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SPECIAL ARTICLE
Interventional cardiology

Pharmacotherapy of cardiovascular diseases from herbs and pills to nucleic acids

A report from the European Society of Cardiology Cardiovascular Roundtable

Ulf Landmesser [1,2,3,*], Thomas Thum [4], Lale Tokgözoğlu[5], Tomasz J. Guzik [6,7], Francesco Cosentino [8,9], Roger Hajjar[10], Alexandra Goncalves[11,12], Andres Laguna-Fernandez[13], Paul Nioi[14], Jürgen H. Prochaska[15], Ricardo Rocha[16], Sekar Kathiresan [17], Julian März[18], Mathew S. Maurer[19], Christopher J. O'Donnell [20], Gabriella Passacquale[21,22], Anna Tavridou[23], Mattias Van Heetvelde [24], Anders Himmelmann[25], Benjamin Meder [26], Lothar Roessig[27], Filippo Crea[28], and Thomas F. Lüscher [29,30]

[1]Department of Cardiology, Angiology and Intensive Care Medicine, Deutsches Herzzentrum Charité (DHZC), Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin, Germany; [2]Friede Springer Cardiovascular Prevention Center@Charité, Hindenburgdamm 30, House IIIA, 12203 Berlin, Germany; [3]German Center of Cardiovascular Research (DZHK), Partner Site Berlin, Germany; [4]Institute for Molecular and Translational Therapeutic Strategies, Medizinische Hochschule, Hannover, Germany; [5]Department of Cardiology, Hacettepe University, Ankara, Turkey; [6]Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK; [7]Department of Internal Medicine, Jagiellonian University, Collegium Medicum, Krakow, Poland; [8]Unit of Cardiology, Department of Medicine Solna, Karolinksa Institutet, Stockholm, Sweden; [9]Heart and Vascular and Neuro Theme, Karolinska University Hospital, Stockholm, Sweden; [10]Gene and Cell Therapy Institute at Mass General Brigham, Cambridge, MA, USA; [11]Digital Health, Bristol, Myers & Squibb, Cambridge, MA, USA; [12]University of Porto Medical School, Porto, Portugal; [13]Global Medical Affairs, Cardiovascular, Renal and Metabolism, Novartis, Basel, Switzerland; [14]Research, Alnylam Pharmaceuticals, Cambridge, MA, USA; [15] Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [16]Medical Affairs, Intellia Therapeutics, Cambridge, MA, USA; [17]Verve Therapeutics, Boston, MA, USA; [18]Institute for Biomedical Ethics and History of Medicine & University Research Priority Program (URPP) Innovative Therapies in Rare Diseases (ITINERARE), University of Zurich, Zurich, Switzerland; [19]Columbia University Irving Medical Center, Vagelos College of Physicians & Surgeons, New York, NY, USA; [20]Cardiovascular and Metabolism Translational Medicine, Novartis BioMedical Research, Cambridge, MA, USA; [21]Innovation and Pharmaceutical Strategy Division, Agenzia Italiana del Farmaco (AIFA), Rome, Italy; [22]Member of the EMA Scientific Advice Working Party and Cardiovascular Working Party; [23]Scientific Advice Office, European Medicines Agency, Amsterdam-Zuid, North Holland, The Netherlands; [24]European Society of Cardiology Patient Forum (Belgium), Sophia Antipolis, France; [25]BioPharmaceuticals Research and Development, AstraZeneca, Gothenburg, Sweden; [26]Precision Digital Health & Informatics for Life, Clinic of Internal Medicine III, University of Heidelberg, Heidelberg, Germany; [27]Asklepios BioPharmaceutical, Inc. (AskBio), Research Triangle Park, NC, USA; [28]Centre of Excellence of Cardiovascular Sciences, Gemelli Isola Hospital, Rome, Italy; [29]Royal Brompton and Harefield Hospitals, Imperial College London and King's College London, London, UK; and [30]Center for Molecular Cardiology, University of Zurich, Zurich, Switzerland

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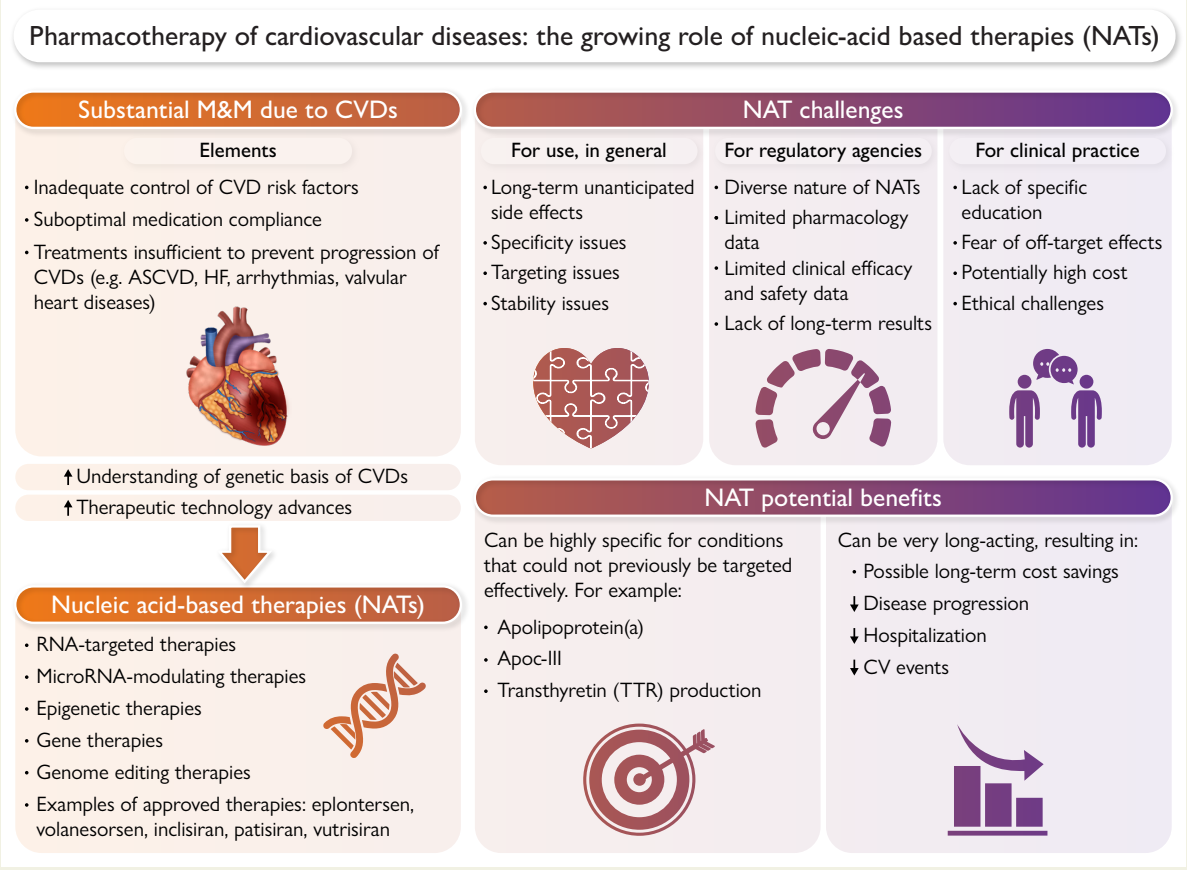
Abstract

Cardiovascular (CV) diseases continue to cause substantial morbidity and mortality. Risk factors are inadequately controlled, compliance with medication remains suboptimal, and treatments are not sufficient to fully prevent the progression of atherosclerotic CV disease, heart failure, arrhythmias, and valvular heart diseases. An increased understanding of the genetic basis of CV diseases and advances in the technology of therapeutics have led to the development of nucleic acid–based therapies (NATs) for prevention and treatment of CV risk factors and diseases. Nucleic acid–based therapies can target disease pathways at the translational level preventing the formation of disease-causing proteins that could not be effectively targeted by other pharmacological therapeutics and will likely improve treatment adherence by providing long-acting effects over many months

* Corresponding author. Tel: 49 (0) 30 450 513702, Fax: 49 (0) 30 450 513999, Email: ulf.landmesser@dhzc-charite.de

rather than daily treatment. These therapies include RNA-targeted therapeutics, gene editing therapeutics, and gene therapies. Challenges around the use of NATs may be unique with each new drug and new target and may include long-term unanticipated side effects, and issues around specificity, targeting, and stability. Assessing NATs for marketing approval continues to pose challenges for regulatory agencies. These include their diverse nature, limited data on pharmacology, clinical safety and efficacy, and the lack of long-term results. Barriers in clinical practice may include the lack of specific education, fear of off target effects, costs, and ethical challenges. Implementation of these novel therapies will require careful patient selection and education. Despite potentially high treatment costs, possible long-term cost savings could result from fewer healthcare visits due to infrequent NAT administrations, and lower rates of disease progression, hospitalization, and CV events due to sustained improvement in control of disease pathways and risk factors.

Graphical Abstract



The future of cardiovascular therapy: potential benefits and challenges of nucleic acid–based therapies (NATs). ApoC-III, apolipoprotein C-III; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; M&M, morbidity and mortality; Tx, therapy.

Keywords Atherosclerotic cardiovascular disease • CRISPR • Gene therapies • Heart failure • Nucleic acid–based therapies • RNA-targeted therapeutics • Transthyretin cardiac amyloidosis

Introduction

Prevention and management of cardiovascular (CV) disease has come a long way since the discovery of digitalis more than 200 years ago.[1] While a variety of herbs have proven useful, they were associated with poorly characterized toxicities. Pills containing purified and standardised doses of the active ingredient and better characterized safety have now become a mainstay of CV medicine. However, in the almost 40 years since the approval of the first oral statin and in particular after a more detailed understanding of the causal genetic basis of several CV diseases, and advances in the technology of therapeutics (including targeting), nucleic acid–based therapeutics (NATs) for prevention and treatment of CV diseases are rapidly developing and are becoming increasingly important.[2–4]

The discovery of a wide variety of targets for medication and biologics, including cell surface receptors (e.g. angiotensin II type 1 receptors, platelet $P2Y_{12}$ receptors), enzymes (e.g. angiotensin-converting enzyme, neprilysin), ion/metabolite transporters (e.g. sodium-glucose co-transporter 2), and other pathways have led to the rapid growth of new treatments for dyslipidaemia, hypertension, type 2 diabetes mellitus, atherosclerotic CV disease (ASCVD), cardiomyopathies, and heart failure (HF).[5] In particular, NATs including RNA-targeted therapeutics,

microRNA-modulating and epigenetic therapies, gene therapies, and genome-editing therapies are going to markedly advance CV medicine and are being developed based on an advanced understanding of the genetic basis of CV disease.[6,7] RNA therapeutics are designed to silence single specific genes, whereas microRNA-modulating or epigenetic therapies target transcriptional networks, and genome editing aims to repair genes at the DNA level.[5]

This article summarizes the discussions among various stakeholders during a Cardiovascular Round Table (CRT) organised by the European Society of Cardiology (ESC). The goal of this paper is to provide an overview of new NATs, their current and future potential to address unmet medical needs, and to discuss important issues around the safety, ethics, patient perspectives, and implementation of these novel therapeutic strategies (*Graphical Abstract*).

Unmet needs in cardiovascular disease

Cardiovascular diseases continue to be a major cause of death and morbidity. In the 2023 survey of ESC member countries, CV disease remained the most common cause of death, accounting for 40% of deaths in females and 35% in males, with the most common causes being ischaemic heart disease and stroke.[8] The annual economic burden of CV diseases across 27 EU countries was estimated at €282 billion and is likely to grow.[9]

There continue to be major unmet needs in prevention and treatment of CV diseases. Among these are suboptimal compliance with prescribed medication leading to uncontrolled hypertension, dyslipidaemia, and diabetes and inability to fully prevent progression of ASCVD, HF with reduced or preserved ejection fraction, as well as arrhythmias and valvular heart diseases.[10] In particular, there is a need for novel and improved personalized treatment strategies in patients with HF to lower their residual risk, such as those with cardiac amyloidosis.

In addition, underprescribing by physicians, leading to suboptimal implementation of guideline-directed medical therapy (GDMT) in CV patients, complicated access to novel medications (e.g. prior authorisation forms, extensive pretreatment testing), and poor adherence by patients are major factors contributing to the failure to achieve optimal treatment targets. For example, the SANTORINI (Treatment of high and very high riSk dyslipidemic pAtients for the preveNTion of cardiOvasculaR events in Europe–a multInatioNal observatIonal) study found that only 20% of adults at high and very high CV risk across 14 European countries achieved guideline recommended (2019) low-density lipoprotein cholesterol goals.[11] Overall, 22% of patients were not on lipid-lowering therapy (LLT), 54% were receiving monotherapy, and only 24% were receiving combination LLT. In this regard, NATs for dyslipidaemia and hypertension are currently available or being intensely developed. More recently, the International Action on Secondary Prevention through Intervention to Reduce Events (INTERASPIRE) study conducted in 14 countries showed that just 9.0% (inter-country range 3.8%–20.0%) of patients reported attending cardiac rehabilitation, and 1.0% (inter-country range 0%–2.4%) achieved the study definition of optimal guideline adherence.[12] Patient adherence can also be impacted by polypharmacy.[13] Increasing numbers of older people have multiple comorbid conditions and require five or more daily medications. Many do not take their medications correctly, leading to increases in hospitalizations and mortality, and suggesting the need for longer-acting strategies.

Transthyretin cardiac amyloidosis (ATTR-CA) can now also be treated by NATs and a gene-editing investigational therapy using CRISPR/Cas9 technologies is already far advanced in clinical trials. While current therapies for ATTR-CA can reduce morbidity and mortality, patients still progress on therapy.[14] The future of effective treatments may well lie in correcting underlying genetic variants—at least initially in monogenetic cardiac conditions that are identifiable in about a third of patients with cardiomyopathies. For example, in animal studies, delivery of RNA-guided Cas9 nuclease effectively inactivated the hypertrophic cardiomyopathy pathogenic variant in ≥70% of ventricular cardiomyocytes and prevented disease,[15–18] demonstrating the potential to provide a cure rather than life-long treatment.

Nucleic acid–based therapies are providing novel opportunities for long-acting treatments of chronic cardio-renal-metabolic conditions (e.g. dyslipidaemia and hypertension) that are likely to support treatment adherence. Of note, a survey of cardiologist conducted by the ESC and European Atherosclerosis Society found that physician's attributed failure to optimize LLT to patient-related factors, particularly non-adherence, although physician inertia around intensifying treatment also appeared to be a factor.[19] In fact, one study found that among 601 934 patients with ASCVD, younger patients, female patients, and those with higher Charlson comorbidity score were less likely to be prescribed any statin. Only 22.5% were on a high-intensity statin but had the highest adherence at 1 year.[20] In fact, failure to prescribe GDMT at discharge after acute coronary syndromes was a major factor predicting adherence in the Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events (CONCORDANCE) registry.[21] Further, a survey of U.S. patients in the PALM (Patient and Provider Assessment of Lipid Management) registry found that of those eligible for statin therapy, a substantial proportion were not on treatment, and of those 40% had declined or discontinued therapy mainly citing concerns around side effects.[22] However, 60–70% of patients were willing to reconsider statin therapy if offered. An analysis of the SWEDEHEART registry confirmed that intensive early and sustained lowering of non-high-density lipoprotein cholesterol after myocardial infarction (MI) markedly improved the prognosis, thus challenging the current stepwise approach for cholesterol lowering after MI, which inevitably results in delaying goal attainment and possible harm.[23]

The lack of optimal treatments for some CV diseases, as well as patient non-adherence, underscore the need for more effective therapies and better treatment strategies, especially those providing long-acting effects or cure rather than daily treatment.

Rapid emergence of novel NATs

Advances in design and delivery to target organs [e.g. GalNAc-conjugation for liver-targeting; lipid nanoparticle and advanced viral vectors] have led to a rapid increase in the development of NATs for prevention and management of diseases (*Figure 1*).[5,24] Although a large proportion of these therapies are in the area of oncology, there is now growing interest for their use in CV diseases.

Nucleic acid–based therapeutics include RNA-targeted therapeutics, microRNA-modulating and epigenetic therapies, gene therapies in the sense of target overexpression and gene editing.[5] Among the therapies that are most advanced in the CV area are the single-stranded RNA-targeted antisense oligonucleotides (ASOs), the double-stranded small-interfering RNA (siRNA) therapeutics, and CRISPR/Cas9 gene-editing therapeutics, while the microRNA-modulating therapies are at earlier stages, with only a few

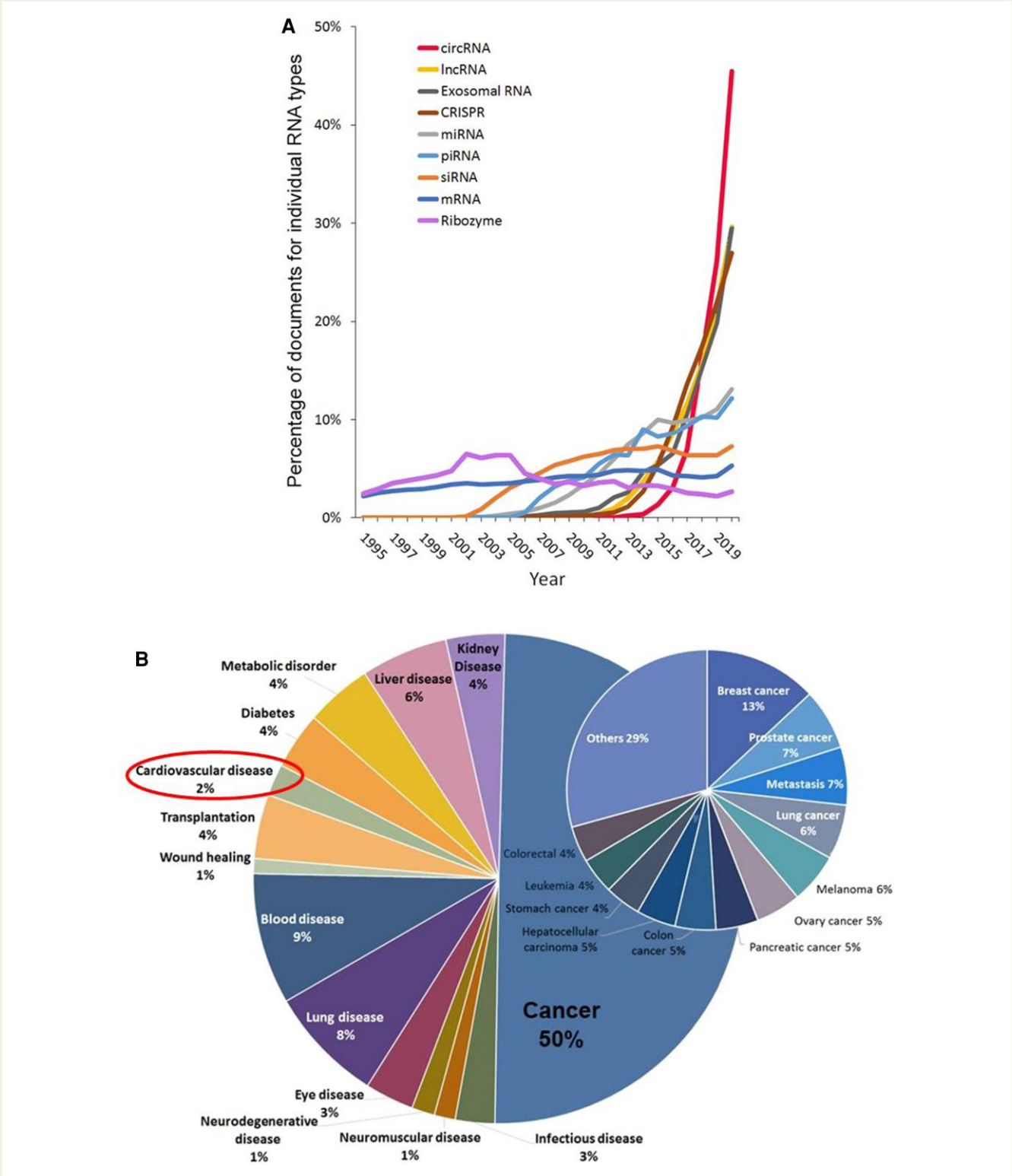


Figure 1 Rapid increase in publications related to RNA-based treatments. Reprinted from Sasso *et al.*,[24] as per open access licence: https://creativecommons.org/licenses/by/4.0/. *(A)* Trends in publication volume for different RNA types in the years 1995–2020. Percentages are calculated with yearly publication numbers for each individual RNA type, normalized by total publications in the years 1995–2020 for the same RNA type. Example: percentage of circRNA documents in 2020 = (number of circRNA documents in 2020)/(total number of circRNA documents from 1995 to 2020). *(B)* Percentage of publications associated with RNAs in medical applications.

Table 1 Examples of nucleic acid-based therapies available or in development for prevention and treatment of cardiovascular diseases

Examples	Targets	Investigated indications	Key clinical trials	Regulatory status in EU
RNA-targeted therapeutics				
—Antisense oligonucleotides (ASO)				
Eplontersen	TTR	TTR amyloidosis	NEURO-TTRansform (NCT04136184)[25] CARDIO-TTRansform (NCT04136171)[26]	Approved for hATTR amyloidosis (PN)
Pelacarsen	Apolipoprotein(a)	ASCVD secondary prevention Slow progression of aortic stenosis	Lp(a) HORIZON (NCT04023552)[27] Lp(a) FRONTIERS CAVS (NCT05646381)	
Volanesorsen	APOC3	FCS	APPROACH (NCT02211209)[28]	Approved for FCS
—Small interfering RNA (siRNA)				
Inclisiran	PCSK9	Dyslipidaemia HeFH MACE	Multiple ORION and VICTORION trials[29]	Approved for hypercholesterolemia or mixed dyslipidaemia
Lepodisiran	Apolipoprotein(a)	ASCVD secondary prevention	ACCLAIM-Lp(a) (NCT06292013)	
Olpasiran	Apolipoprotein(a)	ASCVD secondary prevention	OCEAN(a)—Outcomes Trial (NCT05581303)	
Patisiran	TTR	TTR amyloidosis	APOLLO (NCT01960348)[30]	Approved for hATTR amyloid PN
Plozasiran	APOC3	Hyperlipidaemia Persistent chylomicronemia	MUIR (NCT04998201)[31] PALISADE (NCT05089084)[32]	
Solbinsiran	ANGPTL3	Hyperlipidaemia	Phase 1 (NCT04644809)[41]	
Vutrisiran	TTR	TTR amyloidosis	HELIOS-A (NCT03759379)[33] HELIOS-B (NCT04153149)[34]	Approved for hATTR amyloid PN
Zerlasiran	Apolipoprotein(a)	Hyperlipidaemia	Phase 1 (NCT04606602)[35]	
Zilebesiran	AGT synthesis	Hypertension	KARDIA-1 (NCT04936035)[36] KARDIA-3 (NCT06272487)	
Zodasiran	ANGPTL3	Hyperlipidaemia	ARCHES-2 (NCT04832971)[37]	
MicroRNAs (miRNAs)				
CDR132L	miR-132 inhibition	Heart failure	HF-REVERT (NCT05350969)[38]	

Continued

Table 1 *Continued*

Examples	Targets	Investigated indications	Key clinical trials	Regulatory status in EU
Gene therapy				
SRD-001 (AAV1.SERCA2a)	SERCA2 inhibition	HFrEF DMD-cardiomyopathy	SERCA-LVAD (NCT00534703)[39] MUSIC-HFrEF (NCT04703842) MUSIC-DMD (NCT06224660)	
AB-1002 (AAV2i8)	Protein phosphatase Inhibitor-1	Non-ischaemic cardiomyopathy	GenePHIT (NCT05598333)	
Gene editing				
VERVE-101	Base editing *PCSK9* gene	HeFH ASCVD secondary prevention	Phase 1b Heart-1 (NCT05398029)[40]	
VERVE-102	Base editing *PCSK9* gene	HeFH Premature CAD	Phase 1b Heart-2 (NCT06164730)	
VERVE-201	Base editing *ANGPTL3* gene	HoFH Refractory hypercholesterolaemia	Phase 1b trial Pulse-1 (NCT06451770)	
Nexiguran ziclumeran (NTLA-2001)	CRISPR-based TTR Inactivation	TTR amyloidosis-cardiomyopathy	Phase 3 MAGNITUDE (NCT06128629)	
CTX-310 and CTX-320	Base editing *ANGPTL3* gene	Dyslipidaemia ASCVD secondary prevention	Non-human primates	

AAV1, adeno-associated virus vector; ACS, acute coronary syndrome; AGT, angiotensinogen; ANGPTL3, angiopoietin-like 3; APOC3, apolipoprotein C3; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; DMD, Duchenne muscular dystrophy; FCS, familial chylomicronemia syndrome; hATTR, hereditary transthyretin amyloidosis; HeFH, heterozygous familial hypercholesterolemia; HFrEF, heart failure with reduced ejection fraction; HoFH, homozygous familial hypercholesterolaemia; LNP, lipid nanoparticle; MACE, major adverse cardiovascular events; PCSK9, proprotein convertase subtilisin/kexin type 9; PN, polyneuropathy; SERCA2, sarcoplasmic/endoplasmic reticulum calcium ATPase; T2DM, type 2 diabetes mellitus; TTR, transthyretin.

Table 2 Potential benefits and challenges of nucleic acid–based therapies

Potential benefits
• Address specific targets that previously could not be effectively treated: e.g. APOC3, apolipoprotein(a), TTR
• Potential cure for monogenetic CV diseases
• More potent and sustained long-term efficacy (e.g. profound lipid lowering, including the potential for single-course treatments with permanent effects, TTR knockdown)
• Potential for fewer side effects
• Improved adherence with less frequent administration
• Facilitate personalized therapy and better meet patient expectations
• Potential to de-escalate or de-prescribe prior therapies
• Reduced healthcare resource utilization due to simplified treatment regimens and potential clinical benefits
Potential challenges
• Specificity: targeted delivery to specific cell types and organs, and avoiding off-target effects
• Toxicities related to vectors or lipid nanoparticles
• Immunogenicity
• Endonuclease degradation
• Difficulties in assessing potential long-term side effects
• Regulatory challenges
• Costs associated with manufacturing for some complex therapies (e.g. viral vector gene therapies)
• Ethical considerations—in particular: reimbursement, pricing and access; informed consent; research ethics
• Public education to counter potential negative opinions and avoid misinformation

Adapted from references.[5,42–44].
APOC3, apolipoprotein C3; CV, cardiovascular; TTR, transthyretin.

progressing to clinical testing.[5] *Table 1* provides a brief, updated overview of some therapies that are approved or in development for CV diseases.[25–41]

Potential benefits of NATs

Two of the most important expected benefits of NATs are (i) they can be highly specific for conditions that previously could not be targeted effectively and (ii) they have the potential to be very long acting, which can mitigate the challenges of adherence and lead to better risk factor control in primary and secondary prevention of CV disease (*Table 2*).[5,42–44] Finally, if conjugated to a ligand selectively targeting an organ or cell (e.g. triantennary *N*-acetylgalactosamine or GalNAc binding to the asialoglycoprotein receptor on hepatocytes), these tools are highly organ specific.

RNA-targeted siRNA and antisense oligonucleotides

RNA therapeutics have the potential to precisely address previously 'undruggable' targets by silencing expression of pathogenic proteins or signalling pathways. For example, eplontersen, patisiran, and vutrisiran target TTR production, halting progression of hereditary TTR amyloidosis and possibly enabling regression.[25,26,30,33,34,45] In terms of durability, lipid lowering with inclisiran is associated with about 50% reductions in low-density lipoprotein cholesterol after an injection at day 1 and again at 3 months.[46]

Gene editing (DNA-targeted) therapies

In addition to treatments with the potential for once-yearly administration, gene-editing therapies may potentially generate a permanent therapeutic benefit after a single administration. For example, the CRISPR-based, gene-editing therapy nexiguran ziclumeran, which is been evaluated for the treatment of ATTR amyloidosis, has been shown to knockdown TTR synthesis with ~90% long-term reductions, potentially once in a lifetime, with a single dose in ATTR-CA and evidence of stability or improvement in several markers of disease progression.[45,47] The potential clinical benefits of this approach are being further evaluated in a phase 3 trial (*Table 1*). Given their high specificity and infrequent administration, NATs will allow for greater personalization and enhanced effectiveness of CV therapies.[48,49]

Potential challenges associated with NATs

Concerns around NATs centre on the potential for unexpected side effects, and issues around specificity, targeting, and stability (*Table 2*).[5,42–44] In addition, classical pharmacodynamic and pharmacokinetic models do not apply to NATs, and drug monitoring is not currently possible. Because randomized controlled trials enrol highly selective patients, issues of inclusion and patient representativeness should be considered even for the rare disease for which NATs are being developed.[50]

RNA-targeted siRNA and antisense oligonucleotides

These challenges may be unique with every new drug and every new therapeutic target.[5] Indeed, at the moment, the liver is the target of most NAT therapies, since it can be relatively easily targeted via the asialoglycoprotein receptor by conjugating the therapeutics with GalNAc. Safety concerns related to NATs include off-target effects at the cellular level, immunogenicity (including the nanoparticles), systemic mis-targeting and accumulation, as well as the potential for delayed-onset side effects.[5,44]

Many of the issues such as instability of RNA, short half-life, pH sensitivity, specificity, endonuclease degradation, immunogenicity, and safety have been overcome with technological improvements. Chemical modifications can reduce off-target binding and immunogenicity, encapsulation, or other formulations (including chemical modifications) can be used to protect therapeutic RNAs from enzyme degradation and enhance cellular uptake, and delivery mechanisms have been developed to improve bioavailability and efficacy.[43]

Gene therapy and gene-editing approaches targeting the myocardium

There have been advances in delivery to target sites through the use of lipid nanoparticle and viral vectors. Recombinant adeno-associated viral (AAVs) vectors have been the most commonly used vehicles for *in vivo* cardiac gene transfer.[51] Naturally occurring AAV serotypes with varying cardiac specificity such as AAV1, AAV6, AAV8, AAV9, AAVrH10, and AAVrh74 have been widely used in experimental animal models.[52] Among them, AAV9 has been characterized by high transduction

efficiency to the myocardium in rodents and larger animal models. The AAV capsids have been further modified to yield even higher cardiac tropism while de-targeting the liver. These modifications have been accomplished through directed evolution, which has produced among others, the myoAAV vector with very high cardiac directed tropism.[53] Other alterations have been achieved through re-engineering and have generated cardiac tropic and liver de-targeted capsids such as AAV2i8.[54] Many of the vectors have entered clinical trials for cardiac gene therapy, as mentioned below. AAV1 for delivery of SERCA2a to treat different HF and cardiomyopathies,[55] AAV2i8 for delivery of I-1c to target non-ischaemic cardiomyopathy,[56] AAV9 delivery of LAMP2B for the treatment of cardiac hypertrophy in Danon disease[57] and delivery of MYBPC3 for the treatment of hypertrophic cardiomyopathy.[58]

Toxicities associated with AAV vectors

In recent clinical trials, AAV vectors have been delivered either systemically or through intracoronary injections. Intravenous injections require very high doses 3–10 E13 viral genomes/kg and can trigger AAV specific toxicities. These include hepatotoxicity, thrombotic microangiopathy, thrombocytopenia, acute kidney failure, complement activation, and myocarditis.[57] There is a temporal cadence to these toxicities with thrombocytopenia and complement activation occurring in the first few days post-injection while hepatoxicity is based on a T-cell response to the capsid and/or the therapeutic transgene and occurs 2–8 weeks post-injection. These toxicities have occurred despite immunosuppression with steroids, sirolimus, and anti-CD20 monoclonal antibody (rituximab). Intracoronary injections require lower doses (<1 E12 vg/kg) and have not necessitated immunosuppression.[52] As novel, more cardiac tropic AAV vectors are developed, the injected doses will decrease thereby mitigating the observed toxicities.

Targeted delivery

Targeted delivery to the site remains a challenge, particularly in CV medicine outside the pathogenic mechanisms that can be addressed by liver-targeted approaches. To date, targeting cardiomyocytes or cardiac fibroblasts has not been very efficient, because highly specific binding sites have not yet been identified. However, the introduction of GalNAc, pioneered in CV disease with the siRNA inclisiran, has made liver-targeting much more successful, and GalNAc addition is now being utilized across multiple classes of NATs.[29] However, while the liver offers an accessible target, hepatotoxicity has been an issue with higher-dosed untargeted ASOs, mipomersen and vupanorsen, which led to their discontinuation.[59] In addition, there is still room for improvements to address endosomal escape, enhance potency, and long-term storage.[43,60,61]

In the case of gene-editing therapies, CRISPR-based therapies can be developed with high precision by using a highly-specific single-guide RNA targeting a specific segment in the target gene to minimize the risk of off-target effects.

Gene editing is also associated with unique ethical concerns around genome editing in humans. Patient and physician education, and robust ethical practices will be necessary to promote trust in these treatments and enhance their acceptability and explainability.

Regulatory aspects

From a regulatory perspective, NATs include synthetic oligonucleotides (ASO and siRNAs), which are at the interface of small molecules and biologicals, as well as gene therapies which fall under the category of advanced therapy medicinal products.[62] The European Medicines Agency (EMA) has published guidance documents for academics and industry to support the development of NATs. The draft guideline on the development and manufacture of oligonucleotides addresses specific aspects regarding the manufacturing process, characterisation, specifications and analytical control for synthetic oligonucleotides.[63] In general, International Council for Harmonisation (ICH) M3(R2) and especially ICH S6(R1) guidelines should be followed for non-clinical development of synthetic oligonucleotides. Several EMA guidelines cover quality, non-clinical and clinical aspects of gene therapies.[64] EMA also offers scientific advice upon request and encourages developers to seek assistance early and frequently in the development process to generate robust evidence on a medicine's benefits and risks, thus facilitating drug development.[65]

Table 3 Challenges in the evaluation of nucleic acid–based therapies from the regulatory perspective

• Limited clinical pharmacology studies, clinical data, and follow-up
• Limited relevance of animal models
• Limited precedents and experience
• Product specific and multifactorial risk factors

Several synthetic oligonucleotides have been approved in the EU for CV diseases with CV benefit demonstrated (*Table 1*).[25–41] To date, approved gene addition therapies largely consist of AAV gene addition treatments for rare diseases and *ex vivo* AAV, lenti- and retroviral treatments. The only EMA approved CRISPR-based therapy is exagamglogene autotemcel, an *ex vivo* hematopoietic stem cell targeted therapy for the treatment of sickle cell disease and beta thalassaemia. Currently, there are no EMA approved gene addition or gene editing therapies for CV diseases. The AAV gene therapy alipogene tiparvovec was approved for the treatment of lipoprotein lipase deficiency by the EMA in 2012, but the marketing authorization was not renewed in 2017. Assessing NATs for approval continues to pose challenges for regulatory agencies (*Table 3*).

Since NATs are diverse in nature, EMA uses a flexible risk-based approach to assess the potential risks associated with their clinical use.[66] The risk-based approach is defined as a strategy aiming to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorization application. Risk factors may relate to biological characteristics, the manufacturing process, and the specific therapeutic use of the product. Adequate risk mitigation strategies are required for both early risk identification and post-marketing monitoring. Long-term follow-up of patients treated with gene therapy medicinal products can be extended up to 15 years, based on the safety specifications in consultation with regulatory authorities.[67,68]

Implementation

In addition to secondary prevention and treatment of patients with ASCVD, different NATs are also being studied in familial hypercholesterolaemia, familial chylomicronemia syndrome, hereditary and wild type ATTR amyloidosis, and in patients with high lipoprotein(a) blood levels or hypertriglyceridaemia (*Table 1*).[25–41] Furthermore, the population eligible for such treatments continues to expand,

Table 4 Barriers and strategies to facilitate implementation of nucleic acid–based therapies

Patient	Physician	Healthcare system
Barriers to implementation		
• Poor health literacy • Lack of specific education • Fear of side effects • Misinformation on hazards • Cost and access issues • Social problems • Negative public opinions • Multiple morbidities • Polypharmacy	• Inadequate GDMT prescription • Lack of knowledge/adherence to guideline recommendations • Lack of structured clinical pathway • Therapeutic inertia • Knowledge gap between levels of care • Complex medication regime	• Administrative barriers to drug prescription (e.g. prior approval) • Cost of novel therapies • Barriers to reimbursement • Limited availability of cardiac rehabilitation programmes • Poor coordination among healthcare stakeholders • Limited time for patient
Strategies to facilitate implementation		
• Improve health literacy • Education on disease, treatments and side effects • Fewer meds, less frequent administration • Develop and distribute tools to improve adherence (reminders, remote monitoring, etc.) • Need for awareness and patient advocacy groups (need to lobby at EU level) • Provide ongoing patient support	• Educate and empower physicians and other healthcare providers • Use structured, team-based, patient-centred interventions • Personalize risk prediction and management: define patient profiles that will benefit most • Provide clear protocols for treatment • Ensure necessary infrastructure • Optimize delivery system	• Enhance medication accessibility (reimbursement: consider cost-effectiveness and benefit to society) • Start with highest risk but expand to broader patient subsets • Shift focus from volume of services to patient outcomes achieved • Consider incentive-driven reimbursement

Based on references.[19,21,22,69–71,73,74]
EU, European Union; GDMT, guideline-directed medical therapy.

which emphasizes the importance of educating patients and their doctors, representatives of healthcare system, and the population at large.

Patient selection

Optimal patient selection will be paramount for the successful clinical use of NATs. First the patient must have the target mechanism as the relevant cause of their specific CV disease. Nucleic acid–based therapies are often first evaluated in people who already receive optimal GDMT, yet have uncontrolled risk factors or continue to progress or have CV conditions with neither effective nor disease-modifying pharmacotherapy. Use of NATs will be optimally deployed by careful personalization of therapy using structured, team-based, patient-centred approaches involving family, pharmacist, and other healthcare workers to individually tailor interventions.[69–71]

Patient preference

Patient understanding and willingness to undergo NATs will be critical to the successful implementation of these therapies in clinical practice. In one patient preference survey, it was found that over one-third of patients would choose a one-time gene-editing procedure over more frequently administered therapies.[72] Indeed, most patients expect and hope for a cure when seeing a doctor and not lifelong pill taking.

A representative from the ESC Patient Forum provided some important insight from a group of patients who have undergone NAT for CV and hereditary eye diseases that have no treatments or low adherence to, and/or side effects from conventional therapies. These patients had a high level of understanding and an ongoing desire for education about their condition. Before treatment, their attitude toward NATs was generally positive but was influenced by their mental state, the severity and stage of their disease, and their support network. After undergoing therapy their attitude toward the therapy was impacted by the occurrence of side effects, the success of the treatment from the patient point of view, and the strength of their support network. There continues to be an ongoing unmet need for support for and from treating clinicians and allied healthcare professionals, society, family, and other patients.

Barriers and facilitators around the use of NATs in clinical practice

Although the barriers and facilitators for the use of NATs may vary for different treatments (RNA-targeted therapeutics vs gene editing, etc.), and different CV diseases (rare conditions such as ATTR amyloidosis vs hypercholesterolaemia or mixed dyslipidaemia, etc.), they must be identified and addressed for successful implementation of these treatments in clinical practice. There will be barriers at the level of the patient, physician, and healthcare systems. Some of these barriers as well as strategies to address them are shown in *Table 4*.[19,21,22,69–71,73,74]

Ethical considerations

NATs—in particular, gene therapies and genome-editing approaches—raise several ethical challenges. Two particularly pressing challenges are reimbursement, pricing and access; and informed consent (in clinical practice and clinical research settings).

Many NATs have very high treatment costs. For instance, the estimated annual treatment cost of inotersen for hereditary TTR

amyloidosis amyloidosis was between €338 000 and €676 000 in Germany in 2018, and that of patisiran for the same condition was between €344 000 and €515 000.[75] Most (one-time) gene therapies approved by the FDA in recent years have US list prices exceeding USD 2 million. These high treatment costs, in combination with constrained healthcare budgets, may prevent implementation for many innovative NATs in most countries. In this context, the following ethical questions become paramount: (i) For payers (health insurers/tax-funded healthcare providers): Under which conditions should such medicinal products be reimbursed? Which prices should be reimbursed to pharmaceutical companies? (ii) For pharmaceutical companies: Which prices are ethically justifiable, and under which conditions? (iii) For healthcare professionals: Which innovative medicines should be recommended to patients, particularly in cases of high out-of-pocket costs? and (iv) For all: Which patients should be given access to innovative therapies in situations of limited availability?

Another major ethical challenge relates to informed consent, particularly in the context of gene therapies and genome-editing approaches. In this regard, the World Medical Association Declaration of Reykjavik states that '*Patient autonomy should be respected, and informed consent should always be obtained. This informed consent process should include disclosure of the risks of gene therapy and editing, including the fact that the patient may have to undergo multiple rounds of gene therapy, the risk of an immune response, the potential problems arising from the use of viral vectors and off-target genome effects*'.[76]

Obtaining informed consent can be particularly challenging in highly vulnerable patients participating in clinical trial, e.g. critically ill children or patients under extreme distress, shock or despair. In addition, therapeutic misconception and lack of understanding regarding, e.g. the side-effects and long-term uncertainties can further complicate the task of facilitating informed consent.

Programs for implementation of NATs

NATs hold the promise of improving the long-term management of CV risk factors and disease, eventually reducing the rate of CV events and complications. When combined with patient education on CV diseases and lifestyle interventions, the infrequent administration of NATs (or potential for cure) is a major advantage in the approach to improving achievement of treatment targets. Specific implementation studies should be conducted to ensure fidelity, adaptability, and sustainability of the appropriate use of NATs based on published evidence, as well as to identify and address the barriers to successful use of NATs in clinical practice.

Healthcare system and policy strategies for sustainability

In addition to targeted programs aimed at patients and clinicians, successful deployment of NATs will require long-term strategies within healthcare systems and among policy makers (*Table 4*).[19,21,22,69–71,73,74] Although these treatments may be associated with high costs, the potential for long-term cost savings is considerable. Infrequent administration will result in fewer healthcare visits, and sustained improvement in risk factors and reductions in CV event rates will result in lower rates of hospitalization and CV interventions. However, to achieve such benefits, it will be necessary to enhance accessibility of medications, which requires a shift from fee for volume of services to fee for achievement of patient outcomes.[77,78] Data-driven benchmarking, such as achievement of quality indicators, should be used to assess performance and foster continuous improvement.[79] These types of value-based healthcare initiatives will be necessary if NATs are to be a sustainable option once their use has moved beyond patients at the highest risk and has expanded to lower risk patients.[77–80]

Perspectives

A more detailed understanding of the causal genetic and epigenetic basis of CV diseases, and advances in the technology of therapeutics, have led to the rapid development and increasing importance of NATs for prevention and treatment of CV diseases.

NATs provide novel opportunities to target pathways that could not be effectively controlled by classical pharmacological therapies and for long-acting treatments of CV diseases and risk factor such as dyslipidaemia and hypertension. They are likely to improve treatment adherence by providing long-acting or potentially permanent effects rather than daily treatment. Nucleic acid–based therapeutics include RNA-targeted therapeutics, microRNA-modulating and epigenetic therapies; gene therapies; and gene editing. The therapies that are most advanced in the CV area are the RNA-targeted ASO, siRNA therapeutics, and CRISPR-based gene-editing therapies.

Among the most important expected benefits of NATs is their high specificity to target conditions that previously lacked effective therapies and in their extended dosing intervals, in some cases consisting of a single dose with life-long effects. Challenges associated with the use of NATs may be unique with every new drug and every new therapeutic target and may include the potential for unexpected side effects, and issues around specificity, targeting and stability.

Assessing NATs for marketing approval continues to pose challenges for regulatory agencies. These include the availability of limited data on their pharmacology, long-term safety and efficacy, and limited clinical experience.

There are a number of barriers around the use of NATs in clinical practice including lack of specific education, fear of side effects, costs, and ethical considerations regarding genome editing. Implementation of these therapies will require careful patient selection, and physician, patient and public education on diseases, treatments, and side effects.

Successful implementation of NATs will require long-term strategies within healthcare systems and among policy makers. Despite potentially high initial treatment costs, there is an opportunity for long-term cost savings including fewer healthcare visits due to infrequent administrations, and lower rates of hospitalization and CV interventions that may result from sustained improvement in control of risk factors and leading to a decrease in CV event rates.

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Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

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References

1. Wilkins MR, Kendall MJ, Wade OL. William withering and digitalis, 1785 to 1985. *Br Med J (Clin Res Ed)* 1985;**290**:7–8. https://doi.org/10.1136/bmj.290.6461.7
2. Hajar R. Statins: past and present. *Heart Views* 2011;**12**:121–7. https://doi.org/10.4103/1995-705X.95070
3. Aragam KG, Jiang T, Goel A, Kanoni S, Wolford BN, Atri DS, *et al.* Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants. *Nat Genet* 2022;**54**:1803–15. https://doi.org/10.1038/s41588-022-01233-6
4. Landmesser U, Hazen S. HDL-cholesterol, genetics, and coronary artery disease: the myth of the 'good cholesterol'? *Eur Heart J* 2018;**39**:2179–82. https://doi.org/10.1093/eurheartj/ehy299
5. Landmesser U, Poller W, Tsimikas S, Most P, Paneni F, Luscher TF. From traditional pharmacological towards nucleic acid-based therapies for cardiovascular diseases. *Eur Heart J* 2020;**41**:3884–99. https://doi.org/10.1093/eurheartj/ehaa229
6. Tamargo J, Agewall S, Borghi C, Ceconi C, Cerbai E, Dan GA, *et al.* New pharmacological agents and novel cardiovascular pharmacotherapy strategies in 2022. *Eur Heart J Cardiovasc Pharmacother* 2023;**9**:353–70. https://doi.org/10.1093/ehjcvp/pvad034
7. Tamargo J, Agewall S, Borghi C, Ceconi C, Cerbai E, Dan GA, *et al.* New pharmacological agents and novel cardiovascular pharmacotherapy strategies in 2023. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:219–44. https://doi.org/10.1093/ehjcvp/pvae013
8. Timmis A, Aboyans V, Vardas P, Townsend N, Torbica A, Kavousi M, *et al.* European society of cardiology: the 2023 atlas of cardiovascular disease statistics. *Eur Heart J* 2024;**45**:4019–62. https://doi.org/10.1093/eurheartj/ehae466
9. Luengo-Fernandez R, Walli-Attaei M, Gray A, Torbica A, Maggioni AP, Huculeci R, *et al.* Economic burden of cardiovascular diseases in the European union: a population-based cost study. *Eur Heart J* 2023;**44**:4752–67. https://doi.org/10.1093/eurheartj/ehad583
10. Figtree GA, Broadfoot K, Casadei B, Califf R, Crea F, Drummond GR, *et al.* A call to action for new global approaches to cardiovascular disease drug solutions. *Circulation* 2021;**144**:159–69. https://doi.org/10.1161/CIR.0000000000000981
11. Ray KK, Haq I, Bilitou A, Manu MC, Burden A, Aguiar C, *et al.* Treatment gaps in the implementation of LDL cholesterol control among high- and very high-risk patients in

Europe between 2020 and 2021: the multinational observational SANTORINI study. *Lancet Reg Health Eur* 2023;**29**:100624. https://doi.org/10.1016/j.lanepe.2023.100624
12. McEvoy JW, Jennings C, Kotseva K, De Bacquer D, De Backer G, Erlund I, *et al.* Variation in secondary prevention of coronary heart disease: the INTERASPIRE study. *Eur Heart J* 2024;**45**:4184–96. https://doi.org/10.1093/eurheartj/ehae558
13. Tamargo J, Kjeldsen KP, Delpon E, Semb AG, Cerbai E, Dobrev D, *et al.* Facing the challenge of polypharmacy when prescribing for older people with cardiovascular disease. A review by the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy. *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:406–19. https://doi.org/10.1093/ehjcvp/pvac005
14. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, *et al.* Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–16. https://doi.org/10.1056/NEJMoa1805689
15. Kaur S, Desai M. Unmet needs and future directions in hypertrophic cardiomyopathy. *Prog Cardiovasc Dis* 2023;**80**:1–7. https://doi.org/10.1016/j.pcad.2023.08.001
16. Reichart D, Newby GA, Wakimoto H, Lun M, Gorham JM, Curran JJ, *et al.* Efficient in vivo genome editing prevents hypertrophic cardiomyopathy in mice. *Nat Med* 2023;**29**:412–21. https://doi.org/10.1038/s41591-022-02190-7
17. Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. *N Engl J Med* 2011;**364**:1643–56. https://doi.org/10.1056/NEJMra0902923
18. Ormondroyd E, Grace C, Borsari W, Goel A, McDonough B, Rose J, *et al.* Genetic therapies for cardiomyopathy: survey of attitudes of the patient community for the CureHeart project. *Eur J Hum Genet* 2024;**32**:1045–52. https://doi.org/10.1038/s41431-024-01660-5
19. Koskinas KC, Catapano AL, Baigent C, Tokgozoglu L, Mach F. Current perceptions and practices in lipid management: results of a European Society of Cardiology/European Atherosclerosis Society Survey. *Eur J Prev Cardiol* 2022;**28**:2030–7. https://doi.org/10.1093/eurjpc/zwaa156
20. Nelson AJ, Haynes K, Shambhu S, Eapen Z, Cziraky MJ, Nanna MG, *et al.* High-intensity statin use among patients with atherosclerosis in the U.S. *J Am Coll Cardiol* 2022;**79**:1802–13. https://doi.org/10.1016/j.jacc.2022.02.048
21. Brieger D, Chow C, Gullick J, Hyun K, D'Souza M, Briffa T, *et al.* Improving patient adherence to secondary prevention medications 6 months after an acute coronary syndrome: observational cohort study. *Intern Med J* 2018;**48**:541–9. https://doi.org/10.1111/imj.13736
22. Bradley CK, Wang TY, Li S, Robinson JG, Roger VL, Goldberg AC, *et al.* Patient-reported reasons for declining or discontinuing statin therapy: insights from the PALM registry. *J Am Heart Assoc* 2019;**8**:e011765. https://doi.org/10.1161/JAHA.118.011765
23. Schubert J, Leosdottir M, Lindahl B, Westerbergh J, Melhus H, Modica A, *et al.* Intensive early and sustained lowering of non-high-density lipoprotein cholesterol after myocardial infarction and prognosis: the SWEDEHEART registry. *Eur Heart J* 2024;**45**:4204–15. https://doi.org/10.1093/eurheartj/ehae576
24. Sasso JM, Ambrose BJB, Tenchov R, Datta RS, Basel MT, DeLong RK, *et al.* The progress and promise of RNA medicine—an arsenal of targeted treatments. *J Med Chem* 2022;**65**:6975–7015. https://doi.org/10.1021/acs.jmedchem.2c00024
25. Coelho T, Marques W Jr, Dasgupta NR, Chao CC, Parman Y, Franca MC Jr, *et al.* Eplontersen for hereditary transthyretin amyloidosis with polyneuropathy. *JAMA* 2023;**330**:1448–58. https://doi.org/10.1001/jama.2023.18688
26. Maurer M, Benson M, Michela B, Buchele G, Falk R, Geary R, *et al.* P010. Evaluation of the efficacy and safety of AKCEA-TTR-LRx (ION-682884) in patients with transthyretin-mediated amyloid cardiomyopathy: the CARDIO-TTRansform study. *Heart Lung* 2021;**50**:565–6. https://doi.org/10.1016/j.hrtlng.2021.03.065
27. Yeang C, Karwatowska-Prokopczuk E, Su F, Dinh B, Xia S, Witztum JL, *et al.* Effect of pelacarsen on lipoprotein(a) cholesterol and corrected low-density lipoprotein cholesterol. *J Am Coll Cardiol* 2022;**79**:1035–46. https://doi.org/10.1016/j.jacc.2021.12.032
28. Witztum JL, Gaudet D, Freedman SD, Alexander VJ, Digenio A, Williams KR, *et al.* Volanesorsen and triglyceride levels in familial chylomicronemia syndrome. *N Engl J Med* 2019;**381**:531–42. https://doi.org/10.1056/NEJMoa1715944
29. Katsiki N, Vrablik M, Banach M, Gouni-Berthold I. Inclisiran, low-density lipoprotein cholesterol and lipoprotein (a). *Pharmaceuticals (Basel)* 2023;**16**:577. https://doi.org/10.3390/ph16040577
30. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, *et al.* Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med* 2018;**379**:11–21. https://doi.org/10.1056/NEJMoa1716153
31. Ballantyne CM, Vasas S, Azizad M, Clifton P, Rosenson RS, Chang T, *et al.* Plozasiran, an RNA interference agent targeting APOC3, for mixed hyperlipidemia. *N Engl J Med* 2024;**391**:899–912. https://doi.org/10.1056/NEJMoa2404143
32. Watts GF, Rosenson RS, Hegele RA, Goldberg IJ, Gallo A, Mertens A, *et al.* Plozasiran for managing persistent chylomicronemia and pancreatitis risk. *N Engl J Med* 2025;**392**:127–37. https://doi.org/10.1056/NEJMoa2409368
33. Adams D, Tournev IL, Taylor MS, Coelho T, Plante-Bordeneuve V, Berk JL, *et al.* Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid* 2023;**30**:18–26. https://doi.org/10.1080/13506129.2022.2091985
34. Fontana M, Berk JL, Gillmore JD, Witteles RM, Grogan M, Drachman B, *et al.* Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med* 2025;**392**:33–44. https://doi.org/10.1056/NEJMoa2409134
35. Nissen SE, Wolski K, Watts GF, Koren MJ, Fok H, Nicholls SJ, *et al.* Single ascending and multiple-dose trial of zerlasiran, a short interfering RNA targeting lipoprotein(a): a randomized clinical trial. *JAMA* 2024;**331**:1534–43. https://doi.org/10.1001/jama.2024.4504
36. Bakris GL, Saxena M, Gupta A, Chalhoub F, Lee J, Stiglitz D, *et al.* RNA interference with zilebesiran for mild to moderate hypertension: the KARDIA-1 randomized clinical trial. *JAMA* 2024;**331**:740–9. https://doi.org/10.1001/jama.2024.0728
37. Rosenson RS, Gaudet D, Hegele RA, Ballantyne CM, Nicholls SJ, Lucas KJ, *et al.* Zodasiran, an RNAi therapeutic targeting ANGPTL3, for mixed hyperlipidemia. *N Engl J Med* 2024;**391**:913–25. https://doi.org/10.1056/NEJMoa2404147
38. Bauersachs J, Solomon SD, Anker SD, Antorrena-Miranda I, Batkai S, Viereck J, *et al.* Efficacy and safety of CDR132L in patients with reduced left ventricular ejection fraction after myocardial infarction: rationale and design of the HF-REVERT trial. *Eur J Heart Fail* 2024;**26**:674–82. https://doi.org/10.1002/ejhf.3139
39. Lyon AR, Babalis D, Morley-Smith AC, Hedger M, Suarez Barrientos A, Foldes G, *et al.* Investigation of the safety and feasibility of AAV1/SERCA2a gene transfer in patients with chronic heart failure supported with a left ventricular assist device—the SERCA-LVAD TRIAL. *Gene Ther* 2020;**27**:579–90. https://doi.org/10.1038/s41434-020-0171-7
40. Horie T, Ono K. VERVE-101: a promising CRISPR-based gene editing therapy that reduces LDL-C and PCSK9 levels in HeFH patients. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:89–90. https://doi.org/10.1093/ehjcvp/pvad103
41. Ray KK, Ruotolo G, Michael L, Shen X, Ma X, Lim S, *et al.* Solbinsiran, a GalNAc-conjugated sirna targeting ANGPTL3, reduces atherogenic lipoproteins in individuals with mixed dyslipidaemia in a durable and dosedependent manner. *JACC* 2024;**83**:1673–. https://doi.org/10.1016/S0735-1097(24)03663-5
42. Carugo S, Sirtori CR, Gelpi G, Corsini A, Tokgozoglu L, Ruscica M. Updates in small interfering RNA for the treatment of dyslipidemias. *Curr Atheroscler Rep* 2023;**25**:805–17. https://doi.org/10.1007/s11883-023-01156-5
43. Ali Zaidi SS, Fatima F, Ali Zaidi SA, Zhou D, Deng W, Liu S. Engineering siRNA therapeutics: challenges and strategies. *J Nanobiotechnology* 2023;**21**:381. https://doi.org/10.1186/s12951-023-02147-z
44. Lee Y, Jeong M, Park J, Jung H, Lee H. Immunogenicity of lipid nanoparticles and its impact on the efficacy of mRNA vaccines and therapeutics. *Exp Mol Med* 2023;**55**:2085–96. https://doi.org/10.1038/s12276-023-01086-x
45. Fontana M, Solomon SD, Kachadourian J, Walsh L, Rocha R, Lebwohl D, *et al.* CRISPR-Cas9 gene editing with nexiguran ziclumeran for ATTR cardiomyopathy. *N Engl J Med* 2024;**391**:2231–41. https://doi.org/10.1056/NEJMoa2412309
46. Wright RS, Ray KK, Raal FJ, Kallend DG, Jaros M, Koenig W, *et al.* Pooled patient-level analysis of inclisiran trials in patients with familial hypercholesterolemia or atherosclerosis. *J Am Coll Cardiol* 2021;**77**:1182–93. https://doi.org/10.1016/j.jacc.2020.12.058
47. Gillmore JD, Gane E, Taubel J, Kao J, Fontana M, Maitland ML, *et al.* CRISPR-Cas9 in vivo gene editing for transthyretin amyloidosis. *N Engl J Med* 2021;**385**:493–502. https://doi.org/10.1056/NEJMoa2107454
48. Damase TR, Sukhovershin R, Boada C, Taraballi F, Pettigrew RI, Cooke JP. The limitless future of RNA therapeutics. *Front Bioeng Biotechnol* 2021;**9**:628137. https://doi.org/10.3389/fbioe.2021.628137
49. Damase TR, Sukhovershin R, Godin B, Nasir K, Cooke JP. Established and emerging nucleic acid therapies for familial hypercholesterolemia. *Circulation* 2024;**150**:724–35. https://doi.org/10.1161/CIRCULATIONAHA.123.067957
50. Zannad F, Berwanger O, Corda S, Cowie MR, Gamra H, Gibson CM, *et al.* How to make cardiology clinical trials more inclusive. *Nat Med* 2024;**30**:2745–55. https://doi.org/10.1038/s41591-024-03273-3
51. Hastie E, Samulski RJ. Adeno-associated virus at 50: a golden anniversary of discovery, research, and gene therapy success–a personal perspective. *Hum Gene Ther* 2015;**26**:257–65. https://doi.org/10.1089/hum.2015.025
52. Ishikawa K, Weber T, Hajjar RJ. Human cardiac gene therapy. *Circ Res* 2018;**123**:601–13. https://doi.org/10.1161/CIRCRESAHA.118.311587
53. Tabebordbar M, Lagerborg KA, Stanton A, King EM, Ye S, Tellez L, *et al.* Directed evolution of a family of AAV capsid variants enabling potent muscle-directed gene delivery across species. *Cell* 2021;**184**:4919–38.e22. https://doi.org/10.1016/j.cell.2021.08.028
54. Asokan A, Conway JC, Phillips JL, Li C, Hegge J, Sinnott R, *et al.* Reengineering a receptor footprint of adeno-associated virus enables selective and systemic gene transfer to muscle. *Nat Biotechnol* 2010;**28**:79–82. https://doi.org/10.1038/nbt.1599
55. Jaski B, Cheng R, Rudy J, Li R, Hajjar R. A phase 1 clinical trial of high dose AAV1.SERCA2a in patients with heart failure: modulation of SERCA2a of intra- myocytic calcium trafficking in heart failure with reduced ejection fraction (MUSIC-HFrEF) [abstract]. *Mol Ther* 2024;**31**:3.
56. Henry T, Chung E, Jay T, Reynolds K, Alvisi M, Ervin L, *et al.* A first-in-human phase 1 clinical gene therapy trial for the treatment of heart failure using a novel re-engineered adeno- associated vector molecular therapy [abstract]. *Mol Ther* 2022;**30**:14–6. https://doi.org/10.1016/j.ymthe.2021.12.007

57. Greenberg B, Taylor M, Adler E, Colan S, Ricks D, Yarabe P, *et al.* Phase 1 study of AAV9.LAMP2B gene therapy in Danon disease. *N Engl J Med* 2024;**392**:972–83. https://doi.org/10.1056/NEJMoa2412392
58. Desai Milind Y. The promise of gene therapy in hypertrophic cardiomyopathy: emergence of human experience. *Cardiovascular Research* 2024;**120**:e33–e35. https://doi.org/10.1093/cvr/cvae107
59. Nazarenko N, Seo J, Nagraj S, Palaiodimos L, Kokkinidis DG. RNA interference-based therapies for the reduction of cardiovascular risk. *Curr Mol Pharmacol* 2024;**17**:e18761429264553. https://doi.org/10.2174/0118761429264553231204115314
60. Zhang C, Zhang B. RNA therapeutics: updates and future potential. *Sci China Life Sci* 2023;**66**:12–30. https://doi.org/10.1007/s11427-022-2171-2
61. Youssef M, Hitti C, Puppin Chaves Fulber J, Kamen AA. Enabling mRNA therapeutics: current landscape and challenges in manufacturing. *Biomolecules* 2023;**13**:1497. https://doi.org/10.3390/biom13101497
62. European Medicines Agency. *Reflection paper on classification of advanced therapy medicinal products*. 2015, https://www.ema.europa.eu/system/files/documents/scientific-guideline/wc500187744_en.pdf (26 February 2024, date last accessed).
63. European Medicines Agency. *Guideline on the development and manufacture of oligonucleotides—Draft*. 2024, https://www.ema.europa.eu/en/development-manufacture-oligonucleotides-scientific-guideline (6 November 2024, date last accessed).
64. European Medicines Agency. *Guidelines relevant for advanced therapy medicinal products*. 2024, https://www.ema.europa.eu/en/human-regulatory-overview/advanced-therapy-medicinal-products-overview/guidelines-relevant-advanced-therapy-medicinal-products (26 February 2024, date last accessed).
65. Tavridou A, Rogers D, Bonelli M, Schiel A, Hidalgo-Simon A. Towards a better use of scientific advice for developers of advanced therapies. *Br J Clin Pharmacol* 2021;**87**:2459–64. https://doi.org/10.1111/bcp.14672
66. European Medicines Agency. *Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products*. 2013, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-based-approach-according-annex-i-part-iv-directive-200183ec-applied-advanced-therapy-medicinal-products_en.pdf (20 March 2024, date last accessed).
67. European Commission. *Guideline on good clinical practice specific to advanced therapy medicinal products*. 2019, https://health.ec.europa.eu/document/download/2d8842cb-e785-488f-bfd0-bf8f2dab1efe_en (20 March 2024, date last accessed).
68. U.S. Food and Drug Administration. *Long term follow-up after administration of human gene therapy products: Guidance for industry*. https://www.fda.gov/media/113768/download (20 March 2024, date last accessed).
69. Fentanes E, Vande Hei AG, Holuby RS, Suarez N, Slim Y, Slim JN, *et al.* Treatment in a preventive cardiology clinic utilizing advanced practice providers effectively closes atherosclerotic cardiovascular disease risk-management gaps among a primary-prevention population compared with a propensity-matched primary-care cohort: a team-based care model and its impact on lipid and blood pressure management. *Clin Cardiol* 2018;**41**:817–24. https://doi.org/10.1002/clc.22963
70. Kolandaivelu K, Leiden BB, O'Gara PT, Bhatt DL. Non-adherence to cardiovascular medications. *Eur Heart J* 2014;**35**:3267–76. https://doi.org/10.1093/eurheartj/ehu364
71. Tokgozoglu L, Torp-Pedersen C. Redefining cardiovascular risk prediction: is the crystal ball clearer now? *Eur Heart J* 2021;**42**:2468–71. https://doi.org/10.1093/eurheartj/ehab310
72. Verve Therapeutics. *Transforming the care of cardiovascular disease through single-course gene editing medicines*. 2024, https://ir.vervetx.com/static-files/f6ab65c0-556a-42a8-b310-89393551b1b2 (20 March 2024, date last accessed).
73. Catapano AL, De Caterina R, Jukema JW, Klempfner R, Landmesser U, Schiele F, *et al.* Addressing current challenges in optimization of lipid management following an ACS event: outcomes of the ACS EuroPath III initiative. *Clin Cardiol* 2023;**46**:407–15. https://doi.org/10.1002/clc.23988
74. Wilson P, Dixon S, Vell T, Bower P, Rootkin L, Williams C, *et al.* Implementation of inclisiran in UK primary care for patients with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents: rationale and design of VICTORION-spirit, a pragmatic phase IIIb, randomised controlled study. *Int J Clin Trials* 2023;**10**:156–63. https://doi.org/10.18203/2349-3259.ijct20231106
75. IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. *Inotersen (hereditäre transthyretin amyloidose mit polyneuropathie) bewertung gemäß 35a Abs. 1 Satz 11 SGB V*, 2018. https://www.g-ba.de/downloads/92-975-2643/2018-10-01_Bewertung-Therapiekosten-Patientenzahlen-IQWiG_Inotersen-D-381.pdf (6 November 2024, date last accessed).
76. World Medical Association. *WMA Declaration of Reykjavik—Ethical considerations regarding the use of genetics in health care*. 2020, https://www.wma.net/policies-post/wma-statement-on-genetics-and-medicine/ (6 November 2024, date last accessed).
77. Stamm T, Bott N, Thwaites R, Mosor E, Andrews MR, Borgdorff J, *et al.* Building a value-based care infrastructure in Europe: the health outcomes observatory. *NEJM Catal Innov Care Deliv* 2021;**2**. https://doi.org/10.1056/CAT.21.0146
78. Sandhu AT, Heidenreich PA, Borden W, Farmer SA, Ho PM, Hammond G, *et al.* Value-based payment for clinicians treating cardiovascular disease: a policy statement from the American Heart Association. *Circulation* 2023;**148**:543–63. https://doi.org/10.1161/CIR.0000000000001143
79. Bhati D, Deogade MS, Kanyal D. Improving patient outcomes through effective hospital administration: a comprehensive review. *Cureus* 2023;**15**:e47731. https://doi.org/10.7759/cureus.47731
80. Cossio-Gil Y, Omara M, Watson C, Casey J, Chakhunashvili A, Gutierrez-San Miguel M, *et al.* The roadmap for implementing value-based healthcare in European university hospitals-consensus report and recommendations. *Value Health* 2022;**25**:1148–56. https://doi.org/10.1016/j.jval.2021.11.1355