwot, T.T., Gold, A., Gona, P.N., Goto, A., Habtewold, T.D., Hadush, K.T., Hafezi-Nejad, N., Hay, S.I., Horino, M., Islami, F., Kamal, R., Kasaeian, A., Katikireddi, S.V., Kengne, A.P., Kesavachandran, C.N., Khader, Y.S., Khang, Y.-H., Khubchandani, J., Kim, D., Kim, Y.J., Kinfu, Y., Kosen, S., Ku, T., Defo, B.K., Kumar, G.A., Larson, H.J., Leinsalu, M., Liang, X., Lim, S.S., Liu, P., Lopez, A.D., Lozano, R., Majeed, A., Malekzadeh, R., Malta, D.C., Mazidi, M., McAlinden, C., McGarvey, S.T., Mengistu, D.T., Mensah, G.A., Mensink, G.B.M., Mezgebe, H.B., Mirakhorimov, E.M., Mueller, U.O., Noubiap, J.J., Obermeyer, C.M., Ogbo, F.A., Owolabi, M.O., Patton, G.C., Pourmalek, F., Qorbani, M., Rafay, A., Rai, R.K., Ranabhat, C.L., Reinig, N., Safiri, S., Salomon, J.A., Sanabria, J.R., Santos, I.S., Sartorius, B., Sawhney, M., Schmidhuber, J., Schutte, A.E., Schmidt, M.I., Sepanlou, S.G., Shamsizadeh, M., Sheikhbahaei, S., Shin, M.-J., Shiri, R., Shiue, I., Roba, H.S., Silva, D.A.S., Silverberg, J.I., Singh, J.A., Stranges, S., Swaminathan, S., Tabarés-Seisdedos, R., Tadese, F., Tedla, B.A., Tegegne, B.S., Terkawi, A.S., Thakur, J.S., Tonelli, M., Topor-Madry, R., Tyrovolas, S., Ukwaja, K.N., Uthman, O.A., Vaezghasemi, M., Vasankari, T., Vlassov, V.V., Vollset, S.E., Weiderpass, E., Werdecker, A., Wesana, J., Westerman, R., Yano, Y., Yonemoto, N., Yonga, G., Zaidi, Z., Zenebe, Z.M., Zipkin, B., Murray, C.J.L., 2017. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N. Engl. J. Med.* 377, 13–27. doi:10.1056/NEJMoa1614362
- Giugliano, R.P., Pedersen, T.R., Park, J.-G., De Ferrari, G.M., Gaciong, Z.A., Ceska, R., Toth, K., Gouni-Berthold, I., Lopez-Miranda, J., Schiele, F., Mach, F., Ott, B.R., Kanevsky, E., Pineda, A.L., Somaratne, R., Wasserman, S.M., Keech, A.C., Sever, P.S., Sabatine, M.S., FOURIER Investigators, 2017. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet* 390, 1962–1971. doi:10.1016/S0140-6736(17)32290-0

- Gnjidic, D., Le Couteur, D.G., Kouladjian, L., Hilmer, S.N., 2012. Deprescribing trials: methods to reduce polypharmacy and the impact on prescribing and clinical outcomes. *Clin. Geriatr. Med.* 28, 237–253. doi:10.1016/j.cger.2012.01.006
- Goday, A., Bellido, D., Sajoux, I., Crujeiras, A.B., Burguera, B., García-Luna, P.P., Oleaga, A., Moreno, B., Casanueva, F.F., 2016. Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus. *Nutr Diab* 6, e230–e230. doi:10.1038/nutd.2016.36
- Goff, D.C., Lloyd-Jones, D.M., Bennett, G., Coady, S., D'Agostino, R.B., Gibbons, R., Greenland, P., Lackland, D.T., Levy, D., O'Donnell, C.J., Robinson, J.G., Schwartz, J.S., Shero, S.T., Sorlie, P., Stone, N.J., Wilson, P.W.F., Jordan, H.S., Nevo, L., Wnek, J., Anderson, J.L., Halperin, J.L., Albert, N.M., Bozkurt, B., Brindis, R.G., Curtis, L.H., DeMets, D., Hochman, J.S., Kovacs, R.J., Ohman, E.M., Pressler, S.J., Sellke, F.W., Shen, W.-K., Smith, S.C., Tomaselli, G.F., American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 2014. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. doi:10.1161/01.cir.0000437741.48606.98
- Gregg, E.W., Gu, Q., Cheng, Y.J., Narayan, K.M.V., Cowie, C.C., 2007. Mortality trends in men and women with diabetes, 1971 to 2000. *Ann Intern Med* 147, 149–155.
- Hallberg, S.J., McKenzie, A.L., Williams, P.T., Bhanpuri, N.H., Peters, A.L., Campbell, W.W., Hazbun, T.L., Volk, B.M., McCarter, J.P., Phinney, S.D., Volek, J.S., 2018. Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study. *Diabetes Therapy* 387, 1513–30. doi:10.1007/s13300-018-0373-9
- Henry, R.R., Gumbiner, B., Ditzler, T., Wallace, P., Lyon, R., Glauber, H.S., 1993. Intensive conventional insulin therapy for type II diabetes. Metabolic effects during a 6-mo outpatient trial. *Diabetes Care* 16, 21–31.
- Heussinger, N., Marina, Della, A., Beyerlein, A., Leiendecker, B., Hermann-Alves, S., Dalla Pozza, R., Klepper, J., 2017. 10 patients, 10 years - Long term follow-up of cardiovascular risk factors in Glut1 deficiency treated with ketogenic diet therapies: A prospective, multicenter case series. *Clin Nutr*. doi:10.1016/j.clnu.2017.11.001
- Hubert, H.B., Feinleib, M., McNamara, P.M., Castelli, W.P., 1983. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 67, 968–977.
- Hussain, T.A., Mathew, T.C., Dashti, A.A., Asfar, S., Al-Zaid, N., Dashti, H.M., 2012. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition* 28, 1016–1021. doi:10.1016/j.nut.2012.01.016
- Iyer, S., Naganathan, V., McLachlan, A.J., Le Couteur, D.G., 2008. Medication withdrawal trials in people aged 65 years and older: a systematic review. *Drugs Aging* 25, 1021–1031. doi:10.2165/0002512-200825120-00004
- Jafar, T.H., Schmid, C.H., Landa, M., Giatras, I., Toto, R., Remuzzi, G., Maschio, G., Brenner, B.M., Kamper, A., Zucchelli, P., Becker, G., Himmelmann, A., Bannister, K., Landais, P., Shahinfar, S., de Jong, P.E., de Zeeuw, D., Lau, J., Levey, A.S., 2001. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 135, 73–87.
- Kannel, W.B., Anderson, K., Wilson, P.W., 1992. White blood cell count and cardiovascular disease. Insights from the Framingham Study. *JAMA* 267, 1253–1256.
- Kapetanakis, M., Liuba, P., Odermarsky, M., Lundgren, J., Hallböök, T., 2014. Effects of ketogenic diet on vascular function. *European Journal of Paediatric Neurology* 18, 489–494. doi:10.1016/j.ejpn.2014.03.006
- Kotronen, A., Peltonen, M., Hakkarainen, A., Sevastianova, K., Bergholm, R., Johansson, L.M., Lundbom, N., Rissanen, A., Ridderstråle, M., Groop, L., Orho-Melander, M., Yki-Järvinen, H., 2009. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. *Gastroenterology* 137, 865–872. doi:10.1053/j.gastro.2009.06.005
- Law, M.R., Wald, N.J., Rudnicka, A.R., 2003. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 326, 1423–O. doi:10.1136/bmj.326.7404.1423
- Libby, P., Ridker, P.M., Hansson, G.K., Leducq Transatlantic Network on Atherothrombosis, 2009. Inflammation in atherosclerosis: from pathophysiology to practice. *Journal of the American College of Cardiology* 54, 2129–2138. doi:10.1016/j.jacc.2009.09.009
- Lorenz, M.W., Price, J.F., Robertson, C., Bots, M.L., Polak, J.F., Poppert, H., Kavousi, M., Dörr, M., Stensland, E., Ducimetiere, P., Ronkainen, K., Kiechl, S., Sitzer, M., Rundek, T., Lind, L., Liu, J., Bergström, G., Grigore, L., Bokemark, L., Frier, A., Yanez, D., Bickel, H., Ikram, M.A., Völzke, H., Johnsen, S.H., Empana, J.P., Tuomainen, T.-P., Willeit, P., Steinmetz, H., Desvarieux, M., Xie, W., Schmidt, C., Norata, G.D., Suarez, C., Sander, D., Hofman, A., Schminke, U., Mathiesen, E., Plichart, M., Kauhanen, J., Willeit, J., Sacco, R.L., McLachlan, S., Zhao, D., Fagerberg, B., Catapano, A.L., Gabriel, R., Franco, O.H., Bülbül, A., Scheckenbach, F., Pflug, A., Gao, L., Thompson, S.G., 2015. Carotid intima-media thickness progression and risk of vascular events in people with diabetes: results from the PROG-IMT collaboration. *Diabetes Care* 38, 1921–1929. doi:10.2337/dc14-2732
- Mansoor, N., Vinknes, K.J., Veierød, M.B., Retterstøl, K., 2016. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. *Br J Nutr* 115, 466–479. doi:10.1017/S0007114515004699
- Mardinoglu, A., Wu, H., Bjornson, E., Zhang, C., Hakkarainen, A., Räsänen, S.M., Lee, S., Mancina, R.M., Bergentall, M., Pietiläinen,

- K.H., Söderlund, S., Matikainen, N., Ståhlman, M., Bergh, P.-O., Adiels, M., Piening, B.D., Granér, M., Lundbom, N., Williams, K.J., Romeo, S., Nielsen, J., Snyder, M., Uhlén, M., Bergström, G., Perkins, R., Marschall, H.-U., Bäckhed, F., Taskinen, M.-R., Borén, J., 2018. An Integrated Understanding of the Rapid Metabolic Benefits of a Carbohydrate-Restricted Diet on Hepatic Steatosis in Humans. *Cell Metabolism*. doi:10.1016/j.cmet.2018.01.005
- Martín-Timón, I., Sevillano-Collantes, C., Segura-Galindo, A., Del Cañizo-Gómez, F.J., 2014. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World J Diabetes* 5, 444–470. doi:10.4239/wjd.v5.i4.444
- Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C., 1985. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28, 412–419. doi:10.1007/BF00280883
- McCoy, R.G., Lipska, K.J., Yao, X., Ross, J.S., Montori, V.M., Shah, N.D., 2016. Intensive Treatment and Severe Hypoglycemia Among Adults With Type 2 Diabetes. *JAMA Intern Med* 176, 969–978. doi:10.1001/jamainternmed.2016.2275
- McKenzie, A., Hallberg, S., Creighton, B.C., Volk, B.M., Link, T., Abner, M., Glon, R., McCarter, J., Volek, J.S., Phinney, S.D., 2017. A Novel Intervention Including Individualized Nutritional Recommendations Reduces Hemoglobin A1c Level, Medication Use, and Weight in Type 2 Diabetes. *JMIR Diabetes* 2, e5.
- Mente, A., Dehghan, M., Rangarajan, S., McQueen, M., Dagenais, G., Wielgosz, A., Lear, S., Li, W., Chen, H., Yi, S., Wang, Y., Diaz, R., Avezum, A., Lopez-Jaramillo, P., Seron, P., Kumar, R., Gupta, R., Mohan, V., Swaminathan, S., Kutty, R., Zatonska, K., Iqbal, R., Yusuf, R., Mohammadifard, N., Khatib, R., Nasir, N.M., Ismail, N., Oguz, A., Rosengren, A., Yusufali, A., Wentzel-Viljoen, E., Puoane, T., Chifamba, J., Teo, K., Anand, S.S., Yusuf, S., Prospective Urban Rural Epidemiology (PURE) study investigators, 2017. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. *THE LANCET Diabetes & Endocrinology*. doi:10.1016/S2213-8587(17)30283-8
- Moreno, B., Bellido, D., Sajoux, I., Goday, A., Saavedra, D., Crujeiras, A.B., Casanueva, F.F., 2014. Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. *Endocrine* 47, 793–805. doi:10.1007/s12020-014-0192-3
- Nielsen, J.V., Joensson, E.A., 2008. Low-carbohydrate diet in type 2 diabetes: stable improvement of bodyweight and glycemic control during 44 months follow-up. *Nutr Metab* 5, 14–6. doi:10.1186/1743-7075-5-14
- Noakes, T.D., Windt, J., 2017. Evidence that supports the prescription of low-carbohydrate high-fat diets: a narrative review. *British Journal of Sports Medicine* 51, 133–139. doi:10.1136/bjsports-2016-096491
- Nordmann, A.J., Nordmann, A., Briel, M., Keller, U., Yancy, W.S., Brehm, B.J., Bucher, H.C., 2006. Effects of Low-Carbohydrate vs Low-Fat Diets on Weight Loss and Cardiovascular Risk Factors: A Meta-analysis of Randomized Controlled Trials. *Arch. Intern. Med.* 166, 285–293. doi:10.1001/archinte.166.3.285
- Orozco-Beltran, D., Gil-Guillen, V.F., Redon, J., Martin-Moreno, J.M., Pallares-Carratala, V., Navarro-Perez, J., Valls-Roca, F., Sanchis-Domenech, C., Fernandez-Gimenez, A., Perez-Navarro, A., Bertomeu-Martinez, V., Bertomeu-Gonzalez, V., Cordero, A., Pascual de la Torre, M., Trillo, J.L., Carratala-Munuera, C., Pita-Fernandez, S., Uso, R., Durazo-Arvizu, R., Cooper, R., Sanz, G., Castellano, J.M., Ascaso, J.F., Carmena, R., Tellez-Plaza, M., ESCARVAL Study Group, 2017. Lipid profile, cardiovascular disease and mortality in a Mediterranean high-risk population: The ESCARVAL-RISK study. *PLoS ONE* 12, e0186196. doi:10.1371/journal.pone.0186196
- Otvos, J.D., Mora, S., Shalauova, I., Greenland, P., Mackey, R.H., Goff, D.C., 2011. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *Journal of Clinical Lipidology* 5, 105–113. doi:10.1016/j.jacl.2011.02.001
- Portillo-Sanchez, P., Bril, F., Maximos, M., Lomonaco, R., Biernacki, D., Orsak, B., Subbarayan, S., Webb, A., Hecht, J., Cusi, K., 2015. High Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels. *J. Clin. Endocrinol. Metab.* 100, 2231–2238. doi:10.1210/jc.2015-1966
- Poudel, D.R., Acharya, P., Ghimire, S., Dhital, R., Bharati, R., 2017. Burden of hospitalizations related to adverse drug events in the USA: a retrospective analysis from large inpatient database. *Pharmacoepidemiol Drug Saf* 26, 635–641. doi:10.1002/pds.4184
- Ramsden, C.E., Zamora, D., Majchrzak-Hong, S., Faurot, K.R., Broste, S.K., Frantz, R.P., Davis, J.M., Ringel, A., Suchindran, C.M., Hibbeln, J.R., 2016. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73). *BMJ* 353, i1246. doi:10.1136/bmj.i1246
- Ravnskov, U., Diamond, D.M., Hama, R., Hamazaki, T., Hammarckjöld, B., Hynes, N., Kendrick, M., Langsjoen, P.H., Malhotra, A., Mascitelli, L., McCully, K.S., Ogushi, Y., Okuyama, H., Rosch, P.J., Schersten, T., Sultan, S., Sundberg, R., 2016. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. *BMJ Open* 6, e010401. doi:10.1136/bmjopen-2015-010401
- Rizzo, M., Berneis, K., 2007. Small, dense low-density-lipoproteins and the metabolic syndrome. *Diabetes Metab. Res. Rev.* 23, 14–20. doi:10.1002/dmrr.694
- Sackner-Bernstein, J., Kanter, D., Kaul, S., 2015. Dietary Intervention for Overweight and Obese Adults: Comparison of Low-Carbohydrate and Low-Fat Diets. A Meta-Analysis. *PLoS ONE* 10, e0139817. doi:10.1371/journal.pone.0139817
- Saslow, L.R., 2017. An Online Intervention Comparing a Very Low-Carbohydrate Ketogenic Diet and Lifestyle Recommendations

- Versus a Plate Method Diet in Overweight Individuals With Type 2 Diabetes: A Randomized Controlled Trial. *J Med Internet Res* 19, e36. doi:10.2196/jmir.5806
- Saslow, L.R., Daubenmier, J.J., Moskowitz, J.T., Kim, S., Murphy, E.J., Phinney, S.D., Ploutz-Snyder, R., Goldman, V., Cox, R.M., Mason, A.E., Moran, P., Hecht, F.M., 2017. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. *Nutr Diab* 7, 304. doi:10.1038/s41387-017-0006-9
- Saslow, L.R., Kim, S., Daubenmier, J.J., Moskowitz, J.T., Phinney, S.D., Goldman, V., Murphy, E.J., Cox, R.M., Moran, P., Hecht, F.M., 2014. A randomized pilot trial of a moderate carbohydrate diet compared to a very low carbohydrate diet in overweight or obese individuals with type 2 diabetes mellitus or prediabetes. *PLoS ONE* 9, e91027. doi:10.1371/journal.pone.0091027
- Schmieder, R.E., Ruilope, L.-M., Barnett, A.H., 2011. Renal protection with angiotensin receptor blockers: where do we stand. *J. Nephrol.* 24, 569–580. doi:10.5301/JN.2011.6445
- Shai, I., Schwarzfuchs, D., Henkin, Y., Shahar, D.R., Witkow, S., Greenberg, I., Golan, R., Fraser, D., Bolotin, A., Vardi, H., Tangi-Rozental, O., Zuk-Ramot, R., Sarusi, B., Brickner, D., Schwartz, Z., Sheiner, E., Marko, R., Katorza, E., Thiery, J., Fiedler, G.M., Blüher, M., Stumvoll, M., Stampfer, M.J., 2008. Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet. *N. Engl. J. Med.* 359, 229–241. doi:10.1056/NEJMoa0708681
- Shai, I., Spence, J.D., Schwarzfuchs, D., Henkin, Y., Parraga, G., Rudich, A., Fenster, A., Mallett, C., Liel-Cohen, N., Tirosh, A., Bolotin, A., Thiery, J., Fiedler, G.M., Blüher, M., Stumvoll, M., Stampfer, M.J., DIRECT Group, 2010. Dietary intervention to reverse carotid atherosclerosis. *Circulation* 121, 1200–1208. doi:10.1161/CIRCULATIONAHA.109.879254
- Shalaurova, I., Connelly, M.A., Garvey, W.T., Otvos, J.D., 2014. Lipoprotein Insulin Resistance Index: A Lipoprotein Particle-Derived Measure of Insulin Resistance. *Metabolic Syndrome and Related Disorders* 12, 422–429. doi:10.1089/met.2014.0050
- Siri-Tarino, P.W., Sun, Q., Hu, F.B., Krauss, R.M., 2010a. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *American Journal of Clinical Nutrition* 91, 535–546. doi:10.3945/ajcn.2009.27725
- Siri-Tarino, P.W., Sun, Q., Hu, F.B., Krauss, R.M., 2010b. Saturated fat, carbohydrate, and cardiovascular disease. *American Journal of Clinical Nutrition* 91, 502–509. doi:10.3945/ajcn.2008.26285
- Superko, R.H., 2001. Lipoprotein subclasses and atherosclerosis. *Front. Biosci.* 6, D355–65.
- Targher, G., Byrne, C.D., 2015. Circulating Markers of Liver Function and Cardiovascular Disease Risk. *Arteriosclerosis, Thrombosis, and Vascular Biology* 35, 2290–2296. doi:10.1161/ATVBAHA.115.305235
- Tay, J., Luscombe-Marsh, N.D., Thompson, C.H., Noakes, M., Buckley, J.D., Wittert, G.A., Yancy, W.S., Jr, Brinkworth, G.D., 2014. A Very Low-Carbohydrate, Low-Saturated Fat Diet for Type 2 Diabetes Management: A Randomized Trial. *Diabetes Care* 37, 2909–2918. doi:10.2337/dc14-0845
- the ACCORD Study Group, 2011. Long-Term Effects of Intensive Glucose Lowering on Cardiovascular Outcomes. *N. Engl. J. Med.* 364, 818–828. doi:10.1056/NEJMoa1006524
- Volek, J.S., Phinney, S.D., Forsythe, C.E., Quann, E.E., Wood, R.J., Puglisi, M.J., Kraemer, W.J., Bibus, D.M., Fernandez, M.L., Feinman, R.D., 2008. Carbohydrate Restriction has a More Favorable Impact on the Metabolic Syndrome than a Low Fat Diet. *Lipids* 44, 297–309. doi:10.1007/s11745-008-3274-2
- Westman, E.C., Yancy, W.S., Mavropoulos, J.C., Marquart, M., McDuffie, J.R., 2008. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. *Nutr Metab* 5, 36. doi:10.1186/1743-7075-5-36
- Whelton, P.K., Carey, R.M., Aronow, W.S., Casey, D.E., Collins, K.J., Dennison Himmelfarb, C., DePalma, S.M., Gidding, S., Jamerson, K.A., Jones, D.W., MacLaughlin, E.J., Muntner, P., Ovbigele, B., Smith, S.C., Spencer, C.C., Stafford, R.S., Taler, S.J., Thomas, R.J., Williams, K.A., Williamson, J.D., Wright, J.T., 2017. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. doi:10.1016/j.jacc.2017.11.006
- Williamson, J.D., Supiano, M.A., Pajewski, N.M., 2016. Intensive vs Standard Blood Pressure Control for Older Adults-Reply. *JAMA* 316, 1923–1923. doi:10.1001/jama.2016.14936
- Wood, R.J., Volek, J.S., Liu, Y., Shachter, N.S., Contois, J.H., Fernandez, M.L., 2006. Carbohydrate restriction alters lipoprotein metabolism by modifying VLDL, LDL, and HDL subfraction distribution and size in overweight men. *J. Nutr.* 136, 384–389.
- Wood, T.R., Hansen, R., Sigurdsson, A.F., Jóhannsson, G.F., 2016. The cardiovascular risk reduction benefits of a low-carbohydrate diet outweigh the potential increase in LDL-cholesterol. *Br J Nutr* 115, 1126–1128. doi:10.1017/S0007114515005450
- Yancy, W.S., Foy, M., Chalecki, A.M., Vernon, M.C., Westman, E.C., 2005. A low-carbohydrate, ketogenic diet to treat type 2 diabetes. *Nutr Metab* 2, 34. doi:10.1186/1743-7075-2-34
- Zuliani, G., Volpato, S., Dugo, M., Vigna, G.B., Morieri, M.L., Maggio, M., Cherubini, A., Bandinelli, S., Guralnik, J.M., Ferrucci, L., 2017. Combining LDL-C and HDL-C to predict survival in late life: The InChianti study. *PLoS ONE* 12, e0185307. doi:10.1371/journal.pone.0185307