How do we implement new therapeutics to change the paradigm?

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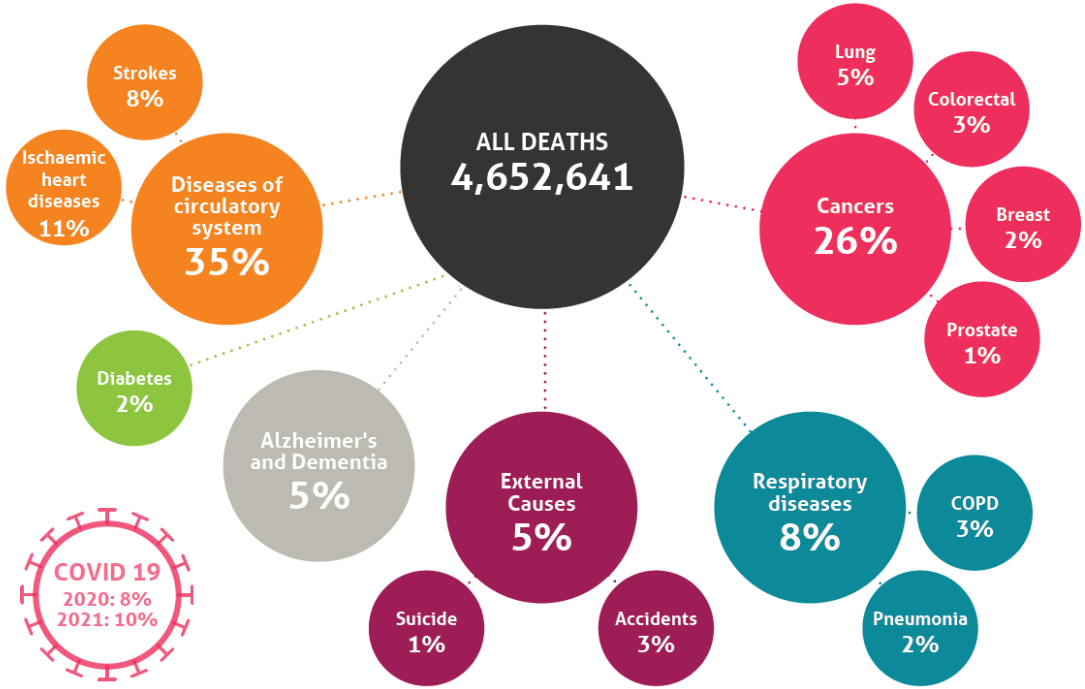
Content of today's presentation

- Cardiovascular disease burden in Europe: Recent figures
- Development of new drugs: General facts and the opportunity of RNA-targeted therapeutics
- Implementation of new therapeutics: Findings from recent publications

Cardiovascular disease burden in Europe: Recent figures

Main causes of mortality in EU countries (2019 or nearest year)

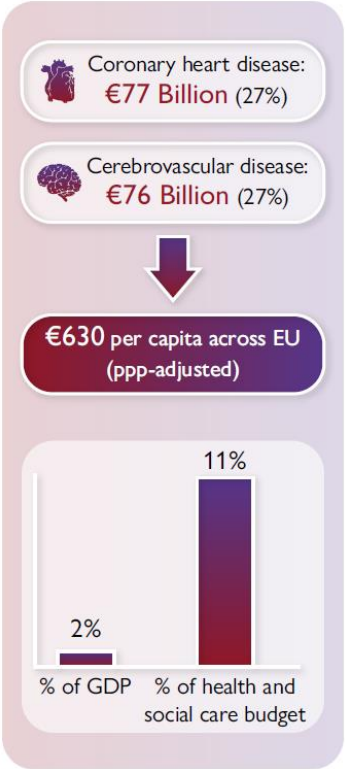
- Diseases of the **circulatory system** represented **35% of total mortality in EU** in 2019
- Ischemic heart disease and strokes had a substantial impact on that figure
- There is a **huge opportunity to improve current situation**

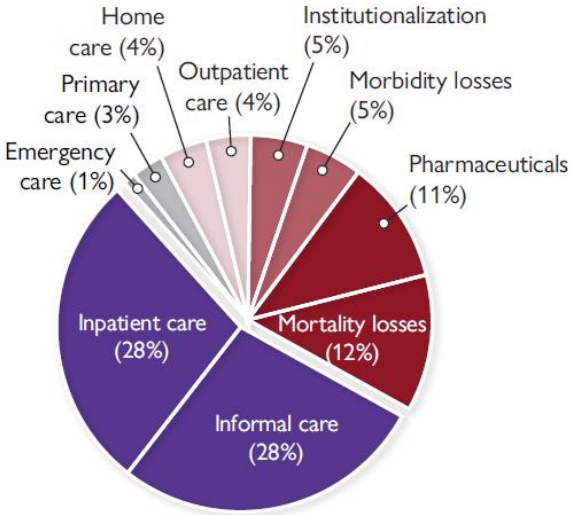


Note: The other causes of death not shown in this figure represent 18% of all deaths. Data refer to 2017 for France
Source: Eurostat Database, complemented with OECD Health Statistics 2022 for COVID-19 mortality, Health at a Glance: Europe 2022, OECD & European Commission, page 95.

Economic burden of cardiovascular diseases - European Union

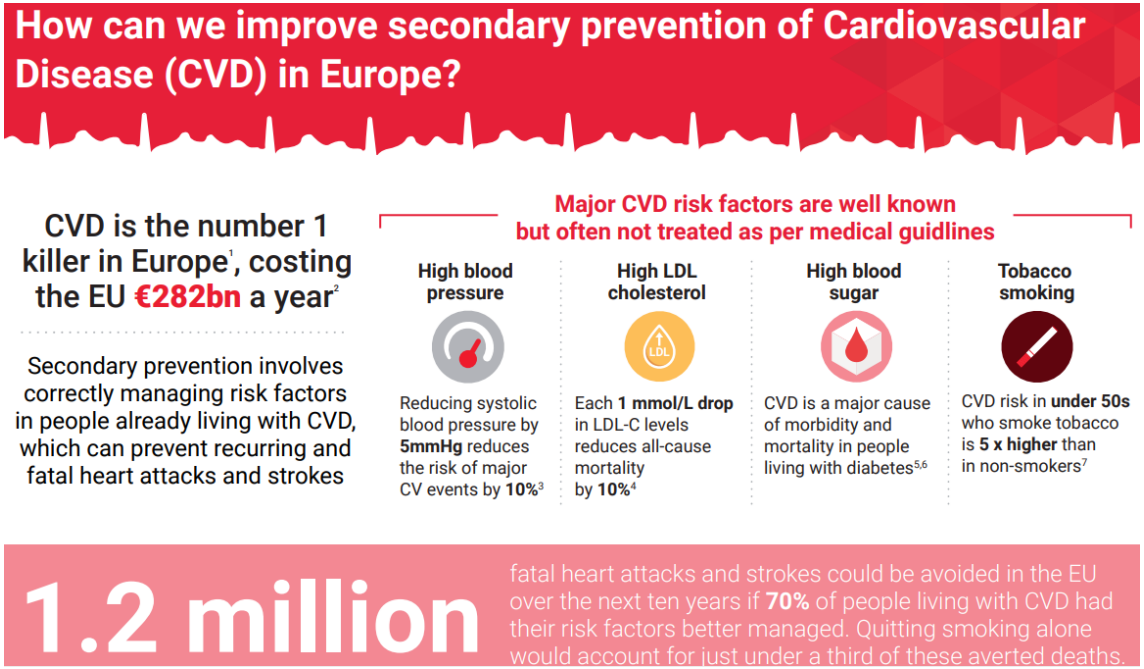
- The **economic burden of CVD in EU27** countries is **€282 billion annually**
- CVD currently represents **2% of the EU27 gross domestic product** (GDP) and **11% of health and social care budget**
- Costs by categories: **Inpatient care and informal care** are main drivers of cost
- **Pharmaceutical products account for 11% of costs**





Luengo-Fernandez et al, European Heart Journal (2023) 44, 4752–4767.

How can we improve secondary prevention of CVD in EU?



What else could be done?

RNA-targeted therapeutics may offer advantages *vs* existing therapies, for example:

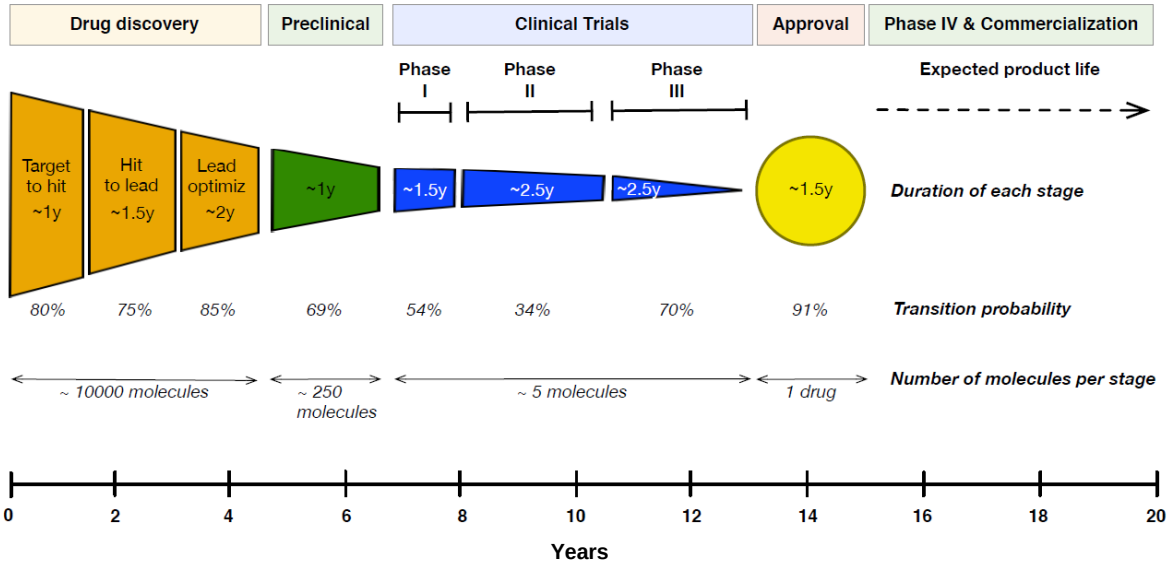
- Potential for once-a-year administration
- Potential to manage additional risk factors

RNA-targeted therapeutics have the potential to **change the management of CVD** and to **alleviate healthcare-associated costs**

Report from London School of Economics commissioned by the European Federation of Pharmaceutical Industries and Associations (Online on 23 January 2024)
https://efpia.eu/news-events/the-efpia-view/statements-press-releases/cardiovascular-disease-lse-report-highlights-life-saving-potential-of-secondary-prevention/

Development of new drugs: General facts and the opportunity of RNA-targeted therapeutics

Drug development is a long, costly and complex process



Key estimates associated with **bringing a new medicine to patients** (across therapeutic areas):

- Average **probability of success**[1]: **8.3 – 13.8%** (for 1993-2015)
- Average **investment needed**[2]: **$2,284 million** (in 2022)
- Average **14 years before approval**
- **Adoption of new medicines is uncertain**, and varies according to **geographies**

Figure adapted from: Laguna-Fernandez A, & Wadell C: Towards a Swedish megafund for life science innovation (2017), Swedish Agency for Growth Policy Analysis
1. Early Value Assessment report (2020), Deloitte; 2. Seize the digital momentum report (2023), Deloitte.

RNA-targeted therapeutics *vs* other therapeutic strategies

1 Therapeutic antibodies

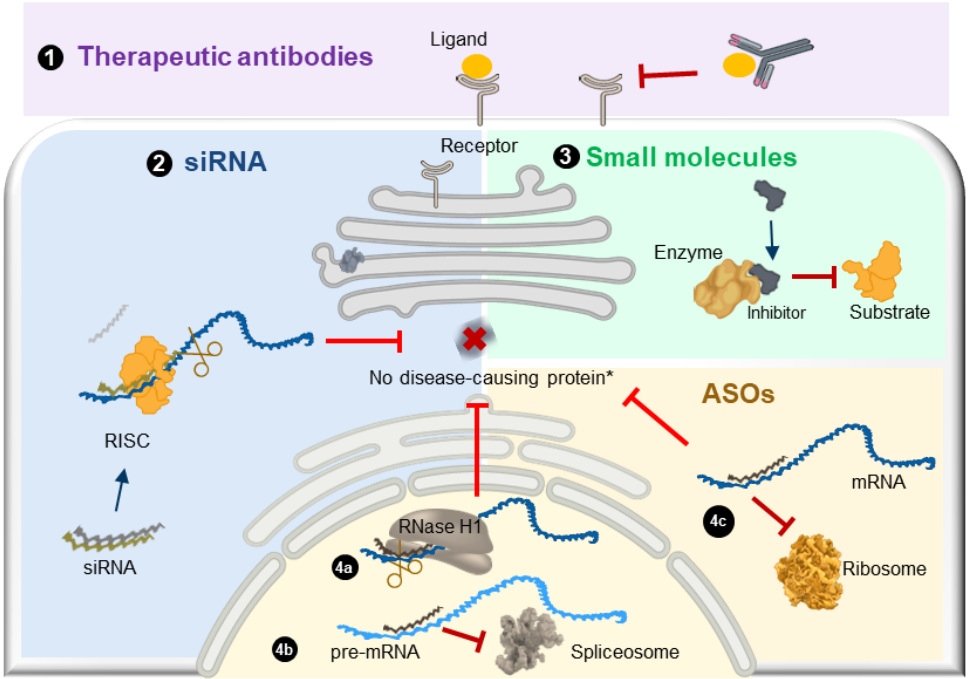
Designed to recognize specific molecular regions. Bind to extracellular or plasma proteins to modulate downstream signaling

2 siRNA

Small, double-stranded RNA molecules that harness the endogenous RNA interference machinery to silence target gene expression. The guide strand (a.k.a antisense strand) of the siRNA (complementary to the target mRNA) is loaded onto RISC complex and binds to its target mRNA. Ago2, a component of the RISC, mediates target mRNA degradation

3 Small molecules

Low molecular weight organic compounds that modulate the function of target protein by altering its activity and/or its interaction with other molecules



4 ASOs

ASOs are single-stranded oligonucleotides that can be designed to work via the following mechanisms:

4a RNase H1-mediated degradation of mRNA

DNA-like ASOs bind to their target RNA (mostly in the nucleus). This mimics the DNA/RNA structure that is recognized by RNase H1, which leads to mRNA degradation

4b Modulation of splicing

These ASOs bind to specific nucleotide sequences, blocking the recruitment of splicing factors that facilitate the removal of the intronic sequences, thus altering pre-mRNA splicing

4c Modulation of translation

Binding of ASOs to the target mRNA creates steric block for recruitment of ribosomes preventing protein synthesis

Ago2, argonaute 2; a.k.a, also known as; ASOs, antisense oligonucleotides; mRNA, messenger RNA; RISC, RNA-induced silencing complex; RNase H1, ribonuclease H1; siRNA, small interfering RNA. Figure adapted from: Ginsburg et al (2017), Genomic and Precision Medicine Foundations, Translation and Implementation. Elsevier

History of development of RNA-targeted therapeutics

1944 Discovery of **DNA as hereditary material**

1964 Synthesis of **2'-F** modification

1966 First synthesis of **PS** backbone

1969 Synthesis of **2'-O-Me** modification

1987 Patent for today's widely used gapmer design filed

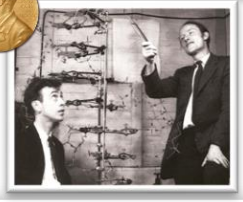
2001 Discovery of RNAi mechanism in mammalian cells by **A Z Fire and C C Mello**[4]

2003 Completion of the **human genome project**

2005 First siRNA clinical trial started (Bevasiranib)[2,3]

1940s | 1950s | 1960s | 1970s | 1980s | 1990s | 2000s | 2010s

1953 Discovery of the **helical structure of DNA** by **J D Watson, F H C Crick and M Wilkins**[5]



1978 Birth of the antisense concept: using a synthetic ASO to control gene expression

1979 Discovery of **RNase-H mechanism** to cleave RNA hybridized to DNA

1995 Discovery of **2'-MOE** chemistry

1997,1998 Discovery of conformationally constrained **locked nucleic acids**

1998 Discovery of **RNAi** mechanism

1998 Fomivirsen, the first ASO **approved**

2014 Development of **GalNAc** conjugated siRNA*

2013 Mipomersen approved

2016 Defibrotide, eteplirsen and the first IT delivered ASO, nusinersen, approved

2018 Inotersen and the first siRNA, patisiran, approved

Milestones in biology

Milestones in chemistry

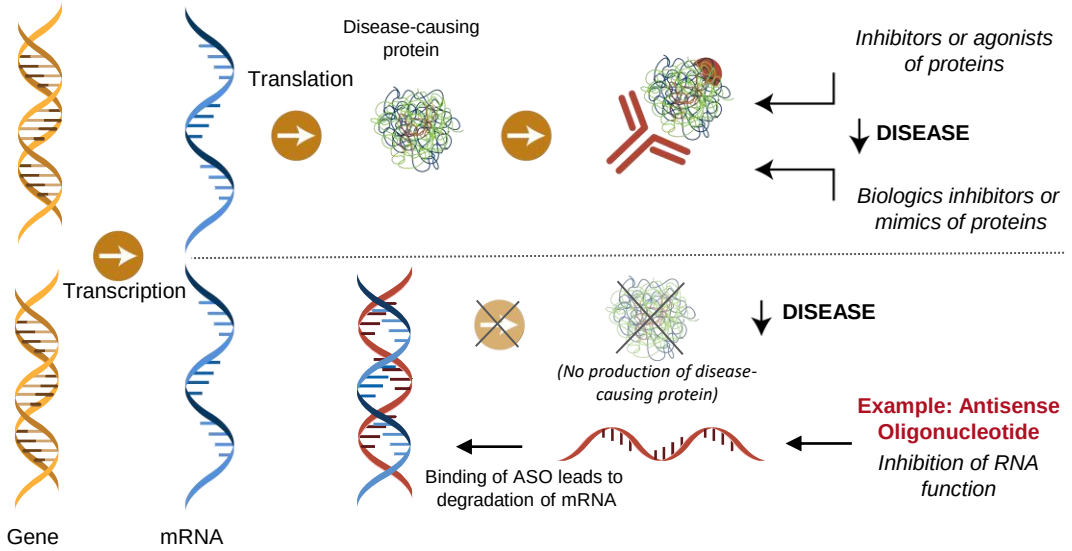
Clinical milestones

1. Yin, et al. Clin Transl Sci. 2019;12(2):98-112; 2. https://clinicaltrials.gov/ct2/show/NCT00259753; 3. Burnett, et al. Biotechnol J. 2011;6(9):1130-46; 4. Fire, et al. Nature. 1998; 391(6669):806-11; 5. Watson, et al. Nature 1953;171, 737–738.

RNA-targeted therapeutics: a revolutionary platform

- A significant number of the proteins encoded by the human genome are **undruggable** by conventional therapies[1,2]
- **RNA-targeted therapeutics:**[1,2,3]
  - can be rationally **designed against virtually any genetic target** and thus potentially address a **broad range of risk factors / diseases**
  - bind to target mRNA with **high selectivity and affinity**, and should, in principle, be **more specific** than small molecules[2]
  - due to their structural characteristics, mechanism of action and specificity, they **may offer better efficacy/safety profile**, **less frequent administration**, **better adherence to treatment** and other benefits *vs* conventional therapies

Conventional therapies target disease-causing proteins/ receptors[3]



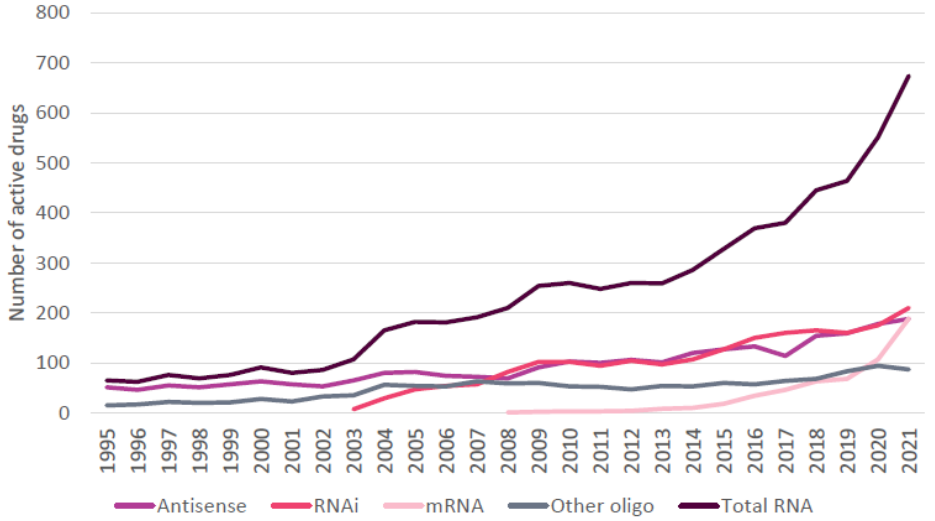
RNA-targeted therapeutics inhibit cognate mRNA to prevent synthesis of disease-causing protein[3]

ASOs, antisense oligonucleotides; mRNA, messenger RNA; siRNA, small interfering RNA

1. Yu, et al. Pharmacol Ther. 2019;196:91-104; 2. Crooke, et al. Cell Metab. 2018;27(4):714-739; 3. Tsimikas, et al. Curr Opin Lipidol. 2018;29(6):459-466.

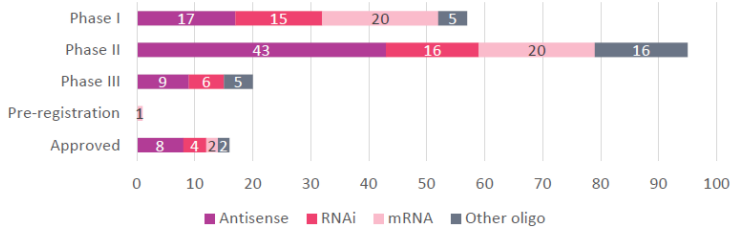
RNA-targeted therapeutics pipeline (as of 2021)

Historical evolution



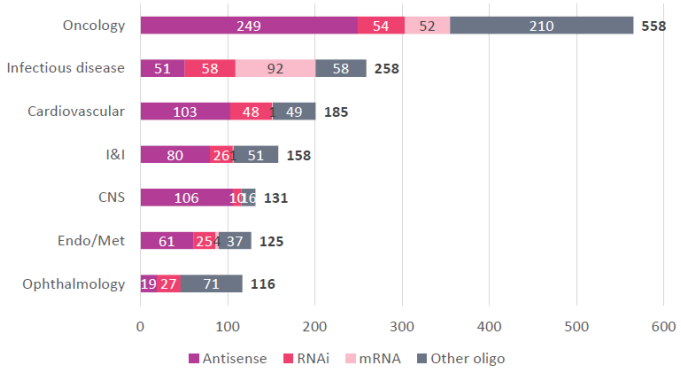
Annual snapshots taken in May each year; all clinical development stages shown

Pipeline by stage of development



~500 known preclinical assets not shown

Number of trials by therapy area



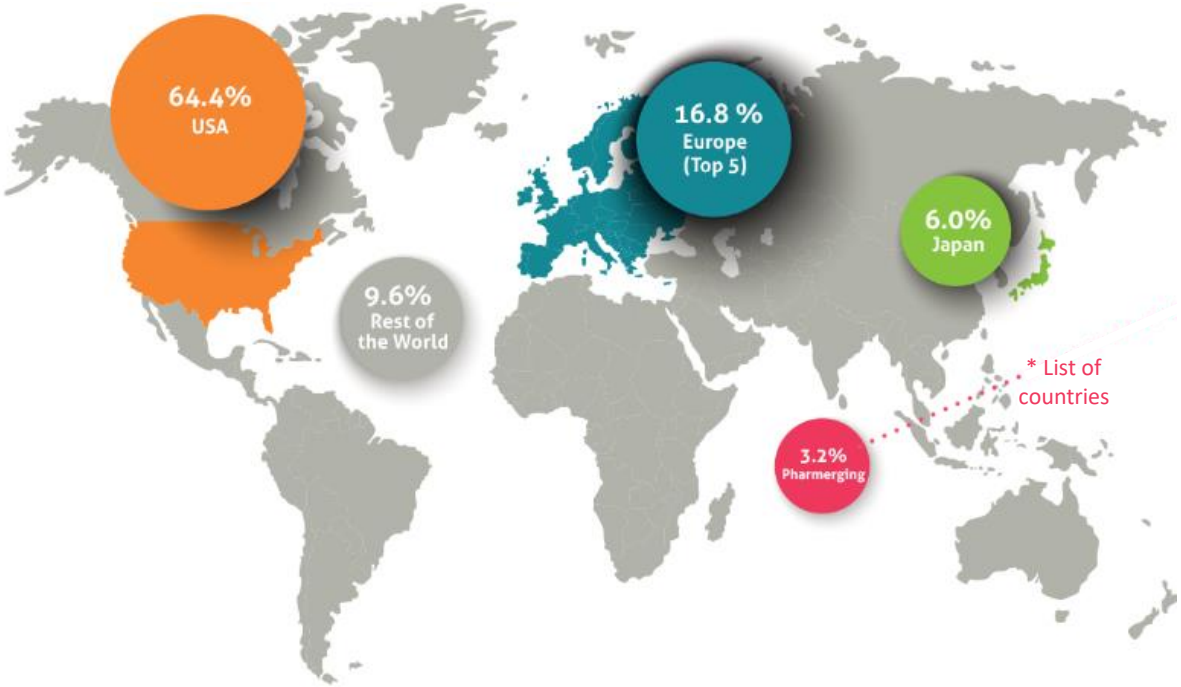
Unlocking the potential of RNA therapies (2021), PharmaIntelligence

Implementation of new therapeutics: Findings from recent publications

Geographical breakdown of sales of new medicines launched during the period 2016-2021

Commercialization of new according to regions/countries:

- **USA** (pop size: 331m) **remains top country** in terms of sales of new medicines
- **EU5** (pop size: 323m) **occupies second place** as region in which new medicines were commercialized
- Data not shown reveals that **China and Japan are growing rapidly**



*New medicines cover all new active ingredients marketed for the first time on the world market during the period 2017-2022. Europe (Top 5) comprises France, Germany, Italy, Spain and United Kingdom. * Pharmerging comprises 21 countries ranked by IQVIA as high-growth pharmaceutical markets (Algeria, Argentina, Bangladesh, Brazil, Colombia, Chile, China, Egypt, India, Indonesia, Kazakhstan, Mexico, Nigeria, Pakistan, Philippines, Poland, Russia, Saudi Arabia, South Africa, Turkey and Vietnam).*
Source: IQVIA (MIDAS May 2023)

The root cause of unavailability and delay to innovative medicines in Europe: Perspective of EFPIA

Category	Potential root causes
The time prior to marketing authorisation	1. The speed of the regulatory process 2. Accessibility of medicines prior to marketing authorisation
The price and reimbursement process	3. Initiation of the process 4. The speed of the national timelines and adherence
The value assessment process	5. Misalignment on evidence requirements 6. Misalignment on value and price 7. The value assigned to product differentiation and choice
Health system constraints and resources	8. Insufficient budget to implement decisions 9. Diagnosis, supporting infrastructure and relevance to patients
The sub-national approval process	10. Multiple layers of decision-making process

- "*The unprecedented speed of innovation exhibited over the last five years and the promise of the industry pipeline provides an **important opportunity to improve outcomes for patients**. There is common agreement that the **value of innovation is only realised when patients benefit from advances in treatment***"
- "*EFPIA documented the root cause of access inequality and found there are **10 interrelated factors that explain unavailability and delay** (defined as length of time from European marketing authorisation to availability at Member State level) to innovative medicines*"
- "*As the **root causes are multifactorial**, they **can only be solved by different stakeholders working together***"
- "*The industry considers that the **root causes of unavailability and delay could be addressed through collaborative work with Member States, European Commission and other stakeholders** on proposals to improve availability and reduce delays*"

The root cause of unavailability and delay to innovative medicines: Reducing the time before patients have access to innovative medicines (2023), European Federation of Pharmaceutical Industries and Associations (EFPIA)

Relevant perspectives can be found in the scientific literature

Circulation

SPECIAL REPORT

A Call to Action for New Global Approaches to Cardiovascular Disease Drug Solutions

Gemma A. Figtree; Keith Broadfoot; Barbara Casadei; Robert Califf; Filippo Crea; Grant R. Drummond; Jane E. Freedman; Tomasz J. Guzik; David Harrison; Derek J. Hausenloy; Joseph A. Hill; James L. Januzzi; Bronwyn A. Kingwell; Carolyn S.P. Lam; Calum A. MacRae; Frank Misselwitz; Tetsuji Miura; Rebecca H. Ritchie; Maciej Tomaszewski; Joseph C. Wu; Junjie Xiao; Faiez Zannad

European Journal of Preventive Cardiology

Original scientific paper

Implementation, target population, compliance and barriers to risk guided therapy

Lale Tokgozoglu[1] and Eric Bruckert[2]

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DOI: 10.1177/2047487312448989
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Figtree et al, Eur Heart J. 2021 Apr 14;42(15):1464-1475; Tokgozoglu & Bruckert, Eur J Prev Cardiol. 2012 Aug;19(2 Suppl):37-41.

Summary

- Cardiovascular disease is the leading cause of death in Europe. The economic burden of CVD in EU27 countries is €282 billion annually (2% of GDP)
- Drug development is a long, costly and complex process
- RNA-targeted therapeutics have the potential to change the management of CVD and to alleviate healthcare-associated costs
- Multiple factors contribute to availability and implementation of new therapies in Europe. Different stakeholders working together could improve current situation

Thank you