

## Residual Vascular Risk: A global call to action



Opening the R<sup>3</sup>i symposium at SOCESP, **Professor Jean-Charles Fruchart, President of the R<sup>3</sup>i Foundation** emphasised: 'The launch of the R<sup>3</sup>i in Latin America is a very important day for the Foundation. Latin America poses a real challenge, due to escalating rates of obesity, diabetes and cardiometabolic disease. There is also poor control of metabolic risk factors, including atherogenic dyslipidaemia. The integration

of Latin America – Argentina, Brazil, Chile, Colombia, Mexico, Peru, Uruguay and Venezuela – within the



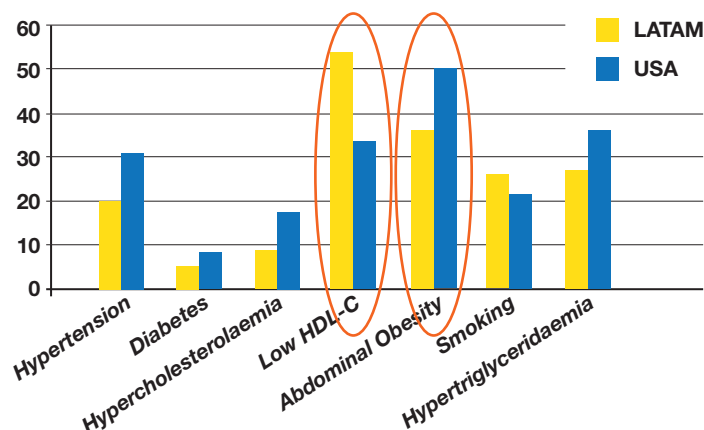
Foundation provides an important opportunity for the R<sup>3</sup>i to educate clinicians and their patients with the ultimate aim of reducing the high residual cardiovascular and microvascular risk in this region.'

### Low HDL-C and obesity: Key drivers of metabolic syndrome

Latin America is a heterogeneous region with multiple issues, exacerbated by economic transition, as discussed by **Professor Raul Santos, Heart Institute (InCor), University of Sao Paulo, Sao Paulo, Brazil**. Rapid demographic, epidemiological and nutritional changes, while undoubtedly important for tackling undernutrition in this region, have also contributed to the escalation in cardiometabolic disease. Diets have shifted to contain more processed, calorie-dense, and high-sugar foods and beverages, and the extent of physical activity has dropped dramatically. In general, about one in four adult people in the region have metabolic syndrome, although this can be as high as one in two in some countries.<sup>[1-3]</sup>



The profile of metabolic syndrome characteristics in Latin America differs from Western regions, as highlighted by the Latin American Consortium of Studies in Obesity (LASO) (*Figure 1*). While obesity is a consistent feature across both regions, Latin America is also characterised by a higher prevalence



**Figure 1. Low HDL-C, in addition to obesity, are the predominant metabolic criteria in Latin America driving cardiovascular risk.** Data from Miranda et al (2013).<sup>[2]</sup>

of low high-density lipoprotein cholesterol (HDL-C), affecting more than 50% of individuals (53.3% vs. 33.7% in the USA); prevalence rates for hypertriglyceridaemia tend to be similar to those in the USA (~30%).<sup>[2]</sup> There are, however, differences in the prevalence of risk factors between the countries in this region. Notably, the Mexican population shows a substantial predisposition to low HDL-C, with estimates indicating that over 75% of the population is affected.<sup>[4]</sup> It is likely that this pattern of cardiovascular risk factors reflects a combination of genetic, socio-behavioural and clinical factors.<sup>[5]</sup>

Escalating rates of metabolic syndrome will also impact non-alcoholic fatty liver disease and hepatic steatosis. In Brazil, studies indicate that hepatic steatosis is present in about one-third (36%) of asymptomatic middle-aged individuals without cardiovascular disease, and is closely associated with atherogenic dyslipidaemia. This association was shown to be independent of obesity, physical activity, hyperglycaemia and systemic inflammation and thus may confer increased cardiovascular risk directly.<sup>[6]</sup> Mechanistically, overproduction of triglyceride-rich very low-density lipoproteins may drive both low plasma concentrations of HDL-C by increasing HDL particle catabolism, as well as modify the cardioprotective properties of HDL. Thus, this scenario of metabolic syndrome, atherogenic dyslipidaemia and hepatic steatosis act synergistically to escalate rates of cardiovascular disease in the region.

However, the future looks even bleaker given marked increases in the prevalence of dyslipidaemia among the young, especially lower-income individuals. Indeed, it has been estimated that more than 50 million children (aged 0–19 years) in Latin America are obese, which represents about one-quarter of the population of this region.<sup>[7]</sup> The rapid escalation in obesity in the young is multifactorial, including changes in lifestyle as a result of economic transition, lack of education about a healthy diet and a bias in public policy to prevention of undernutrition.<sup>[8]</sup> Given that fast foods and sweetened drinks are low-cost, it is not surprising that lower-income individuals are particularly affected, reinforcing the social inequalities in this region, as indicated by the CARMELA (Cardiovascular Risk Factor Multiple Evaluation in Latin America) study.<sup>[9]</sup> Health promotion policies lag behind the obesity epidemic in Latin America. For example, while Chile has introduced nutrition and physical activity initiatives to reduce obesity in pre-school children,<sup>[10]</sup> this has so far not sufficiently impacted the rising rate of obesity.

**Based on obesity projections, Brazil will top the league table for cardiovascular disease mortality by 2040. This is a challenge that we need to face and take urgent action now'**

*Prof. Raul Santos*

Increasing obesity not only predisposes to escalation in rates of metabolic syndrome and cardiovascular disease, but also sets the scene for an explosion in type 2 diabetes. There may also be a genetic predisposition to diabetes, as indicated for the Mexican population from the Slim Initiative in Genomic Medicine for the Americas (SIGMA), which showed that the SLC16A11 variant may represent a novel locus for diabetes risk in this population.<sup>[11]</sup> In South and Central America diabetes currently affects 24 million people, and this is projected to increase by ~60% to 38 million by 2035.<sup>[12]</sup> This in turn predicts an escalation in diabetes-related microvascular complications. Already diabetic eye disease is becoming a concern as a cause of visual impairment in Latin America;<sup>[13]</sup> diabetic nephropathy is also a key driver of the marked increase in end-stage renal disease.<sup>[14]</sup>

## **Treatment gap: Evidence-based medicine is underused in Latin America**

To counter this looming epidemic of cardiometabolic disease, best evidence-based practice is needed to optimise cardiovascular risk management. Yet studies show that this is not the case.<sup>[15, 16]</sup> In a general population survey, <10% of individuals with hypercholesterolaemia were adequately controlled. Moreover, total cholesterol was measured in <50% of patients. Given the high prevalence of atherogenic dyslipidaemia, elevated non-HDL-C is an important secondary target, as recommended by both the R<sup>3</sup>i and the International Atherosclerosis Society (IAS).<sup>[17, 18]</sup> However, attainment of non-HDL-C goal lags even further behind that for LDL-C goal. This is especially evident among individuals with elevated triglycerides (>200 mg/dL or 2.3 mmol/L) in whom non-HDL-C goal attainment is about 50% lower than in patients with lower triglycerides (35% vs. 69%).<sup>[16]</sup>

Management of other atherothrombotic risk factors is also far from ideal, despite the availability of established and inexpensive treatments for the secondary prevention setting. This is illustrated by the PURE (Prospective Urban Rural Epidemiology) study, in which the use of antiplatelet drugs, beta-blockers, drugs affecting the renin-angiotensin system or statins was substantially lower in Latin America than

North America and Europe, and also decreased in line with decreasing country economic status. Notably, the use of statins for prevention of coronary heart disease (CHD) or stroke was 3-fold and 5-fold lower, respectively in Latin America than in North America/Europe (19% versus 57%; and 8% versus 39%).<sup>[19]</sup>

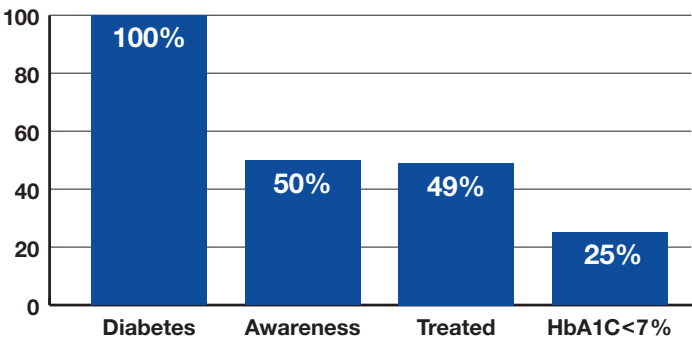
**Education is a priority to overcome clinical inertia and improve management of established cardiovascular risk factors with the long-term use of effective yet inexpensive preventive measures.'**

Prof. Raul Santos

As highlighted by **Professor Michel Hermans, Cliniques universitaires St-Luc, Université Catholique de Louvain, Brussels, Belgium**, this treatment gap also extends to the management of diabetes. Guideline-recommended control of glycaemia and blood pressure are mandatory to the prevention of diabetes-related microangiopathy, as supported by evidence from the United Kingdom Prospective Diabetes Study.<sup>[20, 21]</sup> Yet again, however, current practice lags behind guideline recommendations in Latin America. For example, in Mexico, with a diabetes prevalence of ~14%, only 50% of patients are diagnosed and of these 25% are adequately treated (HbA1c <7%) (Figure 2).<sup>[22]</sup>



The STENO-2 study<sup>[23]</sup> showed that best practice, incorporating tight glycaemic and blood pressure control and the use of renin-angiotensin system blockers, aspirin and statins, in addition to lifestyle



**Figure 2.** In Mexico, management of glycaemia is far from ideal with only 25% of patients achieving guideline-recommended targets. Data from Villalpando et al (2010).<sup>[22]</sup>

intervention can reduce the risk of major diabetes-related complications, notably retinopathy and nephropathy. Undoubtedly there are practical difficulties in achieving targets for blood glucose, blood pressure and LDL-C; however, even if these are attainable, best practice cannot prevent the development or progression of microvascular disease in up to 50% of patients with type 2 diabetes. Other approaches are needed, although evidence from recent studies does not support intensification of either blood pressure or glycaemic control beyond that advocated by guidelines.

Emerging data have suggested that both elevated triglycerides and low HDL-C may be implicated in the risk for diabetes-related microvascular complications, specifically diabetic renal disease.<sup>[24, 25]</sup> Recent findings from the REALIST (RESiduAl risk Lipids and Standard Therapies) -Micro study, supported by the R<sup>3</sup>i, provide further support.<sup>[26]</sup> This cross-sectional case-control study included 2,535 type 2 diabetes patients with either diabetic kidney disease (n=1,891), diabetic retinopathy (n=1,218) or both complications (n=574), and 3,683 matched controls, enrolled by 24 sites in 13 countries in Europe, North America, the Middle East, Asia and Australasia. The study showed that both elevated triglycerides and low HDL-C were significantly and independently associated with risk for diabetic microvascular complications, specifically diabetic kidney disease (Table 1).

- Increasing triglycerides by 0.5 mmol/L or ~45 mg/dL increased risk by 23%
- Raising HDL-C by 0.2 mmol/L or ~8 mg/dL decreased risk by 14%
- These associations persisted after adjustment for blood pressure and HbA1c

**Table 1.** Key findings from REALIST-Micro: Impact on diabetic kidney disease risk.

The association was less robust for diabetic retinopathy, which is not surprising given that multiple pathways are implicated in the pathogenesis of this complication. Other studies also implicate atherogenic dyslipidaemia with loss of beta-cell function in type 2 diabetes patients.<sup>[27]</sup>

**Taken together, these findings from REALIST-Micro, a global case-control study, provide a strong rationale for targeting atherogenic dyslipidaemia to reduce the residual risk of diabetic kidney disease'**

Prof. Michel Hermans





## Opportunities for change: the fundamental role of lifestyle intervention

Lifestyle intervention is the fundamental first step for tackling the obesity epidemic in Latin America, as well as reducing the high level of residual vascular risk, commented **Professor César Rodríguez Gilabert, Instituto Nacional de Salud Pública, Mexico.**

Component	Lifestyle intervention*	Control
Weight loss, %	8.6	0.7
Waist circumference, inches	-2.4	-0.2
Triglycerides mg/dL	-30.3	-14.6
HDL-C mg/dL	3.4	1.4
Systolic blood pressure, mmHg	-6.8	-2.8
Fasting plasma glucose, mg/dL	-21.5	-7.2
Metabolic syndrome, %	-14.7	-7.1

\* All significantly better than control,  $p < 0.001$

**Table 2. LookAhead: Impact of lifestyle intervention on metabolic syndrome components at 1 year.**<sup>[28]</sup>

He highlighted the LookAhead study, in which lifestyle intervention was associated with significant improvements in metabolic syndrome components after one year (*Table 2*); improvements in atherogenic dyslipidaemia and diabetes and blood pressure control persisted after 10 years.<sup>[28, 29]</sup> These benefits may be even greater in an obese population, as in Latin America, given synergistic interactions between obesity and dyslipidaemia. Yet, while health promotion in Mexico aimed at increasing physical activity in teenagers has contributed to a doubling in the uptake of exercise within 6 years, this has so far failed to impact obesity rates, due to confounding effects resulting from changes in socioeconomic factors.<sup>[30]</sup>

Sustained lifestyle intervention may also offer benefits beyond control of conventional risk factors. In a recent study, lifestyle intervention involving a very low fat vegetarian diet (<10% of calories from fat), regular exercise (at least 3 hours per week), stress management and patient support was associated with favourable changes in the expression of genes in the peripheral blood controlling leukocyte function, vascular inflammation, and lipid homeostasis.<sup>[31]</sup> Insights from the PREDIMED study are consistent in implicating the transcriptomic response of genes related to cardiovascular risk, in the mechanisms of vascular benefits underlying adoption of a Mediterranean type diet.<sup>[32]</sup>

In conclusion, Professor Rodríguez Gilabert emphasised that the sustainability of lifestyle approaches to reduce cardiometabolic risk not only requires motivation and adherence at the individual level, but also commitment at the public policy level. From the Latin America perspective, a focus on addressing factors responsible for social inequalities in cardiometabolic disease risk is critical.

**‘ Early initiation of effective lifestyle intervention, with or without pharmacotherapy, provides the opportunity to reduce residual cardiovascular risk not only by control of traditional risk factors, but also by effects on emerging risk factors, possibly at the genomic level influencing immunity, lipid homeostasis, and inflammation.’**

*Prof. César Rodríguez Gilabert*

## Opportunities for change: pharmaco-therapy

As highlighted throughout the symposium, the paradigm of dyslipidaemia in Latin America has changed, reflecting escalating rates in obesity, metabolic syndrome and diabetes. While there is irrefutable evidence that statins reduce the risk of cardiovascular events proportional to the intensity of LDL-C reduction, even with optimal statin therapy, a high residual risk of cardiovascular events persists. Undoubtedly, both lipid and non-lipid risk factors contribute to this risk. From the perspective of lipid-related residual risk, extensive evidence supports atherogenic dyslipidaemia as an important contributor, particularly in regions such as Latin America which are characte-



rised by escalating rates of obesity. *Thus, the question arises: which are the most appropriate therapeutic strategies for targeting this dyslipidaemia?*

**Dr Pablo Corral, Instituto Clínica Médica (ICM), Mar del Plata, Argentina** overviewed the evidence for reducing lipid-related residual cardiovascular risk with the available therapeutic options, including fibrates, niacin (nicotinic acid), omega-3 fatty acids and ezetimibe. While the R<sup>3i</sup> recognises that there is a lack of definitive data, in terms of reduction in hard clinical end points for any of these options, the level of evidence is probably strongest for fibrates. Indeed, there are consistent data from subgroup analyses of the major prospective fibrate studies, showing a 35% reduction in cardiovascular risk in individuals with atherogenic dyslipidaemia (defined similarly to the lipid criteria for the Action to Control Cardiovascular Risk in Diabetes [ACCORD] Lipid Trial, i.e. baseline triglycerides in the upper third of the population [ $\geq 204$  mg/dL or 2.3 mmol/L] and baseline HDL-C in the lower third [ $\leq 34$  mg/dL or 0.9 mmol/L]) versus no effect in individuals without this dyslipidaemia.<sup>[33]</sup> Most of this reduction in risk is due to prevention of coronary events.<sup>[34]</sup> In contrast, findings from recent trials are more conflicted for niacin, omega-3 fatty acids or ezetimibe.

Clearly, new therapeutic options are needed that are more effective in reducing residual cardiovascular risk. Monoclonal antibody therapy targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) may offer potential, given efficacy in reducing LDL-C by more than 50% in statin-treated patients, as well as favourable effects on non-HDL-C, triglycerides, lipoprotein(a) and HDL C.<sup>[35]</sup> Although trials have been relatively short-term to date, there is no evidence yet to suggest any significant adverse signal. Their long-term safety and potential for reducing cardiovascular outcomes in statin-treated patients are under evaluation in major prospective trials. Alternative approaches, albeit at earlier stages of development such as ETC-1002, may also offer potential.<sup>[36]</sup>

## Reducing residual microvascular risk

Beyond macrovascular benefits, the fibrates offer preventive effects on diabetes-associated microvascular complications, including preventing progression in early-stage diabetic retinopathy, delaying progression of albuminuria, as well as a potential role in preventing lower-extremity amputations.<sup>[37–41]</sup> While most of the evidence relates to fenofibrate, it is likely that these microvascular benefits are attributable to a class effect of PPAR- $\alpha$  agonists.

Questions have been asked about the clinical relevance of the well-recognised increase in serum creatinine associated with fenofibrate treatment, particularly given that type 2 diabetes patients often have some degree of renal impairment. However, insights from both the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and ACCORD Lipid studies provide reassurance that this functional increase in serum creatinine is transient and reversible within 6–8 weeks of stopping treatment.<sup>[39, 40]</sup> Additionally, a sub-study of FIELD showed that fenofibrate treatment was associated with a lower rate of decline in glomerular filtration rate over 5 years, suggestive of preservation of renal function.<sup>[39]</sup> Finally, post hoc analysis from the FIELD study suggest that the fenofibrate-associated increase in serum creatinine did not appear to detrimentally influence cardiovascular risk.<sup>[42]</sup> However, uncertainties remain about the underlying mechanism(s) of the preventive effects of fenofibrate on diabetic retinopathy, given that these appear to be independent of lipid-modifying effects.

***The available evidence provides a compelling argument for adding fenofibrate to a statin in patients with type 2 diabetes and residual dyslipidaemia to prevent macro and microangiopathy\****

*Dr Pablo Corral*



The role of the R3i in Latin America

Obesity, cardiometabolic disease and diabetes-associated microvascular complications have rapidly become a major public health concern in Latin America.

The mission of the R3i, a world-wide multidisciplinary academic Foundation, is to reduce residual vascular risk. Already established in 48 countries, the launch of the R3i in Latin America means that this is now a world-wide Foundation ideally positioned to address the challenge of residual vascular risk.

To achieve this, the R3i recognises the need for action against both established (such as unhealthy lifestyles, dyslipidaemia, high blood pressure, high blood sugar and obesity) and emerging risk factors to reduce the residual risk of micro- and macro-vascular events that persists in patients in spite of current evidence-based medical care.

The R3i has a remit that is clearly relevant to Latin America. To achieve this, the R3i will:

- Provide an academically-stimulating environment
- Strengthen collaboration across primary and secondary care
- Engage the global and local healthcare community

The R3i has highlighted a number of key priorities for action (Table 3). Education, research and advocacy are critical.

Therapeutic strategies aimed at reducing residual vascular risk in Latin America need to bear in mind that the obesity epidemic here is a socially-generated public health issue; action is needed at both local and national levels with the involvement of policy-makers to ensure sustainable change. Education underpins R3i activities in Latin America. The National Steering Committee, comprising national and regional experts, is crucial to driving education and action at the local level and ensuring collaboration across the region.

**The R3i will build on its strengths in Latin America to improve the management of established and emerging risk factors. Clearly, urgent action is needed now to prevent the challenge of residual vascular risk in this region.'**

Prof. Jean-Charles Fruchart,  
President, R3i Foundation

- Obesity and atherogenic dyslipidaemia are key drivers of metabolic syndrome in Latin America; education to improve lifestyle is a fundamental first step to reducing obesity.
- Reduce residual cardiovascular risk by:
  - Education to improve adoption of a healthy lifestyle at an earlier age
  - Education to improve management of cardiometabolic risk factors, including all lipid targets
  - Consideration of adjunctive fenofibrate therapy to slow progression of diabetic retinopathy in type 2 diabetes patients
- Act at the public policy level to ensure sustainable changes in lifestyle and patient care.

Table 3. Key priorities for Latin America.



## References

1. Márquez-Sandoval F, Macedo-Ojeda G et al. The prevalence of metabolic syndrome in Latin America: a systematic review. *Public Health Nutr* 2011;14:1702–13.
2. Miranda JJ, Herrera VM, Chirinos JA et al. Major cardiovascular risk factors in Latin America: a comparison with the United States. The Latin American Consortium of Studies in Obesity (LASO). *PLoS ONE* 2013;8:e54056.
3. de Carvalho Vidigal F, Bressan J, Babio N, Salas-Salvadó J. Prevalence of metabolic syndrome in Brazilian adults: a systematic review. *BMC Public Health* 2013;13:1198.
4. Rojas R, Aguilar-Salinas C, Jiménez-Corona A et al. Metabolic syndrome in Mexican adults. Results from the National Health and Nutrition Survey 2006. *Salud Publica Mex* 2010;52 (suppl 1): S11–S18.
5. Weissglas-Volkov D, Aguilar-Salinas CA, Nikkola E et al. Genomic study in Mexicans identifies a new locus for triglycerides and refines European lipid loci. *J Med Genet* 2013;50:298–308.
6. Makadia SS, Blaha M, Keenan T et al. Relation of hepatic steatosis to atherogenic dyslipidemia. *Am J Cardiol* 2013;112:1599–604.
7. Rivera JA, de Cossío TG, Pedraza LS et al. Childhood and adolescent overweight and obesity in Latin America: a systematic review. *Lancet Diabetes Endocrinol* 2014;2:321–32.
8. Garmendia ML, Corvalan C, Uauy R. Addressing malnutrition while avoiding obesity: minding the balance. *Eur J Clin Nutr* 2013;67:513–7.
9. Boissonnet C, Schargrodsky H, Pellegrini F et al. Educational inequalities in obesity, abdominal obesity, and metabolic syndrome in seven Latin American cities: the CARMELA Study. *Eur J Cardiovasc Prev Rehabil* 2011;18:550–6.
10. Salinas J, Vio F. Health promotion in Chile. *Rev Chil Nutr* 2002; 50: 164–73.
11. The SIGMA Type 2 Diabetes Consortium. Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico. *Nature* 2013 doi:10.1038/nature12828.
12. International Diabetes Federation. Diabetes Facts and Figures. Available at <http://www.idf.org/worlddiabetesday/toolkit/gp/facts-figures>
13. Furtado JM, Lansingh VC, Carter MJ et al. Causes of blindness and visual impairment in Latin America. *Surv Ophthalmol* 2012;57:149–77.
14. Cusumano AM, Di Gioia C, Hermida O, Lavorato C; Latin American Registry of Dialysis and Renal Transplantation. The Latin American Dialysis and Renal Transplantation Registry Annual Report 2002. *Kidney Int Suppl* 2005;97:S46–52.
15. Silva H, Hernandez-Hernandez R, Vinuela R et al; CARMELA Study Investigators. Cardiovascular risk awareness, treatment, and control in urban Latin America. *Am J Ther* 2010;17:159–66.
16. Santos RD, Waters DD, Tarasenko L et al. A comparison of non-HDL and LDL cholesterol goal attainment in a large, multinational patient population: the Lipid Treatment Assessment Project 2. *Atherosclerosis* 2012;224:150–3.
17. Fruchart JC, Davignon J, Hermans MP et al; Residual Risk Reduction Initiative (R3i). Residual macrovascular risk in 2013: what have we learned? *Cardiovasc Diabetol* 2014;13:26.
18. Expert Dyslipidemia Panel, Grundy SM. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia. *J Clin Lipidol* 2013;7:561–5.
19. Yusuf S, Islam S, Chow CK et al; Prospective Urban Rural Epidemiology (PURE) Study Investigators. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet* 2011;378:1231–43.
20. UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–53.
21. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998; 317: 703–13.
22. Villalpando S et al. Prevalence and distribution of type 2 diabetes mellitus in Mexican adult population A probabilistic survey. *Salud Publica Mex* 2010;52 (suppl 1):S19–S26.
23. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008;358:580–91.
24. Zoppini G, Negri C, Stoico V et al. Triglyceride-high-density lipoprotein cholesterol is associated with microvascular complications in type 2 diabetes mellitus. *Metabolism* 2012;61:22–9.
25. Morton J, Zoungas S, Li Q et al; ADVANCE Collaborative Group. Low HDL cholesterol and the risk of diabetic nephropathy and retinopathy: results of the ADVANCE study. *Diabetes Care* 2012;35:2201–6.
26. Sacks FM, Hermans MP, Fioretto P et al. Association between plasma triglycerides and HDL-cholesterol and microvascular kidney disease and retinopathy in type 2 diabetes: A global case-control study in 13 countries. *Circulation* 2014;129:999–1008.
27. Hermans MP, Ahn SA, Rousseau MF. The atherogenic dyslipidemia ratio [log(TG)/HDL-C] is associated with residual vascular risk, beta-cell function loss and microangiopathy in type 2 diabetes females. *Lipids Health Dis* 2012;11:132.
28. Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, Brancati FL et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care* 2007;30:1374–83.
29. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145–54.
30. ENSA 2000, ENSANUP 2008, ENSANUP 2012 Instituto Nacional de Salud Publica (MX) [www.ensanut.insp.mx](http://www.ensanut.insp.mx).

31. Ellsworth DL, Croft DT, Weyandt J et al. Intensive cardiovascular risk reduction induces sustainable changes in expression of genes and pathways important to vascular function. *Circ Cardiovasc Genet* 2014 Feb 21. [Epub ahead of print].
32. Castañer O, Corella D, Covas MI et al; PREDIMED study investigators. In vivo transcriptomic profile after a Mediterranean diet in high-cardiovascular risk patients: a randomized controlled trial. *Am J Clin Nutr* 2013;98:845–53.
33. Sacks FM, Carey VJ, Fruchart JC: Combination lipid therapy in type 2 diabetes. *N Engl J Med* 2010;363:692–84.
34. Jun M, Foote C, Lv J et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 2010;375:1875–84.
35. Norata GD, Tibolla G, Catapano AL. Targeting PCSK9 for hypercholesterolemia. *Annu Rev Pharmacol Toxicol* 2014;54:273–93.
36. Gutierrez MJ, Rosenberg NL, MacDougall DE et al. Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol -lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol* 2014; 34:676–83.
37. Keech AC, Mitchell P, Summanen PA et al, FIELD study investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007;370:1687–97.
38. ACCORD Study Group; ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *New Engl J Med* 2010;363:233–44.
39. Davis TM, Ting R, Best JD et al; Fenofibrate Intervention and Event Lowering in Diabetes Study investigators. Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Diabetologia* 2011;54:280–90.
40. Bonds DE, Craven TE, Buse J et al. Fenofibrate-associated changes in renal function and relationship to clinical outcomes among individuals with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) experience. *Diabetologia* 2012;55:1641–50.
41. Rajamani K, Colman PG, Li LP et al; FIELD study investigators. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *Lancet* 2009; 373: 1780–8.
42. Ting RD, Keech AC, Drury PL et al; FIELD Study Investigators. Benefits and safety of long-term fenofibrate therapy in people with type 2 diabetes and renal impairment: the FIELD Study. *Diabetes Care* 2012;35:218–25.