International Journal of Cardiology 365 (2022) 61–68

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

How can we optimise health technology assessment and reimbursement decisions to accelerate access to new cardiovascular medicines?

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ARTICLE INFO

Keywords:
Industry-regulatory collaboration
Post-approval processes
Patient access
Payers
Cost-effectiveness

ABSTRACT

Regulatory approvals of, and subsequent access to, innovative cardiovascular medications have declined. How much of this decline relates to the final step of gaining reimbursement for new treatments is unknown. Payers and health technology assessment (HTA) bodies look beyond efficacy and safety to assess whether a new drug improves patient outcomes, quality of life, or satisfaction at a cost that is affordable compared to existing treatments. HTA bodies work within a limited healthcare budget, and this is one of the reasons why only half of newly approved drugs are accepted for reimbursement, or receive restricted or "optimised" recommendations from HTA bodies.

All stakeholders have the common goal of facilitating access to safe, effective, and affordable treatments to appropriate patients. An important strategy to expedite this is providing optimal data. This is demonstrably facilitated by early (and ongoing) discussions between all stakeholders. Many countries have formal programmes to provide collaborative regulatory and HTA advice to developers. Other strategies include aligning regulatory and HTA processes, increasing use of real-world evidence, formally defining the decision-making process, and educating stakeholders on the criteria for positive decision making. Industry should focus on developing treatments for unmet medical needs, seek early engagement with HTA and regulatory bodies, improve methodologies for optimal price setting, develop internal systems to collaborate with national and international stakeholders, and conduct post-approval studies. Patient involvement in all stages of development, including HTA, is critical to capture the lived experience and priorities of those whose lives will be impacted by new treatment approvals.

1. Introduction

Regulatory approvals of, and subsequent access to, innovative cardiovascular (CV) medications have declined, with CV drug approvals by the US Food and Drug Administration (FDA) dropping from 16% of the total new approvals (7/45) in 2015 to 2% (1/53) in 2020 [1]. Similarly, CV drugs accounted for just 3 (3%) of 97 new medicine, and only one of 39 new active substances, approved by the European Medicines Agency (EMA) in 2020 [2].

Regulatory approval of a drug does not ensure patient access – there remains the step of pricing the drug, and getting reimbursement agencies, third-party intermediaries, or patients to agree to pay for it. Evidence-based medicine remains at the heart of all treatment, guideline, and regulatory decisions. In addition, payers ask how well a treatment works compared to existing treatments, and whether it reflects value for money [3]. Does it improve patient outcomes, safety, or satisfaction at a reasonable and affordable cost [3,4]? All stakeholders must cooperate to provide the evidence that payers need to determine

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https://doi.org/10.1016/j.ijcard.2022.07.020
Received 18 March 2022; Received in revised form 26 June 2022; Accepted 12 July 2022
Available online 26 July 2022

the value of new treatments.

This paper builds on discussions among clinical trialists, industry representatives, regulators, and patients, which took place at the 17th Global Cardiovascular Clinical Trialists (CVCT) Forum in December 2020 (www.globalcvctforum.com). The goal was to review the decisions of regulatory, health technology assessment, and pricing and reimbursement organisations, and to suggest ways to improve patient access to evidence- and value-based therapies. Our paper reports on the views of senior representatives of these and other stakeholders from around the world attending the Forum. Throughout, we attempt to capture what emerged from extended discussions at the Forum. This paper is not a consensus statement from those present at the Forum or the organisations they are associated with. It is a contribution to the debate, aiming to stimulate discussion within and between the various stakeholder groups, nationally and internationally.

2. Public and private payers, and the role of health technology assessment (HTA) bodies

Many payers, particularly in countries with universal-coverage healthcare systems, rely on health technology assessment (HTA) bodies to assess new interventions for reimbursement decision making, and to inform the pricing process. HTAs generally use efficacy and safety data from registration trials, patient health-related quality of life (HRQoL), life-expectancy impacts, and cost data to make recommendations. Usually, incremental cost-effectiveness ratios (ICER) are calculated to compare different treatments [4,5]. An ICER (calculated by the difference in total costs [incremental cost] divided by the difference in the chosen measure of health outcome or effect [incremental effect] to provide a ratio of 'extra cost per extra unit of health effect' – for the more expensive therapy vs the alternative), allows comparison across therapies and disease areas. If a treatment falls under a designated threshold it theoretically provides a cost-effective use of resources compared to available therapies that it may displace.

The cost-effectiveness threshold is often described as an upper limit for "willingness-to-pay" for health gain [6]. In general, where it exists, it varies around the world, and may depend on a country's income [7,8]. Interventions that are considered cost-effective in high-income countries, may not be in a middle- or low-income countries. Table 1 provides examples of explicit or implicit cost-effectiveness thresholds used in different countries [9].

Often a treatment may prove cost-effective (below the willingness-to-pay threshold) over existing treatments in only a subgroup of patients (e.g., high-risk) [10]. As a result, many treatments receive "optimised" or "restricted" positive HTA decisions. This narrows the eligible patient population, and pre-approval at the point of prescription is often required [11].

HTA assessment criteria vary widely although are deeply embedded in many high income countries, [12] although there are difference in which domains are used and what role they play for pricing and reimbursement decision making (e.g., clinically meaningful outcomes, and use of patient-reported outcomes and surrogates) [13]. In general, more than half of new drugs receive recommendations for access with restrictions, or are rejected (Fig. 1) [13,14]. For example, Fig. 2 shows the wide variation in recommendations from HTA bodies for 3 CV treatments [14], with additional data from across the European Union also available [15]. The lack of standardisation means manufacturers have to submit multiple individual applications, which requires prioritising applications around the globe. This may contribute to the variation in time to patient access of new treatments from country to country.

To illustrate this variation, we will discuss examples of patient access pathways in the United Kingdom (UK), France, and the United States (US). The UK and US represent two ends of the spectrum from full and transparent HTA process (UK) to no HTA process without even consideration of costs (US), with France somewhere in between.

Table 1
Examples of explicit or implicit cost-effectiveness thresholds in 2015 US dollars PPP from a systematic review of published studies [9].

Country	Cost-effectiveness threshold
Australia	63,096
Brazil	27,620
Canada	98,183
Hungary	25,473
Ireland	84,094
Japan	83,938
Netherlands	132,340
Sweden	50,173
Thailand	4419
UK	65,871
USA	100,000

PPP, purchasing power parity; QALY, quality adjusted life year; USD US dollars

2.1. United Kingdom

NICE conducts HTAs on behalf of the National Health Service (NHS) in England. The NHS is then legally obligated to fund treatments and make them available, typically within 3 months [16]. NICE decisions are generally adopted in Wales and Northern Ireland, but in Scotland reimbursement decisions are made by the Scottish Medicines Consortium. NICE has recognised the need to expand the evidence base beyond randomised trial and cost-effectiveness data [17]. This includes increased use of real-world evidence (RWE) generated by registries and other observational data, and new assessment technology such as artificial intelligence and wearable devices. NICE is working on methods and standards, providing resources, ensuring confidentiality and transparency, and collaborating with other stakeholders [17].

2.2. France

Upon regulatory approval of new drugs, the Transparency Commission in the National Health Authority assesses therapeutic value, considering disease severity and burden, efficacy, safety, effectiveness, and alternative treatments [18,19]. This is followed by price negotiations with the manufacturer, which are impacted by relative effectiveness compared to available treatments [19].

Multiple stakeholder review phases can result in long delays between drug regulatory approval ("marketing approval") and widespread patient access. For example, PCSK9 inhibitors received regulatory approvals in the US and France around the same time, but widespread patient access in France occurred about 2 years later than in the US [19] due to slower reimbursement decision making.

2.3. USA

The US has no single national health programme and HTAs are conducted by uncoordinated public and private initiatives [20,21]. The Centers for Medicare & Medicaid Services (CMS) administers the largest publicly funded programme and makes coverage determinations [20]. Medicare covers interventions that are "reasonable and necessary" for diagnosis or treatment [21]. CMS uses an evidence-based process to make determinations, but does not consider cost effectiveness data [20,21]. Medicare Prescription Drug Plans (e.g., Part D) are offered by private companies, which must provide a minimum level of coverage set by Medicare. Research suggests that policies governing Medicare may result in funding many drugs that HTAs in other countries deem to have insufficient evidence of efficacy or value to support coverage [20]. For example, Part D companies must include all drugs in six "protected" categories: HIV antivirals, cancer drugs, immunosuppressants, antipsychotics, antidepressants, and anticonvulsants [22].

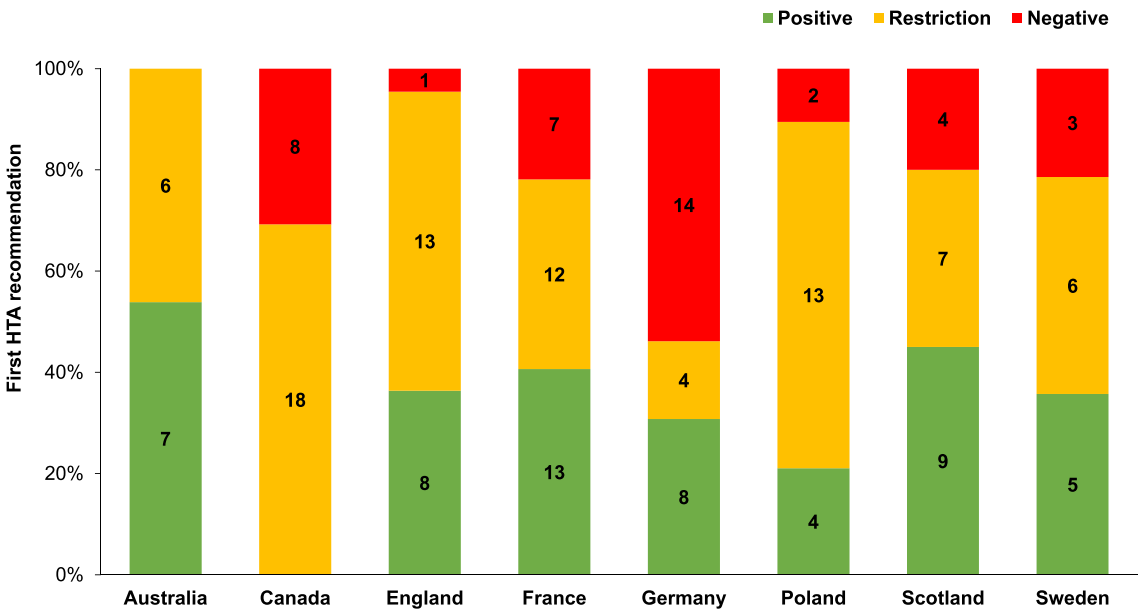

Fig. 1. Recommendations for access to new drugs in eight countries, showing that more than half of new drugs receive recommendations for access with restrictions, or are rejected. Based on data from Refs 13 & 14.

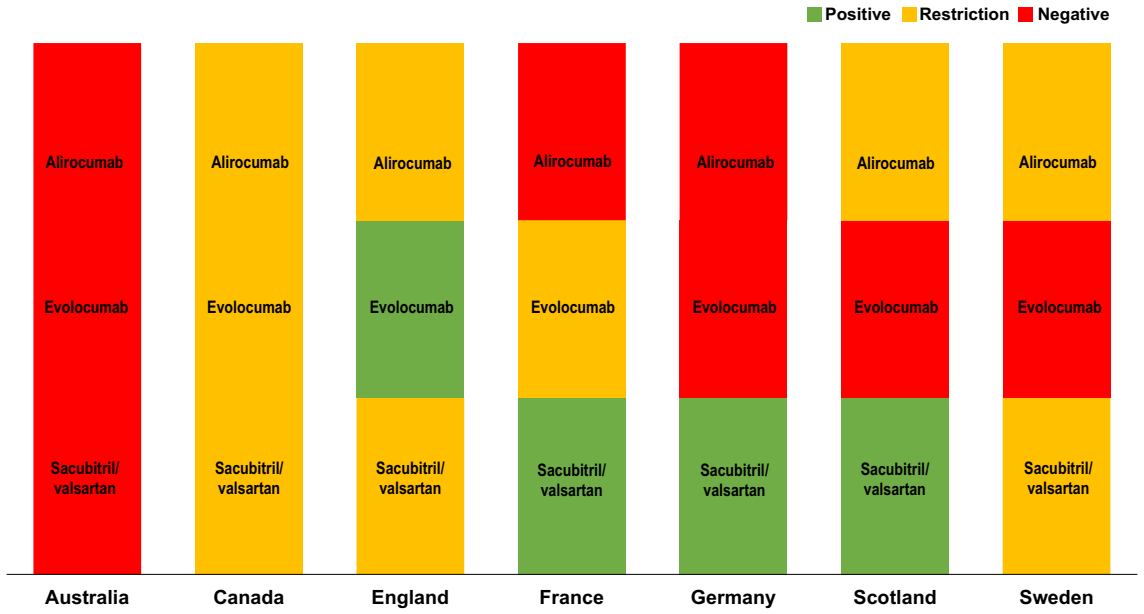

Fig. 2. Variation in recommendations from HTA bodies for 3 cardiovascular treatments (Alirocumab, Evolocumab, and Sacubitril with Valsartan) in seven countries. Based on data from Ref 14.

3. Variable patient involvement in HTA processes

Patient involvement in the HTA process is critical [23]. While involvement is increasing, many countries are not yet systematically involving patients throughout the process [23,24]. Barriers to patient involvement include unclear goals and roles, and the under-valuing of patient evidence by HTA members [24]. Without this viewpoint, randomised controlled trials and technology assessment processes may overlook measures that are important to patients and real-world perspectives from outside the clinic [23].

Technology has increased the collection and means to analyse individual patient-generated data. Websites, smartphones, and wearables, have increased the ability to conduct trials remotely, collect RWE, and facilitate patient involvement in HTA processes [25–28]. This approach increased during the COVID-19 pandemic [28], is well accepted by patients [29], and will become common in future trials. This type of data can provide individual patient insights, rather than only those of the generalised patient trial population.

HTAs in several countries have reformed their reimbursement processes to place a greater emphasis on HRQoL and its use in cost-effectiveness analysis (cost-utility) rather than life expectancy alone [23,30,31]. Countries that use QALY (UK, Canada, Australia, Netherlands, Sweden, etc) rely significantly on HRQoL. In the past few years, patient and public involvement increased interest in HRQoL in countries such as France, Germany, and US, but they have not yet adopted the use of QALY. Strategies for involvement include websites (to provide information), surveys and focus groups (for consultation), or more active advisory committee participation (for policy and

programme development) [32].

Patient groups, as well as other social and political factors, also influence the regulatory approval and pricing of innovative therapies. However, the prevalence of patient-advocacy organisations related to cancer far outweigh those in CV diseases (37% vs. 5%) [33]. In parallel, regulatory approvals of oncology drugs drastically outweigh approvals of CV drugs [1,2,34]. The patient voice is sub-optimal in cardiology [33], but should be considered more often during the HTA and pricing processes, such as is the case with NICE in the UK.

4. Decline in investment in new CV treatments

Innovation and drug approvals for new CV treatments are decreasing (Graphical Abstract). In 2020, <5% of new drug approvals in the US [1], and Europe [2] were for CV indications. Similarly, few CV drugs are being submitted for reimbursement decisions. Over the past 10 years (2010–19), of 559 NICE recommendations, only 4% were for CV, compared to 46% for cancer treatments [11]. Only about 22 CV drugs (but 194 cancer drugs) were given positive or optimised/restricted NICE decisions over the past decade.

Over the past 20 years, the proportion of pharmaceutical company revenue from CV drugs in the US dropped from 27% (in 1997) to 1% (in 2018) [35]. Similarly, investment in CV companies has declined; spending was just $534 million in 2019 (about 10 times less than spending on cancer drug developers [$5.6 billion]) [36]. Public funding for CV research is also relatively low. Among National Institutes of Health (NIH) funding for new drugs approved from 2010 to 2016, CV research accounted for <1/3 that for cancer therapies [37]. Similarly, the CardioScape project found that CV funding by the European Commission declined from almost €200 million in 2010 to less than €50 million in 2019 [38]. One of the reasons may be the slow, expensive process of CV research, often necessitating mega-trials with long follow-up.

The lack of investment may contribute to the lack of CV drugs in company pipelines. Of 891 clinical programmes at 20 major drug companies, just 47 (5%) included CV drugs, compared to 335 (38%) for oncology/haematology [36]. CV trials accounted for <300 of almost 5000 clinical trials conducted in 2019/20 [36].

Low investment in CV may also be related to perceived low rate of clinical events, however, for CV diseases such as heart failure (HF) mortality remains high [39]. Focussing on patient subgroups with high unmet needs may increase the value of new treatments, enhance regulatory and HTA approvals, and investor and drug company interest in the CV category. For example, patient at high thrombotic risk who cannot take oral anticoagulants because of bleeding risk. “Orphan” status can be awarded by regulatory authorities to drugs that may be of benefit to people with rare conditions, and is associated with various incentives to encourage drug development. Drugs being developed for patients with specific uncommon phenotypes previously lacking current therapies, such as transthyretin amyloid cardiomyopathy, have gained such status. There are also a number of “accelerated” approval or assessment processes at both the FDA and EMA, where the regulators speed up their assessment process for drugs that treat serious conditions, and that fill an unmet medical need. Neither designation is transferable from one regulator to another.

Registry-based randomised trials can more efficiently identify and follow-up large numbers of patients, and provide data acceptable to regulators for new or extended indications. The DAPA-MI trial is integrating registry data from the Swede-Heart and Myocardial Ischaemia National Audit Project (MINAP) with a randomised clinical trial to evaluate dapagliflozin for prevention of mortality or HF following an acute myocardial infarction [40].

Publicly, CV disease does not evoke the urgency or have the awareness seen with cancer, which translates into less funding for drug development, regulatory approval, and reimbursement. With declining research and funding, adverse trends in CV disease are not being addressed in a timely manner, such as those due to increased rates of obesity, diabetes, and cardiotoxicity of other drugs.

5. Examples of new treatments with limited or no patient access

5.1. Omecamtiv mecarbil (Amgen, Cytokinetics)

Omecamtiv mecarbil (Amgen) is a case where perception of limited therapeutic value, and limited potential for significant pricing/reimbursement, led to withdrawal of the main sponsor. In November 2020, GALACTIC-HF (over 8000 patients) showed that omecamtiv, initially perceived as a promising new treatment for HF, significantly reduced the risk of the primary outcome compared to placebo (first HF event [hospitalisation or urgent visit for HF] or CV death), but the effect was perceived as modest (8% improvement) [41]. The drug did not reduce the risk of CV death. Amgen considered a clinically meaningful primary outcome as a 15% risk reduction [42]. Industry analysts concluded that in light of the weak effect, omecamtiv may not be a commercially viable product [42]. After spending tens of millions ($US) developing the product, Amgen decided to withdraw and returned all rights to Cytokinetics [42]. While concerns around regulatory and reimbursement processes were not cited, they likely had an influence on Amgen’s decision. Cytokinetics, on the other hand, has submitted a New Drug Application (NDA) to the FDA, targeting a subgroup of patients with severe HF [43]. They have initiated the METEORIC-HF trial in patients LVEF ≤35%. Thus, a likely negative decision for use in an overall population can lead to further more formal discussions on restricted coverage.

5.2. Canakinumab (Novartis)

In 2017, CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study), in over 10,000 patients, showed a 15% reduction in the primary outcome (nonfatal myocardial infarction, nonfatal stroke, or CV death) with canakinumab [44]. There was no significant difference in all-cause mortality. Based on these favourable results, Novartis submitted the drug to regulatory bodies for a new indication for secondary CV prevention in a specific patient subgroup. Despite the large, positive trial, the FDA rejected the application citing insufficient support, and European regulators had additional questions [45]. Novartis chose to withdraw from the approval process, likely related to the uncertainty that payers would value a 15% reduction for the drug’s premium price [45]. Canakinumab is already approved and priced as an orphan drug for rare autoimmune conditions, but the company would likely have to lower the price to be considered cost-effective for widespread use in CV disease [46]. With the many unknowns related to the CV indication, Novartis made a business decision to focus the drug in other directions and maintain its orphan drug price and indication.

5.3. Evolocumab (Amgen) and alirocumab (Sanofi/ Regeneron)

Evolocumab and alirocumab (PCSK9 inhibitors), have been shown to further reduce cholesterol levels, CV events, and mortality over optimal statin therapy alone [47–51]. In 2015 these agents received regulatory approval for the treatment of familial hypercholesterolemia, and for secondary prevention in patents who require additional cholesterol lowering over statin alone. They were subsequently approved to prevent heart attack and stroke.

However, the 15% reduction in major adverse CV events (MACE) over optimal statin therapy [48–50] was arguably viewed by payers as modest [52], and importantly, when launched the cost of these drugs was high at US$14–15,000/year. Given the premium price, rates of coverage denial were high and initial uptake was low [53–55].

In 2018–2019, the drug companies reduced the prices by 60% to about US$6000/year [56]. Subsequent analyses demonstrated the treatment to be cost-effective in patients at higher risk of CV events with

higher baseline LDL-C values [10,57]. Assessments of value subgroups are critical to identify patients who will benefit the most to maximise health gain from a limited budget. Despite this, it appears that there are still barriers to prescribing and reimbursement [58], and out-of-pocket costs remain high for many patients [59].

6. Impact of multiple regulatory pathways on reimbursement

Multiple regulatory pathways, including those used for "breakthrough" products or rare conditions may not necessarily speed up patient access to new treatments [14,60,61]. A review of HTA decisions from 2015 to 2019 found that new "orphan" drugs had a longer time post-regulatory decision to HTA recommendation, compared to non-orphan drugs in Australia, Canada and some European countries [14]. Accelerated development and regulatory pathways may result in larger data gaps than are seen with standard pathways [60–62]. Drugs may be approved based on surrogate endpoints from short-term studies, which HTA review may not deem sufficiently robust evidence of incremental benefits over available treatments [61,62].

In the US, the CMS has to cover all drugs that are "reasonable and necessary [21]." Private payers can refuse to cover a drug because of high cost or uncertain efficacy, with the exception of most drugs in the six protected classes mentioned above [22,60]. Thus, accelerated approval that speeds a new product to market can result in no reimbursement or a substantial government investment for a potentially unproven therapy.

Some countries are experimenting with easier access, offering conditional pricing and reimbursement based on agreements that outcomes are confirmed in real world practice (e.g., outcomes-based managed entry agreements, coverage with evidence development) [63,64]. NICE has used such post-launch commitments for appraisal and funding in areas of rare disease and oncology (including the "Cancer Drugs Fund"). [65].

Stakeholders sit on both sides of the argument. Those in favour lauded early patient access to potentially life-saving therapies, and the likely benefits to manufacturers. Critical physicians predicted an increased financial strain on Medicare, use of therapies without sufficient evidence, and an undermining of the CMS authority to assess incremental benefit and make reimbursement decisions.

NICE has also stated an objective of aligning decision-making processes more closely with the UK Medicines and Healthcare Regulatory Agency (MHRA) processes. This includes providing developers with early joint advice [66]. Similar mechanisms are also increasingly available across the European Union, with EUnetHTA and European Medicines Agency Parallel Joint Scientific Consultation. [67].

7. Challenges faced by HTA bodies and payers in assessing evidence

Regulatory and HTA bodies have different mandates, and often there are important differences between the evidence requirements of the two processes (Table 2) [13,68,69]. An analysis of 33 drugs that were EMA and FDA approved between 1995 and 2018 found that the data concerns of regulators centred on safety, while those of HTA bodies more often related to benefits versus comparators. This explains why licenced products (which are effective compared to placebo) may not be reimbursed if available active comparators are cheaper. Thus, HTA bodies frequently require companies to provide additional evidence (~30–70% of submissions) to make their decisions [13].

Some of the challenges that can complicate assessments are shown in Table 2 [13,68,69]. HTA bodies have to consider the long-term use of new treatments. The duration of trials is short compared to patients' expected lifespans, making it difficult to estimate mortality and HRQoL benefits over the long-term. For example, in the EMPA-REG trial, over 90% of participants were alive at the end of the 3-year follow-up; thus, the long-term outcome of the majority of patients remained unknown [70].

Table 2
Challenges in data needs, and areas for alignment across manufacturers, regulatory, and HTA bodies [12,64,65].

Category	Examples
Trial validity	• Inappropriate definition of unmet need • Bias in patient selection, study conduct, attrition, or reporting
Population	• Not representative of practice • Inadequate subgroup data, or inappropriate subgroup analyses
Intervention	• Inadequate information on treatment duration, combination therapy, or drug-drug interactions
Comparators	• Lack of relevant, active comparators • Unreliable indirect comparisons • Inadequate data on appropriate line of therapy
Outcomes	• Unacceptable primary endpoints • Choice of and use of surrogate and secondary endpoints • Lack of patient-reported outcomes and HRQoL measures • Insufficient long-term data
Safety	• Sample size too small • Causality unknown • Insufficient long-term data

HRQoL, health-related quality of life

Another challenge is when a trial excludes a relevant comparator. For example, data were available comparing ticagrelor versus clopidogrel from PLATO (PLATelet inhibition and patient Outcomes) [71], and data comparing prasugrel versus clopidogrel from TRITON-TIMI 38 (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel–Thrombolysis In Myocardial Infarction) [72]. It was necessary to use an indirect comparison based on the common comparator (clopidogrel) to determine the value of ticagrelor relative to prasugrel. In another case, the manufacturer of sacubitril/valsartan used RWE to estimate resource use, but randomised controlled trial data to demonstrate efficacy [73]. While the RWE was more reflective of the target population, it did not reflect the patient population included in the clinical trial, therefore the magnitude of benefits seen in the trial may not be generalizable to that patient population [73].

The use of inadequately validated surrogate endpoints is another problem [74]. A review of 154 HF trials found that only about 40% used mortality outcomes as the primary endpoint, and these trials were more likely to be negative [75]. Thus, surrogate or subjective outcomes may not extrapolate to clinical outcome benefits.

All of these issues may contribute to the fact that many new treatments receive positive HTA decisions, but with restrictions to certain patient populations that will likely benefit the most [11,14].

8. Strategies to facilitate review

Payers do indeed value evidence, but their needs may be very different and not necessarily aligned with those of regulatory bodies, industry, physicians, trialists, and patients (Table 2) [13,68,69]. However, all stakeholders have the common goal of expediting access to safe, effective, affordable treatments to appropriate patients. One strategy to expedite more rapid approvals is providing the right data at the right time. This can be facilitated by frequent and open discussions between all relevant stakeholders [76].

Many countries including Australia, Canada and various European countries have formal programmes to provide collaborative regulatory and HTA advice [68,76]. These bodies have expressed positive views about these collaborations, and manufacturers report a reduction in development programme risk, an increased understanding of unmet medical needs, and better definitions for acceptable innovative study designs [76].

Joint consultations can help a clinical development programme meet the needs of both regulators and HTA bodies [67,77]. A European analysis of 21 studies in which joint consultation was sought found that

manufacturers implemented advice regarding harmonised primary endpoints in all studies [77]. Advice regarding trial comparators that were acceptable to both regulatory and HTA bodies was implemented in about 60% of cases, with manufacturers tending to satisfy regulatory advice more often. Other strategies that could facilitate timely, positive HTA decisions are shown in Table 3 [68,69,78].

In addition to early, collaborative development advice, a number of countries also use parallel review programmes, where data are submitted to both HTA and regulatory bodies simultaneously [67,76,79]. In Australia and Canada these processes shortened the time from regulatory approval to HTA decisions. In Canada, among 49 new treatments, the median time from regulatory to HTA decision was 282 days faster for parallel versus sequential processes [14]. NICE also has a programme to provide joint regulatory advice from the MHRA and NICE Scientific Advice Programme [66].

9. Call to action

Meeting the evidentiary needs of HTAs and other payer groups is critical to speed up access to new treatments for appropriate patients. Trialists and patients can help in this process by assuring that trials are designed to include metrics to estimate cost-effectiveness, relative and absolute efficacy, patient-reported outcomes and preferences, and other elements to allow payers to assess the appropriateness of a therapy for a given group of patients. During assessment processes there are uncertainties related to the generalisability of the patients in the trial to a clinical population and a need for more information on relevant subgroups. Therefore, there is a need for ongoing collection of post-approval evidence such as additional clinical trials, long-term follow-up of ongoing trials, subgroup analyses, and RWE data [68,76]. Closer working between regulators and HTA bodies is being adopted in several geographies, and should be encouraged.

Table 3
Strategies to improve the likelihood of positive HTA decisions [64,65,74].

HTA agencies
• Collaborate with regulatory bodies and manufacturers on evidentiary requirements early in clinical development program
• Align timelines/process between regulatory and HTA bodies
• Increase use of real-world evidence during decision making
• Provide education to all stakeholders, including members of the HTA organisation
• Provide formal documentation of decision-making process, outcomes, and feedback from stakeholders
• Define an international framework to harmonise the decision-making process
Manufacturers
• Focus on developing treatments for unmet medical needs
• Collaborate early with HTA and regulatory bodies
• Implement advice from regulatory and HTA bodies on alignment of evidentiary needs
• Provide high quality evidence
• Improve methodologies for economic modelling, and price setting
• Develop internal systems to facilitate collaboration (e.g., education, sufficient capacity)
• Engage internationally with all relevant stakeholders (acknowledge national differences)
• Lobby for a more predictable and harmonised HTA environment
• Conduct post-approval studies in a timely manner

Disclosures

Cowie: Consulting fees from AstraZeneca, Servier, Medtronic, and Abbott; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Servier, Medtronic, Abbott, and Bayer; served as Chair for ESC-Digital Health Committee (unpaid), Chair for Clinical Advisory Board of Pumping Marvellous Foundation (unpaid), Trustee of the Atrial Fibrillation Association (unpaid), and Non-executive Director of NICE from 2016 to 2020 (paid).

Bozkurt: Consulting fees from Baxter, Bayer, and scPharmaceuticals; participation on Data Safety Monitoring Board or Advisory Board for LivaNova Pharmaceuticals, Abbott Pharmaceuticals, and Relypsa/Vifor; served on the Board of Directors for HFSA.

Butler: Consulting fees from Abbott, Adrenomed, Amgen, Applied Therapeutics, Array, AstraZeneca, Bayer, Boehringer Ingelheim, CVRx, G3 Pharma, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Sequana Medical, and Vifor; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Novartis, BI-Lilly, AstraZeneca, and Janssen.

Briggs: Consulting fees from Allexion, Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Sanofi/Regeneron, Roche/Regeneron, Daiichi Sankyo, Eisai, Boehringer Ingelheim, and Bayer.

Kubin: Employee of Bayer AG; grants or contracts from Bayer AG; stock or stock options from Bayer AG; and equipment, materials, drugs, medical writing, gifts, or other services from Bayer AG.

Jonas: None.

Adler: Received income from NICE as a Chair of a NICE Technology Appraisal Committee, and chair of an Expert Advisory Group and commissioner for the Commission on Human Medicines.

Patrick-Lake: Participation on Data Safety Monitoring Board or Advisory Board for ACC's NCDR Oversight Committee (volunteer); received stock or stock options from Evidation Health.

Zannad: Personal fees from Janssen, Bayer, Amgen, CVRx, Boehringer, AstraZeneca, Cardior, Cereno pharmacuetical, Applied Therapeutics, Merck, Novartis, NovoNordisk, Myokardia, Actelion, Owkin, Cellprothera, and Nestlé HealthScience; is the Co-founder of cardiorenal and Founder of CVCT.

Funding

CVCT meetings are supported by unrestricted educational grants with no allocation for speakers' fees.

Acknowledgements

This article was generated from discussions at the 17th Global Cardiovascular Clinical Trialists (CVCT) Forum held online in December 2020 (https://www.globalcvctforum.com/). The CVCT is a strategic workshop for high level dialogue between clinical trialists, industry representatives, regulatory authorities, and patients. The authors would like to thank Pauline Lavigne and Steven Portelance (unaffiliated, supported by the CVCT) for contributions to writing, and editing the manuscript.

References

[1] US Food and Drug Administration, Compilation of CDER New Molecular Entity (NME) Drug and New Biologic Approvals. https://www.fda.gov/drugs/drug-approvals-and-databases/compilation-cder-new-molecular-entity-nme-drug-and-new-biologic-approvals, Jaunary 25 2022.
[2] European Medicines Agency, Human Medicines Highlights 2020. https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2020_en.pdf, January 25 2022.
[3] J.M. Bae, Value-based medicine: concepts and application, Epidemiol. Health 37 (2015), e2015014.
[4] J.L. Anderson, P.A. Heidenreich, P.G. Barnett, M.A. Creager, G.C. Fonarow, R. J. Gibbons, et al., ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines, Circulation. 129 (2014) 2329–2345.
[5] V. Charlton, NICE and fair? Health technology assessment policy under the UK's National Institute for Health and Care Excellence, 1999-2018, Health Care Anal. 28 (2020) 193–227.
[6] P.J. Neumann, R.J. Willke, L.P. Garrison Jr., A health economics approach to us value assessment frameworks-introduction: an ISPOR Special Task Force report [1], Value Health 21 (2018) 119–123.
[7] M.Y. Bertram, J.A. Lauer, K. De Joncheere, T. Edejer, R. Hutubessy, M.P. Kieny, et al., Cost-effectiveness thresholds: pros and cons, Bull. World Health Organ. 94 (2016) 925–930.

[8] B. Woods, P. Revill, M. Sculpher, K. Claxton, Country-level cost-effectiveness thresholds: initial estimates and the need for further research, Value Health 19 (2016) 929–935.
[9] D. Cameron, J. Ubels, F. Norstrom, On what basis are medical cost-effectiveness thresholds set? Clashing opinions and an absence of data: a systematic review, Glob. Health Action 11 (2018) 1447828.
[10] D.L. Bhatt, A.H. Briggs, S.D. Reed, L. Annemans, M. Szarek, V.A. Bittner, et al., Cost-effectiveness of alirocumab in patients with acute coronary syndromes: the ODYSSEY OUTCOMES trial, J. Am. Coll. Cardiol. 75 (2020) 2297–2308.
[11] M. Bulut, P. O'Neill, A. Cole, NICE 'Optimised' Decisions: What is the Recommended Level of Patient Access? OHE Consulting Report. https://www.ohe.org/publications/nice-%E2%80%98optimised%E2%80%99-decisions-what-recommended-level-patient-access, January 25 2022.
[12] A. Angelis, A. Lange, P. Kanavos, Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries, Eur. J. Health Econ. 19 (2018) 123–152.
[13] T. Wang, N. McAuslane, L. Liberti, H. Gardarsdottir, W. Goettsch, H. Leufkens, Companies' health technology assessment strategies and practices in Australia, Canada, England, France, Germany, Italy and Spain: an industry metrics study, Front. Pharmacol. 11 (2020), 594549.
[14] J. Cai, T. Wang, N. McAuslane, J. Munro, R&D Briefing 78: Review of HTA outcomes and timelines in Australia, Canada and Europe 2015–2019. https://cirsci.org/wp-content/uploads/dlm_uploads/2020/08/CIRS-HTADock-briefing-RDB78.pdf, January 25 2022.
[15] EFPIA Patients W.A.I.T. Indicator 2020 Survey. https://www.efpia.eu/media/602652/efpia-patient-wait-indicator-final-250521.pdf, June 26 2022.
[16] National Institute for Health and Care Excellence, NICE Technology Appraisal Guidance. https://www.nice.org.uk/about/what-we-do/our-programmemes/nice-guidance/nice-technology-appraisal-guidance, January 25 2022.
[17] National Institute for Health and Care Excellence, Increasing Use of Health and Social Care Data in Guidance Development. https://www.nice.org.uk/about/what-we-do/our-programmemes/nice-guidance/nice-guidelines/how-we-develop-nice-guidelines/data-and-analytics-statement-of-intent, January 25 2022.
[18] S.Y. Kang, G. Bai, M.J. DiStefano, M.P. Socal, F. Yehia, G.F. Anderson, Comparative approaches to drug pricing, Annu. Rev. Public Health 41 (2020) 499–512.
[19] K.A. Gavulic, N. Pelletier-Fleury, S.B. Dusetzina, Peer comparisons for drug price setting: why international reference pricing may not provide optimal prices, JAMA Health Forum Am. Med. Assoc. (2020) e200105-e.
[20] A.C. Egilman, J.D. Wallach, S.S. Dhruva, G.S. Gonsalves, J.S. Ross, Medicare spending on drugs and biologics not recommended for coverage by international health technology assessment agencies, J. Gen. Intern. Med. 34 (2019) 2319–2321.
[21] Centers for Medicare & Medicaid Services, Medicare Coverage Determination Process, in: https://www.cms.gov/Medicare/Coverage/DeterminationProcess, January 25 2022.
[22] Centers for Medicare Medicaid Services HHS, Modernizing part D and medicare advantage to lower drug prices and reduce out-of-pocket expenses, Fed. Regist. 83 (2018) 62152–62201.
[23] J.L. Wale, S. Thomas, D. Hamerlijnck, R. Hollander, Patients and public are important stakeholders in health technology assessment but the level of involvement is low - a call to action, Res. Involv. Engag. 7 (2021) 1.
[24] J. Bidonde, M. Vanstone, L. Schwartz, J. Abelson, An institutional ethnographic analysis of public and patient engagement activities at a national health technology assessment agency, Int. J. Technol. Assess. Health Care 37 (2021), e37.
[25] J. Applequist, C. Burroughs, A. Ramirez Jr., P.A. Merkel, M.E. Rothenberg, B. Trapnell, et al., A novel approach to conducting clinical trials in the community setting: utilizing patient-driven platforms and social media to drive web-based patient recruitment, BMC Med. Res. Methodol. 20 (2020) 58.
[26] W.K. Lim, S. Davila, J.X. Teo, C. Yang, C.J. Pua, C. Blocker, et al., Beyond fitness tracking: the use of consumer-grade wearable data from normal volunteers in cardiovascular and lipidomics research, PLoS Biol. 16 (2018), e2004285.
[27] S.R. Cummings, Clinical trials without clinical sites, JAMA Intern. Med. 181 (2021) 680–684.
[28] N. Yuan, J.M. Pevnick, P.G. Botting, Y. Elad, S.J. Miller, S. Cheng, et al., Patient use and clinical practice patterns of remote cardiology clinic visits in the era of COVID-19, JAMA Netw. Open 4 (2021), e214157.
[29] S.P. Hasson, B. Waissengrin, E. Shachar, M. Hodruj, R. Fayngor, M. Brezis, et al., Rapid implementation of telemedicine during the COVID-19 pandemic: perspectives and preferences of patients with cancer, Oncologist 26 (2021) e679-e85.
[30] I. Cleemput, M. Dauvrin, L. Kohn, P. Mistiaen, W. Christiaens, C. Leonard, Developing an agency's position with respect to patient involvement in health technology assessment: the importance of the organizational culture, Int. J. Technol. Assess. Health Care 36 (2020) 569–578.
[31] C. Leopold, C.Y. Lu, A.K. Wagner, Integrating public preferences into national reimbursement decisions: a descriptive comparison of approaches in Belgium and New Zealand, BMC Health Serv. Res. 20 (2020) 351.
[32] L. Weeks, J. Polisena, A.M. Scott, A.P. Holtorf, S. Staniszewska, K. Facey, Evaluation of patient and public involvement initiatives in health technology assessment: a survey of international agencies, Int. J. Technol. Assess. Health Care 33 (2017) 715–723.
[33] M.S. McCoy, M. Carniol, K. Chockley, J.W. Urwin, E.J. Emanuel, H. Schmidt, Conflicts of interest for patient-advocacy organizations, N. Engl. J. Med. 376 (2017) 880–885.
[34] A. Mullard, 2020 FDA drug approvals, Nat. Rev. Drug Discov. 20 (2021) 85–90.
[35] J. Lauerman, J. Paton, Miracle Cancer Drugs are Making Big Pharma Billions. Others are Getting Left Behind. https://www.bloomberg.com/news/articles/2019-12-12/miracle-cancer-drugs-are-making-big-pharma-billions-others-are-getting-left-behind, January 25 2022.
[36] J. Bell, Pharmacquired: Splashy Deals belie a Shallow Pool of Heart Drugs Left to Acquire. https://www.biopharmadive.com/news/pharmacquired-heart-drug-deals-myokardia/586434/, January 25 2022.
[37] E. Cleary, M.J. Jackson, F. Ledley, Government as the First Investor in Biopharmaceutical Innovation: Evidence from New Drug Approvals 2010–2019. https://www.ineteconomics.org/uploads/papers/WP_133-Cleary-et-al-Govt-innovation.pdf, January 25 2022.
[38] CardioScape, Funding over Time: European Commission. https://www.cardioscape.eu/wordpress/index.php/results/funding-changes-in-time/funding-over-time/, January 25 2022.
[39] S.S. Virani, A. Alonso, H.J. Aparicio, E.J. Benjamin, M.S. Bittencourt, C. W. Callaway, et al., Heart disease and stroke statistics-2021 update: a report from the American Heart Association, Circulation. 143 (2021) e254–e743.
[40] Farxiga Granted Fast Track Designation in the US for Heart Failure Following Acute Myocardial Infarction Leveraging an Innovative Registry-Based Trial Design. https://www.astrazeneca.com/media-centre/press-releases/2020/farxiga-granted-fast-track-designation-in-the-us-for-heart-failure-following-acute-myocardial-infarction-leveraging-an-innovative-registry-based-trial-design.html, January 25 2022.
[41] J.R. Teerlink, R. Diaz, G.M. Felker, J.J.V. McMurray, M. Metra, S.D. Solomon, et al., Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure, N. Engl. J. Med. 384 (2021) 105–116.
[42] J. Gardner, Amgen cuts Cytokinetics Loose after Heart Drug Disappointment. https://www.biopharmadive.com/news/amgen-terminate-deal-cytokinetics-heart-failure-omecamtiv/589572/, January 25 2022.
[43] Cytokinetics Inc, Cytokinetics announces FDA Acceptance of New Drug Application for Omecamtiv Mecarbil for the Treatment of Heart Failure with Reduced Ejection Fraction. https://ir.cytokinetics.com/news-releases/news-release-details/cytokinetics-announces-fda-acceptance-new-drug-application, 2022 (Press release) Accessed 25 June.
[44] P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease, N. Engl. J. Med. 377 (2017) 1119–1131.
[45] M. O'Riordan, Hopes Fade for a CV Indication for Canakinumab: What's next for the Inflammatory Hypothesis?. https://www.tctmd.com/news/hopes-fade-cv-indication-canakinumab-whats-next-inflammatory-hypothesis, January 25 2022.
[46] T.S.G. Sehested, J. Bjerre, S. Ku, A. Chang, A. Jahansouz, D.K. Owens, et al., Cost-effectiveness of canakinumab for prevention of recurrent cardiovascular events, JAMA Cardiol. 4 (2019) 128–135.
[47] J.G. Robinson, M. Farnier, M. Krempf, J. Bergeron, G. Luc, M. Averna, et al., Efficacy and safety of alirocumab in reducing lipids and cardiovascular events, N. Engl. J. Med. 372 (2015) 1489–1499.
[48] G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, et al., Alirocumab and cardiovascular outcomes after acute coronary syndrome, N. Engl. J. Med. 379 (2018) 2097–2107.
[49] P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, M.F. Bregeault, A.J. Dalby, et al., Effect of alirocumab on mortality after acute coronary syndromes, Circulation. 140 (2019) 103–112.
[50] M.S. Sabatine, R.P. Giugliano, A.C. Keech, N. Honarpour, S.D. Wiviott, S. A. Murphy, et al., Evolocumab and clinical outcomes in patients with cardiovascular disease, N. Engl. J. Med. 376 (2017) 1713–1722.
[51] M.S. Sabatine, R.P. Giugliano, S.D. Wiviott, F.J. Raal, D.J. Blom, J. Robinson, et al., Efficacy and safety of evolocumab in reducing lipids and cardiovascular events, N. Engl. J. Med. 372 (2015) 1500–1509.
[52] A. Arrieta, T.F. Page, E. Veledar, K. Nasir, Economic evaluation of PCSK9 inhibitors in reducing cardiovascular risk from health system and private payer perspectives, PLoS One 12 (2017), e0169761.
[53] A.M. Navar, B. Taylor, H. Mulder, E. Fievitz, K.L. Monda, A. Fievitz, et al., Association of prior authorization and out-of-pocket costs with patient access to PCSK9 inhibitor therapy, JAMA Cardiol. 2 (2017) 1217–1225.
[54] K.D. Myers, N. Farboodi, M. Mwamburi, W. Howard, D. Staszak, S. Gidding, et al., Effect of access to prescribed PCSK9 inhibitors on cardiovascular outcomes, Circul. Cardiovasc. Quality Outcomes. 12 (2019), e005404.
[55] J.D. Cohen, M.J. Cziraky, T.A. Jacobson, K.C. Maki, D.G. Karalis, Barriers to PCSK9 inhibitor prescriptions for patients with high cardiovascular risk: Results of a healthcare provider survey conducted by the National Lipid Association, J. Clin. lipidol. 11 (2017) 891–900.
[56] P.B. Shaw, Hyperlipidemia: effective disease management with a focus on PCSK9 inhibitors, Am. J. Manag. Care 27 (2021). S63-S9.
[57] G.C. Fonarow, B. van Hout, G. Villa, J. Arellano, P. Lindgren, Updated cost-effectiveness analysis of evolocumab in patients with very high-risk atherosclerotic cardiovascular disease, JAMA Cardiol. 4 (2019) 691–695.
[58] A. Smith, D. Johnson, J. Banks, S.W. Keith, D.G. Karalis, Trends in PCSK9 inhibitor prescriptions before and after the price reduction in patients with atherosclerotic cardiovascular disease, J. Clin. Med. 10 (17) (2021 Aug 26) 3828.
[59] M. Sullivan, D. Whittam, C. OLaughlin, Affordable patient access to PCSK9 inhibitors remains challenging across part D plans in 2020. https://avalere.com/insights/affordable-patient-access-to-pcsk9-inhibitors-remains-challenging-across-part-d-plans-in-2020 (January 25 2022).
[60] W.F. Gellad, A.S. Kesselheim, Accelerated approval and expensive drugs - a challenging combination, N. Engl. J. Med. 376 (2017) 2001–2004.
[61] V.K. Rathi, J.L. Johnston, J.S. Ross, S.S. Dhruva, Medicare's new device-coverage pathway - breakthrough or breakdown? N. Engl. J. Med. 384 (2021), e43.
[62] J.L. Johnston, S.S. Dhruva, J.S. Ross, V.K. Rathi, Clinical evidence supporting US Food and Drug Administration clearance of novel therapeutic devices via the de

novo pathway between 2011 and 2019, JAMA Intern. Med. 180 (2020) 1701–1703.
[63] K.M. Facey, J. Espin, E. Kent, A. Link, E. Nicod, A. O'Leary, et al., Implementing outcomes-based managed entry agreements for rare disease treatments: Nusinersen and tisagenlecleucel, Pharmacoeconomics. 39 (2021) 1021–1044.
[64] M. Dabbous, L. Chachoua, A. Caban, M. Toumi, Managed entry agreements: Policy analysis from the European perspective, Value Health J Inte. Soc. Pharmacoecon. Outcomes Res. 23 (2020) 425–433.
[65] NHS England, Appraisal and funding of cancer drugs from July 2016 (including the new cancer drugs fund): a new deal for patients, taxpayers and industry, Available at: https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf (June 26 2022).
[66] National Institute for Health and Care Excellence, NICE-MHRA scientific advice. https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/nice-mhra-scientific-advice (January 25 2022).
[67] European collaboration between regulators and health technology assessment bodies: Joint work plan (2021-2023) between EMA and European HTA bodies facilitated through EUnetHTA21. https://www.ema.europa.eu/en/documents/work-programme/european-collaboration-between-regulators-health-technology-assessment-bodies-joint-work-plan-2021_en.pdf (June 26 2022).
[68] R.A. Vreman, H. Naci, W.G. Goettsch, A.K. Mantel-Teeuwisse, S.G. Schneeweiss, H. G.M. Leufkens, et al., Decision making under uncertainty: comparing regulatory and health technology assessment reviews of medicines in the United States and Europe, Clin. Pharmacol. Ther. 108 (2020) 350–357.
[69] T. Wang, N. McAuslane, L. Liberti, H. Leufkens, A. Hovels, Building synergy between regulatory and HTA agencies beyond processes and procedures-can we effectively align the evidentiary requirements? A survey of stakeholder perceptions, Value Health J Inte. Soc. Pharmacoecon. Outcomes Res. 21 (2018) 707–714.
[70] B. Zinman, C. Wanner, J.M. Lachin, D. Fitchett, E. Bluhmki, S. Hantel, et al., Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, N. Engl. J. Med. 373 (2015) 2117–2128.
[71] L. Wallentin, R.C. Becker, A. Budaj, C.P. Cannon, H. Emanuelsson, C. Held, et al., Ticagrelor versus clopidogrel in patients with acute coronary syndromes, N. Engl. J. Med. 361 (2009) 1045–1057.
[72] S.D. Wiviott, E. Braunwald, C.H. McCabe, G. Montalescot, W. Ruzyllo, S. Gottlieb, et al., Prasugrel versus clopidogrel in patients with acute coronary syndromes, N. Engl. J. Med. 357 (2007) 2001–2015.
[73] National Institute for Health and Care Excellence, Appraisal consultation document: Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. https://www.nice.org.uk/guidance/ta388/documents/appraisal-consultation-document (Jaunary 25 2022).
[74] S.J. Greene, R.J. Mentz, M. Fiuzat, J. Butler, S.D. Solomon, A.P. Ambrosy, et al., Reassessing the role of surrogate end points in drug development for heart failure, Circulation. 138 (2018) 1039–1053.
[75] A. Samman Tahhan, M. Vaduganathan, A. Kelkar, V.V. Georgiopoulou, A. P. Kalogeropoulos, S.J. Greene, et al., Trends in heart failure clinical trials from 2001-2012, J. Card. Fail. 22 (2016) 171–179.
[76] R. Ofori-Asenso, C.E. Hallgreen, M.L. De Bruin, Improving interactions between health technology assessment bodies and regulatory agencies: a systematic review and cross-sectional survey on processes, progress, outcomes, and challenges, Front. Med. (Lausanne). 7 (2020), 582634.
[77] G. Tafuri, I. Lucas, S. Estevao, J. Moseley, A. d'Andon, H. Bruehl, et al., The impact of parallel regulatory-health technology assessment scientific advice on clinical development. Assessing the uptake of regulatory and health technology assessment recommendations, Br. J. Clin. Pharmacol. 84 (2018) 1013–1019.
[78] M. Bujar, N. McAuslane, S.R. Walker, S. Salek, Quality decision making in health technology assessment: Issues facing companies and agencies, Therapeut. Innov. Regulat. Sci. 54 (2020) 275–282.
[79] US Food and Drug Administration, Payor communication task force. https://www.fda.gov/about-fda/cdrh-innovation/payor-communication-task-force (January 25 2022).