ESC European Society of Cardiology

European Heart Journal (2022) **43**, 249–250
https://doi.org/10.1093/eurheartj/ehab532

CARDIOPULSE

Braunwald's Corner

How to live to 100 before developing clinical coronary artery disease: a suggestion

Eugene Braunwald [1,2]*

[1]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Hale Building for Transformative Medicine, Suite 7022, 60 Fenwood Road, Boston, MA 02115, USA; and [2]Department of Medicine, Harvard Medical School, Boston, MA, USA

Despite extensive basic and clinical research, arteriosclerotic cardiovascular disease (ASCVD) remains the most frequent cause of death worldwide. There is general agreement that low-density lipoprotein cholesterol (LDL-C) is the most important risk factor for atherosclerosis and plays a causal role in the development of ASCVD. Despite the widespread availability of effective, safe cholesterol-lowering drugs, levels of circulating LDL-C still exceed optimum levels in a majority of the population.[1] Therefore, primary prevention of ASCVD remains an elusive goal.

A bit of history

The suggestion that a clinically useful approach to this global problem could be derived from genetic research on a roundworm with an almost unpronounceable name may seem far-fetched. In 1998, Andrew Fire, Craig C. Mello and colleagues published a Letter to *Nature* describing genetic interference by double-stranded RNA in *Caenorhabditis elegans*, a nematode.[2] The biological and pharmacological implications of this 'Letter' (Letters to *Nature* should not be minimized; a Letter to *Nature* described the structure of DNA[3]) were profound and in 2006 Fire and Mello were awarded the Nobel Prize in Physiology or Medicine with this citation:

> In their brilliant paper, Andrew Fire and Craig Mello demonstrated that double-stranded RNA activates an enzymatic mechanism that leads to gene silencing, with the genetic code in the RNA molecule determining which gene to silence.

In the same year, Bumcrot *et al.*[4] recognized the therapeutic potential of interfering with specific RNAs. As a consequence, a new class of drugs, small (21–23 nucleotides), double-stranded interfering ribonucleic acids (siRNA,) has been under development. The first, of interest to cardiologists, is patisiran, which is useful in the treatment of cardiac amyloidosis.[5]

The PCSK9 story is important and well known to the readers of this journal. Briefly, PCSK9 is a proprotein that is synthesized primarily in the liver and increases lysosomal degradation of LDL receptors (LDL-R), interfering with this pathway for LDL-C clearance, thereby raising serum LDL-C concentration. Circulating PCSK9 can be blocked by monoclonal antibodies, reducing circulating LDL-C, and improving clinical outcomes in patients with or at high risk of ASCVD.[6] These antibodies are safe and well tolerated and are quite effective in lowering LDL-C and improving clinical outcome. However, there are two problems related to this approach to lowering LDL-C, in particular for the primary prevention of ASCVD in asymptomatic persons: (i) the relatively short half-life of the antibodies requires subcutaneous injections every 2 or 4 weeks for many years, perhaps for a lifetime, leading to concerns about long-term adherence, and (ii) the relatively large quantities of antibodies required leading to relatively high costs when used for primary prevention in asymptomatic persons with no evidence of ASCVD.

Inclisiran

Gain-of-function mutations of the *PCSK9* gene described by Abifadel *et al.*[7] cause severe hypercholesterolaemia and early-onset ASCVD, while loss-of-function mutations have the opposite effect. Inclisiran is an siRNA, rapidly taken up by the liver where it reduces the expression of PCSK9, thereby inhibiting the lysosomal degradation of LDL-R, increasing their number reaching the cell membrane, and reducing circulating LDL-C.[8] Thus, its effects resemble those of a loss-of-function mutation. This was followed by a series of clinical trials, the ORION Clinical Development Program, which demonstrated safety, tolerability,[9] and efficacy of inclisiran in reducing circulating PCSK9 and LDL-C in normal subjects, in patients with ASCVD and in patients with familial and other forms of hypercholesterolaemia.[8,10] Importantly, its half-life is prolonged to about 300 days and a 300-mg dose administered subcutaneously every 6 months provides an ~50-mg/dL reduction of LDL-C in patients with ASCVD receiving maximally tolerated statin therapy.[10] This regimen was approved by the European Medicines Agency in 2020 for the management of primary hypercholesterolaemia or mixed dyslipidemia in combination with a statin; at the time of this writing, it is under consideration by the FDA. The ORION-4 trial

* Corresponding author. Tel: +1 617 732 8989, Email: ebraunwald@partners.org

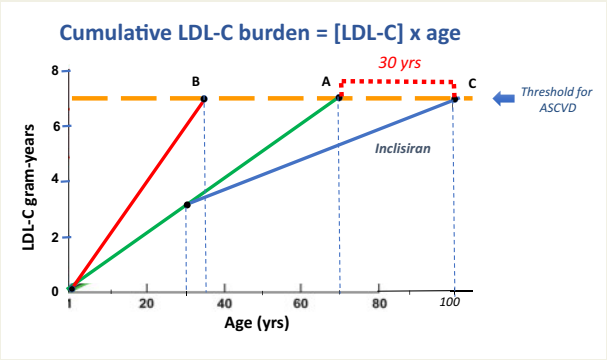

Figure 1 Modified from Horton *et al.*[12]

(HPS-4/TIMI-65, NCT03705234) is a clinical outcome study in patients with ASCVD that is now underway.

When administered just once a year, inclisiran results in a decline in LDL-C reaching a nadir about 2 months after injection followed by a gradual rise, ending the year with a 20% reduction at the time of the next injection.[11] With repeated annual injections, the mean reduction of LDL-C concentration for the year is ~40% below baseline.

Cholesterol-years

The atherogenic effect of LDL-C appears to be dependent on both the level of circulating LDL-C and the duration of this level. It has been known for more than a half century that patients with familial hypercholesterolaemia develop ASCVD at an early age. On the other hand, loss-of-function alleles of the gene encoding PCSK9, which cause only a modest lifetime reduction of LDL-C, are associated with a marked reduction in the development of ASCVD.[12] The atherosclerotic burden can be expressed in 'cholesterol-years'[13,14] or 'LDL-C-years',[10,11] analogous to pack years of smoking. Horton *et al.* have proposed that when the cumulative LDL-C-year burden, expressed in mg-years or gram-years, reaches a threshold, clinical evidence of ASCVD becomes apparent. This concept is illustrated in *Figure 1* modified from Horton.[11] Line A represents a person with an average level of LDL-C of 100 mg/dL (2.6 mmol/L) either naturally or on a statin, who reaches the ASCVD threshold of 7 LDL-C gram-years at the age of 70 years. Line B represents an untreated patient with familial heterozygous hypercholesterolaemia with an LDL-C of 200 mg/dL (5.2 mmol/L), who reaches this threshold at the age of 35. My suggestion is to administer 300 mg of inclisiran once each year, beginning at the age of 30 years, to subjects represented in Line A. As a consequence, their LDL-C would fall from 100 to 60 mg/dL (Line C), the rate of progression of the atherosclerotic burden would decline, and the threshold of 7 gram-years would be reached 30 years later, when the subject reached the age of 100.

Admittedly, this suggestion to delay the onset of clinical manifestations of ASCVD is greatly simplified. The position of the threshold is critical; in the presence of other atherogenic risk factors such as hypertension, diabetes mellitus, and family history, the threshold will be reduced,[12] while a life-long healthy lifestyle would raise it. The delay in reaching the ASCVD threshold is also dependent on the subject's age at which the annual administration of inclisiran is begun; the earlier the better.[15] Also, possible adverse effects of such prolonged intermittent therapy with this new drug are not considered, nor are variations of LDL-C concentration that may occur over the decades of LDL-C lowering.

Nevertheless, I believe that the principle underlying the suggestion is sound. Long-term adherence to a primary prevention regimen in asymptomatic persons with lifetime daily statin ingestion or biweekly injections of a monoclonal antibody is unreliable, despite reminders by healthcare professionals or family members. It would be quite simple to add a subcutaneous injection of inclisiran to the annual injection of influenza (and likely corona virus) vaccines. It appears likely that this approach to primary prevention could delay significantly the onset of clinical manifestations of ASCVD in the large proportion of persons similar to those represented by line A in *Figure 1*, regardless of whether or not they require other lipid-lowering drugs to maintain an LDL-C around 100 mg/dL. Such a positive outcome would be another example of how basic research can provide the seed that can blossom into a clinical triumph.

Conflict of interest: Research grant support through Brigham and Women's Hospital from: AstraZeneca, Daiichi-Sankyo, Merck, and Novartis; consulting for: Amgen, Boehringer-Ingelheim/Lilly, Cardurion, MyoKardia, NovoNordisk, and Verve.

References

1. Braunwald E. Cholesterol: the race to the bottom. *Eur Heart J* 2021;**42**:4612–4613.
2. Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. *Nature* 1998;**391**:806–811.
3. Watson JD, Crick FH. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature* 1953;**171**:737–738.
4. Bumcrot D, Manoharan M, Koteliansky V, Sah DWY. RNAi therapeutics: a potential new class of pharmaceutical drugs. *Nat Chem Biol* 2006;**2**:711–719.
5. Griffin JM, Maurer MS. Transthyretin cardiac amyloidosis: a treatable form of heart failure with a preserved ejection fraction. *Trends in Cardiovasc Med* 2021;**31**:59–66.
6. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–1722.
7. Abifadel M, Varret M, Rabès J-P, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derré A, Villéger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf J-M, Luc G, Moulin P, Weissenbach J, Prat A, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nature Genet* 2003;**34**:154–156.
8. Warden BA, Duell PB. Inclisiran: a novel agent for lowering apolipoprotein B-containing lipoproteins. *J Cardiovasc Pharmacol* 2021;doi:10.1097/FJC.0000000000001053. Online ahead of print.
9. Catapano AL, Pirillo A, Norata GD. Insights from ORION studies: focus on inclisiran safety. *Cardiovasc Res* 2021;**117**:24–26.
10. Wright RS, Ray KK, Raal FJ. Pooled patient-level analysis of inclisiran trials in patients with familial hypercholesterolemia or atherosclerosis. *J Am Coll Cardiol* 2021;**77**:1182–1193.
11. Ray KK, Stoekenbroek RM, Kallend D, Nishikido T, Leiter LA, Landmesser U, Wright RS, Wijngaard PLJ, Kastelein JJP. Effect of 1 or 2 doses of inclisiran on low-density lipoprotein cholesterol levels: one-year follow-up of the ORION-1 randomized clinical trial. *JAMA Cardiol* 2019;**4**:1067–1075.
12. Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. *J Lipid Res* 2009;**50** Suppl:S172–S179.
13. Schmidt HH-J, Hill S, Makariou EV, Feuerstein IM, Dugi KA, Hoeg JM. Relation of cholesterol-year score to severity of calcific atherosclerosis and tissue deposition in homozygous familial hypercholesterolemia. *Am J Cardiol* 1996;**77**:575–580.
14. Shapiro MD, Bhatt DL. "Cholesterol-years" for ASCVD risk prediction and treatment. *J Am Coll Cardiol* 2020;**76**:1517–1520.
15. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, Kahn J, Afonso L, Williams KA, Flack JM. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease. *J Am Coll Cardiol* 2012;**60**:2631–2639.