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BRIEF REPORT

Real-World Efficacy and Safety of Inclisiran

A Single-Country, Multicenter, Observational Study (CHOLINET Registry)

Paola Gargiulo, MD,[a] Federica Marzano, PhD,[a] Mario Crisci, MD,[b] Rossella Marcucci, MD,[c] Dario Bruzzese, PhD,[d] Alessandro Maloberti, MD,[e,f] Filippo Maria Sarullo, MD,[g] Gennaro Galasso, MD,[h] Ciro Indolfi, MD,[i] Giuseppe Musumeci, MD,[j] Antonella Corleto, MD,[k] Paolo Calabrò, MD,[l,m] Stefano Carugo, MD,[n,o] Gavino Casu, MD,[p] Amedeo Picciolo, MD,[q] Marco Matteo Ciccone, MD,[r] Claudio Bilato, MD,[s] Alberto Polimeni, MD,[t,u] Francesco Giallauria, MD,[v] Angelo Catalano, MD,[w] Leonardo De Luca, MD,[x] Giampaolo Niccoli, MD,[y] Elio Venturini, MD,[z] Marco Pepe, MD,[aa] Roberta Montisci, MD,[bb] Natale Daniele Brunetti, MD,[cc] Giuseppe Patti, MD,[dd] Italo Porto, MD,[ee] Alberto Margonato, MD,[ff] Marina Floresta, MD,[gg] Saverio Muscoli, MD,[hh] Matteo Cameli, MD,[ii] Giuseppe Andò, MD,[jj] Emilio Di Lorenzo, MD,[b] Martina Berteotti, MD,[c] Cristina Giannattasio, MD,[e,f] Silvia Sarullo, MD,[kk] Ciro Formisano, MD,[h] Assunta Di Costanzo, MD,[i] Fabrizio Delnevo, MD,[j] Ferdinando Varbella, MD,[k] Arturo Cesaro, MD,[l,m] Monica Franzese, MS,[ll] Costantino Mancusi, MD,[a] Sara Fontanarosa, MD,[a] Mariafrancesca Di Santo, MD,[a] Ciro Cotticelli, MD,[a] Fabrizio Perrone Filardi, PhD,[a] Stefania Paolillo, MD,[a] Giovanni Esposito, MD,[a] Alberto Corsini, MD,[mm] Pasquale Perrone Filardi, MD,[a] the CHOLINET Investigators

From the [a]Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy; [b]Unit of Interventional Cardiology, AORN dei Colli, Monaldi Hospital, Naples, Italy; [c]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [d]Department of Public Health, University of Naples Federico II, Naples, Italy; [e]Cardiology IV, "A. De Gasperis" Department, Ospedale Niguarda Ca' Granda, Milan, Italy; [f]School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; [g]Cardiovascular Rehabilitation Unit, Buccheri La Ferla Fatebenefratelli Hospital, Palermo, Italy; [h]Department of Medicine, Surgery, and Dentistry, University of Salerno, Salerno, Italy; [i]Division of Cardiology, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy; [j]Cardiology Division, AO Ordine Mauriziano, Turin, Italy; [k]Division of Cardiology, Interventional Unit, Infermi Rivoli Hospital Rivoli, San Luigi Gonzaga University Hospital, Orbassano, Italy; [l]Sant'Anna e San Sebastiano Hospital, Caserta, Italy; [m]Division of Cardiology, University of Campania "Luigi Vanvitelli," Caserta, Italy; [n]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [o]Fondazione Ospedale Maggiore IRCCS Policlinico, Milan, Italy; [p]Department of Cardiology, Azienda Ospedaliera Universitaria di Sassari, Sassari, Italy; [q]Division of Cardiology, "V. Fazzi" Hospital, Lecce, Italy; [r]Section of Cardiovascular Diseases, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy; [s]Division of Cardiology, West Vicenza General Hospitals, Arzignano, Vicenza, Italy; [t]Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy; [u]Division of Interventional Cardiology, Annunziata Hospital, Cosenza, Italy; [v]Department of Translational Medical Sciences, Internal Medicine (Precision Medicine Unit), University of Naples Federico II, Naples, Italy; [w]Cardiology Unit, Hospital Maria SS. Addolorata, Eboli, Italy; [x]SC Cardiologia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [y]Cardiology Division, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; [z]Department of Cardiac Rehabilitation, Cecina Civil Hospital, Cecina (LI), Italy; [aa]Casa di cura San Michele, Maddaloni, Italy; [bb]Clinical Cardiology, AOU Cagliari, Department of Medical Science and Public Health, University of Cagliari, Cagliari, Italy; [cc]Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy; [dd]Division of Cardiology, Maggiore della Carità Hospital, University of Eastern Piedmont, Novara, Italy; [ee]Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, IRCCS Italian Cardiology Network, Genova, Italy; [ff]Cardiology Unit, Heart Valve Center, San Raffaele Hospital, Milan, Italy; [gg]UOC Cardiologia e UTIC Villa Sofia, AOR Villa Sofia-Cervello, Palermo, Italy; [hh]Division of Cardiology, Fondazione Policlinico Tor Vergata, Rome, Italy; [ii]Department of Medical Biotechnologies, Division of Cardiology, University of Siena, Siena, Italy; [jj]Department of Clinical and Experimental Medicine, University of Messina, AOU Policlinico "G. Martino," Messina, Italy; [kk]BIND Department, Policlinico Paolo Giaccone University Hospital, University of Palermo, Palermo, Italy; [ll]IRCCS Synlab SDN, Naples, Italy; and the [mm]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy.
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Randomized trials[1] showed that inclisiran effectively and safely reduces low-density lipoprotein cholesterol (LDL-C). Real-world studies reported a median LDL-C reduction (35.5%-38%), with higher reductions (42.2%[2]-45%[3]) in patients on statins. Recently, VICTORION-INITIATE[4] (A Randomized, Multicenter, Open-label Trial Comparing the Effectiveness of an "Inclisiran First" Implementation Strategy to Usual Care on LDL Cholesterol [LDL-C] in Patients With Atherosclerotic Cardiovascular Disease and Elevated LDL-C [≥70 mg/dL] Despite Receiving Maximally Tolerated Statin Therapy) reported significant 53% LDL-C reduction in patients treated with inclisiran vs usual care, underscoring the inertia of traditional approaches. Thus, to address the need for additional real-world data on LDL-C-lowering effects of inclisiran, we designed the CHOLINET (CHOLesterol Italian inclisiran NETwork; NCT06287177) registry, the largest single-country, real-world data set.

METHODS

CHOLINET is a single-country, multicenter, observational, prospective, phase 4 registry of Italian patients initiating inclisiran as part of clinical management. Reimbursement criteria (Italian Medicines Agency [AIFA], GU 231-03.10.2022) include patients at very high cardiovascular (CV) risk with LDL-C of ≥70 mg/dL on statin ± ezetimibe. Lipids were assessed at a median of 17 days before each inclisiran administration. CV risk categorization was performed according to the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines.[5] Main outcomes were LDL-C reduction from baseline and percentage of patients reaching LDL-C target at 3 and 9 months. The study was approved by the Campania 3 Ethical Committee.

STATISTICAL ANALYSIS. Standard descriptive statistics were used to describe the sample: mean ± SD or median (Q1-Q3) for numeric variables and absolute frequency with percentage for categorical factors. Between-group comparisons were based on appropriate statistical tests: Student's *t*-test for independent samples, Mann-Whitney *U* test, chi-square test, or Fisher exact test. Analyses were conducted using the R statistical platform, version 4.2.2 (R Foundation for Statistical Computing).

RESULTS

A total of 659 patients were enrolled across 31 Italian sites between November 2022 and February 2024. Of these, 529 patients reached the 3-month milestone, and 513 patients (97%) received their second dose and had lipid levels measured. Additionally, of the 178 patients who reached the 9-month milestone, 171 (96%) received the third dose and had their lipid levels measured. The mean age was 63 years, and the majority were male (69%). Inclisiran was mostly prescribed by cardiologists (98%) and in ambulatory setting (87%). Of these patients, 20% were diabetic, 15% had familial hypercholesterolemia (FH), and 93% were at very high CV risk. Statin intolerance was reported in 36% of patients. Baseline median LDL-C was 103 mg/dL (Q1-Q3: 80-149 mg/dL), 71% were on statin ± ezetimibe, 16% were on ezetimibe alone, and 13% were not receiving lipid-lowering therapy.

ABBREVIATIONS AND ACRONYMS

CV = cardiovascular

FH = familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

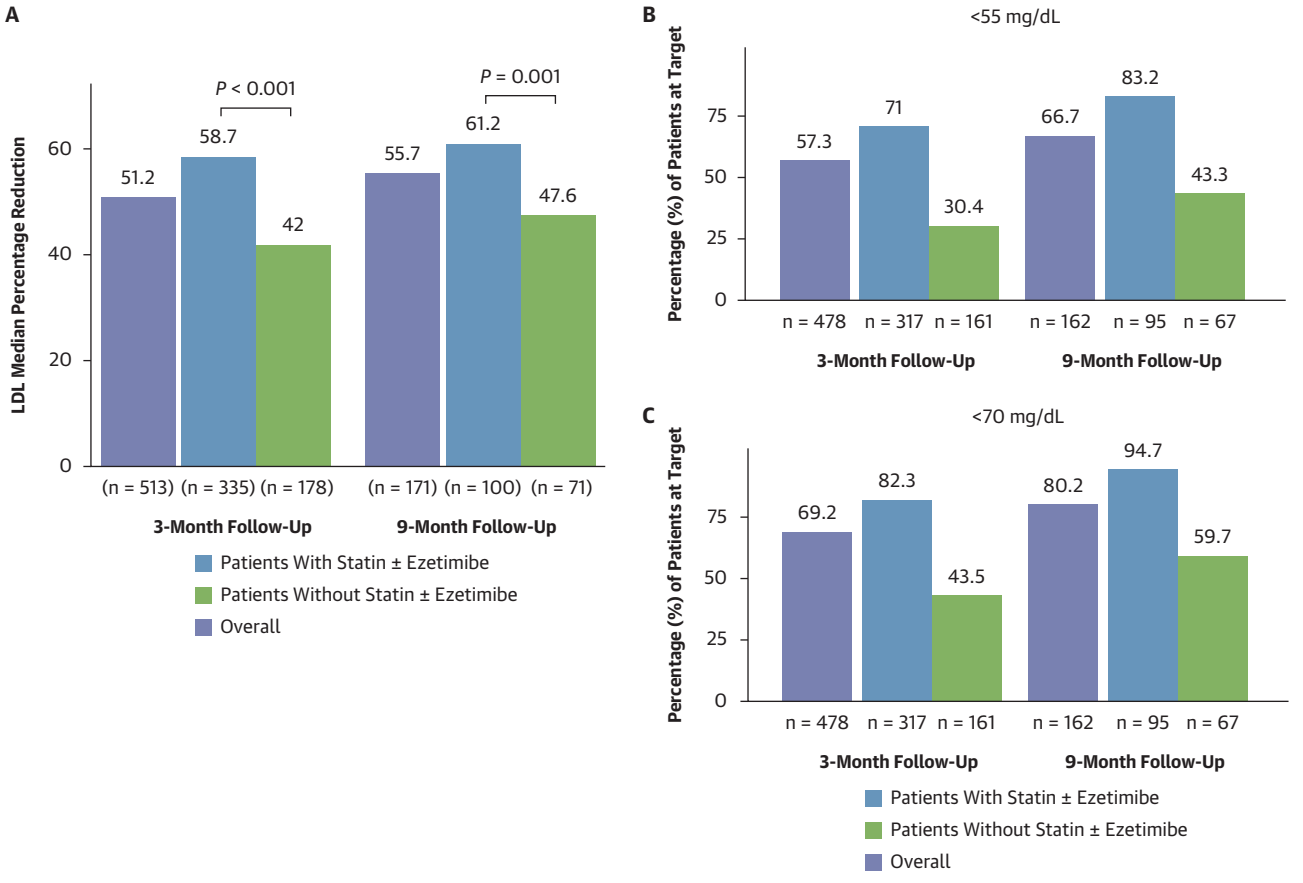
At the 3-month follow-up, median LDL-C reduction was 51% (Q1-Q3: 35%-67%), reaching a median LDL-C level of 50 mg/dL (Q1-Q3: 32-77 mg/dL). In 171 patients at the 9-month follow-up, the median LDL-C reduction was 56% (Q1-Q3: 37%-72%). Among very-high-risk patients, 57% and 69% reached LDL-C targets of <55 mg/dL[5] and <70 mg/dL[6], respectively, at 3 months, increasing to 67% and 80% at 9 months. Patients receiving statin ± ezetimibe showed greater LDL-C reduction compared to those not on combination therapy both at 3 (58% vs 42%; $P < 0.0001$) and 9 months (61% vs 47%; $P < 0.0001$). Similar trends were noted in the very-high-risk group (**Figure 1**).

Univariate predictors of target achievement at 3 months were age (OR: 1.4; 95% CI: 1.17-1.67; $P < 0.001$), male sex (OR: 1.64; 95% CI: 1.12-2.39; $P = 0.01$), hypertension (OR: 1.89; 95% CI: 1.27-2.82; $P = 0.002$), chronic coronary syndrome (OR: 2.35; 95% CI: 1.63-3.38; $P < 0.001$), and statin therapy alone (OR: 4.07; 95% CI: 1.6-10.34; $P = 0.003$) or in combination with ezetimibe (OR: 6.33; 95% CI: 3.65-11; $P < 0.001$). However, previous exposure to anti-PCSK9 antibodies (OR: 0.47; 95% CI: 0.28-0.81; $P = 0.006$) and FH (OR: 0.19; 95% CI: 0.11-0.32; $P < 0.001$) were predictors of failure to achieve LDL-C target. At multivariable analysis, FH (OR: 0.47; 95% CI: 0.23-0.95; $P = 0.036$) and statin/ezetimibe combination (OR: 4.14; 95% CI: 2.23-7.69; $P < 0.001$) remained significant predictors of achieving the LDL-C target.

In 63 patients with previous exposure to anti-PCSK9 antibodies, LDL-C reduction at 3 months was 34% compared to 54% in those without prior exposure ($P < 0.001$). This difference persisted at 9 months.

Overall, 23 patients discontinued inclisiran. The discontinuation cause was not reported in 4, whereas 13 patients stopped inclisiran at 3 months (7 for medical advice, 4 self-discontinued, 2 because of

FIGURE 1 LDL-C Trends and Achievement of Target



(A) Bar graph showing the median percent reduction of LDL-C, in the overall population and further stratified by the presence or absence of concomitant statin ± ezetimibe therapy, in patients at the 3- and 9-month follow-ups. (B, C) Bar graph showing the percentage of very-high-risk patients, overall and further stratified by the presence or absence of concomitant statin ± ezetimibe therapy, achieving (B) the <55-mg/dL and (C) the <70-mg/dL LDL-C target, according to ESC/EAS and American College of Cardiology/American Heart Association guidelines, respectively, at the 3- and 9-month follow-ups. CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol.

injection site reaction). In addition, 6 patients discontinued at 9 months (4 for medical advice, 2 self-discontinued).

DISCUSSION

In this study, a reduction in LDL-C levels was observed in patients receiving inclisiran, with most of them achieving the LDL-C target without significant side effects at 3 and 9 months.

Our data confirm the efficacy observed in randomized studies, reporting an LDL-C reduction of 50% to 55%[1] at day 90 and of 57% to 60.2%[7,8] at 9 months, consistent with our findings showing a 51.2% LDL-C reduction at 3 months and 55.7% at 9 months.

Recently, VICTORION-INITIATE[4] reported an LDL-C reduction of 57.7% and 52% at 3 and 9 months, respectively, aligned with our findings. Notably, 89.8% of patients in the inclisiran arm of VICTORION-INITIATE received background statin therapy[4] compared to 71.5% of our study. In that study, 72% and 68% of patients reached the <55-mg/dL target, and 80.9% and 75.6% the <70-mg/dL target, at 3 and

9 months, respectively. Similarly, our study showed that 71% and 83.2% of very-high-risk patients receiving statin ± ezetimibe reached the <55 mg/dL target, and 82.3% and 94.7% the <70 mg/dL target, at 3 and 9 months, respectively.

Unlike VICTORION-INITIATE,[4] 92.4% of our patients on statin therapy also received ezetimibe, whereas statin/ezetimibe combination was used only in 1.1% of VICTORION-INITIATE[4] patients, possibly explaining the higher LDL-C reduction observed in our registry.

Previous retrospective real-world studies in smaller populations reported a lower efficacy of inclisiran.[2,3] Recently, a small monocentric retrospective registry[9] showed LDL-C reduction at 3 months of 37.9% and 54.1% in primary and secondary prevention with inclisiran, respectively. However, the impact of concomitant statin therapy was not explored. In our study, greater LDL-C reductions were observed in patients who received inclisiran with statin ± ezetimibe background therapy, as previously reported in smaller series.[2,3]

In conclusion, this observational study shows that inclisiran is associated with significant LDL-C reductions in a real-world setting, enabling most very-high-risk patients to reach targets recommended by European or U.S. guidelines, particularly with background statin ± ezetimibe therapy.

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ADDRESS FOR CORRESPONDENCE: Dr Pasquale Perrone Filardi, Department of Advanced Biomedical Sciences, Federico II University of Naples, Via S. Pansini, 5 80131 Naples, Italy. E-mail: fpperron@unina.it.

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