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Drug development in oncology and devices—lessons for heart failure drug development and approval? a review

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Abstract

Heart failure (HF) and cancer are of the most common diseases globally, both associated with significant adverse outcomes and greatly impaired quality of life. Despite those similarities, over the last 15 years, the United States (USA) and European authorities have approved only 5 and 3 new drugs for HF respectively, none using an accelerated process and none for patients with either acute HF (AHF) or with HF and preserved ejection fraction (HFpEF). During the same period, more than 100 new drugs were approved for treatment of various cancers, several receiving accelerated approval. HF drugs in the last 15 years were mostly approved for reduction in mortality, whereas most approved cancer drugs addressed disease progression and surrogate markers. Consequently, the size of the trials in HF were far greater than those in oncology which was associated with lower probability of success. Given the larger study size and smaller probability of approval, pharma progressively reduces the necessary investments in new HF drugs. We suggest for HF drugs be developed, especially those used to treat patients with HFpEF and AHF, consideration of approval based beyond morbidity and mortality on improvements in symptoms and functional capacity and, like oncology, based on measures of disease progression and end organ damage. At the same time, HF drug development should adopt some approaches used in other diseases (such as oncology) focusing on better defining specific phenotypes and defining specific disease-related targets for new drugs.

Keywords Heart failure · Oncology · Clinical studies

Introduction

Although there has been progress in the approval and implementation of novel life-saving medications over the last decades, a deceleration in this trend that has been most notable in cardiology has been observed [1]. A recent review of cardiovascular (CV) guidelines suggests that over the last decade, the level of evidence supporting use of CV therapies has not improved and may have decreased [2]. In parallel, the mortality from heart disease (the most common cause of death in the

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USA) has not decreased among middle-aged Americans in recent years, while cancer deaths (the second most common cause of death) have decreased significantly [3]. Some of this deceleration may relate to the fact that in some of the most common as well as morbid CV diseases such as acute HF (AHF), HF with preserved ejection fraction (HFpEF), and cardiogenic shock, no new medication has been approved in decades as no study has shown positive "approvable" results. Recently, two classes of drugs thought to be effective in HFpEF due to their efficacy in HFrEF had discouraging news in patients with HFpEF [4], again reducing the chances that simple solutions for patients with HFpEF will be found soon. It seems that the "low hanging fruit" in clinical research may have been picked—i.e., where disease states are relatively simple to define and easy to study, such as HF with reduced EF (HFrEF), new interventions have been developed, and patients' outcomes substantially improved, while in disease states which are harder to define and more difficult to study, development has stalled.

In other medical disciplines such as oncology, where the scientific community has acknowledged that new therapies are needed to improve patients' symptoms, morbidity, and mortality, regulators have attempted in some cases to enable easier paths to approval by allowing for simpler and more achievable endpoints to be assessed. These include measures of surrogate endpoints that are related to clinical events, disease progression, end organ damage and/or symptom relief/quality of life, and function measures.

In the current manuscript, we examine the progress achieved in development of novel therapies in oncology, and lessons learned that might be applied to development of new HF drugs.

The disease burden of heart failure and cancer

The leading causes of death worldwide in 2016 were cardiovascular diseases and cancer, both overall and in people older than 14 years, accounting for 31.8 and 17.1% of deaths [5, 6]. The World Health Organization estimated that the majority of non-communicable disease (NCD) deaths in 2012 were from CV diseases (17.5 million deaths, or 46.2% of all NCD deaths) and cancers (8.2 million, or 21.7% of all NCD deaths). In the USA, heart disease and malignant neoplasms were the two most frequent causes of death accounting for 23.1 and 21.8% of all deaths [7]. In contrast to cancer mortality rates, which declined 19% from 1999 to 2017, deaths from heart disease initially declined 22% between 1999 and 2011 and then increased to 2017 [8]. Exact data on HF-related mortality globally is not available, although most authorities quote > 50% of CV deaths being from atherosclerotic CV disease, but much of it is from combined ischemic heart disease and the ensuing HF [9].

Heart failure (HF) is a global pandemic affecting at least 26 million people worldwide and is increasing in prevalence [9]. The global cancer burden is estimated to have risen to 18.1 million new cases in 2018 [10]. Worldwide, the total number of people who are alive within 5 years of a cancer diagnosis, called the 5-year prevalence, is estimated to be 43.8 million [11]. Thus, based on the above numbers, it seems that both diseases are a common morbidity globally with cancer probably around 70% more prevalent than HF [9–11].

A recent study compared survival rates between primary care patients with HF and those with the most common types of cancer [12]. In this analysis from Scotland, a total of 56, 568 patients were enrolled for a total of 147, 938 person-years of follow-up (median follow-up: 2.04 years). In men with HF 5-year survival was 55.8%, worst than prostate cancer (5-year survival: 68.3%), and bladder cancer (57.3%), but better outcomes than lung cancer (8.4%) and colorectal cancer (48.9%). In women, HF (5-year survival: 49.5%) had worse mortality outcomes than breast cancer (77.7%), but better outcomes than colorectal cancer (5-year survival 51.5%), lung cancer (10.4%), and ovarian cancer (38.2%) [12]. This data suggests that HF outcomes are as bad as those of cancer, worst than some but better than others. Although within cancer patients, there are some with more advance disease and hence worst outcome, this is also true for patients with HF where those with advanced HF have very high mortality.

Drug approvals and clinical research in oncology and heart failure

More new drugs have been approved recently by the food and drug administration (FDA) and European medicines agency (EMA) for cancer than for CV disease and HF. We reviewed all new molecular entities (NMEs) approved by the US FDA and EMA in oncological, CV, and HF indications in the last 15 years. In total, well over 100 NMEs were approved by FDA and/or EMA for oncological indications during those years, as compared to less than 50 approved for CV indications, of which only 5 were approved by FDA for HF indications and 3 by EMA (supplemental Table 1 and Table 1). More than 10% of the NMEs approved for oncology in the USA and/or Europe were approved using an accelerated pathway, and none of the new CV or HF medications were approved through this route.

Clinical trials examining the efficacy of cancer and cardiovascular drugs differ substantially. We reviewed all studies in the oncology, cardiology, and heart failure fields that were published in 2017–18 in the Lancet, New England Journal of Medicine, or the Journal of the American Medical Association or were listed among FDA approvals in 2017–

Table 1 Therapies for HF indications approved by EMA and FDA

Drug name	Year of initial EMA approval	Approval process EMA	Year of Initial U.S. approval	Approval process FDA
Vyndamax; vyndaqel	2011	Normal	2019	Normal
Hydralazine hydrochloride and isosorbide dinitrate	N/A	NA	2005	Normal
Ivabradine	2017	Normal	2015	Normal
Metoprolol succinate	N/A	NA	2006	Normal
Sacubitril and valsartan	2015	Normal	2015	Normal

18 (supplemental Table 2). We identified 28 oncology and 15 cardiology studies, only one of which (TRUE-HF) was a HF study. Although the length of follow-up was similar in the oncology and cardiology studies (Table 2), the event rates for the primary endpoint in the control group were considerably higher in the oncology than in the cardiology trials: a median of 70.4 versus 11.3%. It is well known that for a dichotomous outcome, the higher the event rate the lower the sample size required to have reasonable power to detect a relevant treatment effect, e.g., a 20% reduction in risk (Fig. 1). Consequently, the median size of the oncology studies (190 patients) was lesser than 1/10th that of the cardiology trials (2,104 patients, Table 2).

The higher event rates in oncology studies occur because endpoints accepted as proof of efficacy, and used as primary endpoints in most of these trials, are driven primarily by disease progression measured by surrogate endpoints such as imaging as opposed to "hard" events such as myocardial infarction, stroke, HF admission, and death—the primary endpoints deemed "approvable" in HF studies.

Drug and device approvals in the USA and Europe for HF indications

Generally, less rigorous clinical evidence is required to obtain market approval for medical devices, even those deemed "high risk" (and certain high-risk devices with a predicate may not require any clinical studies). Since 2004, the FDA has approved the premarket approval application (the most exacting process) for roughly 15 new medical devices for heart failure [13]. Similar figures are not obtainable from Europe, because no database of medical device approvals is publicly available. However, as an example, the BAROSTIM NEO® System was granted market approval on the basis of a single study (BeAT-HF) providing 6 months follow-up of 294 patients randomized to either device implantation or medical management alone, with statistically significant effects demonstrated on 6-min walk distance, quality of life evaluated by Minnesota Living with Heart Failure Questionnaire; no effect was demonstrated on changes in NT-proBNP, the third efficacy endpoint. Demonstration of safety is based on the lower bound of the 95% confidence interval for the rate of survival

Table 2 Summary of oncology and cardiology studies published 2017-2018 in Lancet, New England Journal of Medicine, or the Journal of the American Medical Association; or leading to FDA approval in 2017-2018

Parameter	Statistic	Oncology trials ($N = 28$)	Cardiology trials ($N = 15$)
Event rate for placebo/control arm	*n*	24	15
	Mean (SD)	0.653 (0.2087)	0.208 (0.2305)
	Median	0.704	0.113
	Q1, Q3	0.520, 0.819	0.065, 0.210
	Min, max	0.07, 0.89	0.04, 0.77
Median/mean FU time or analysis time-point, months	*n*	17	14
	Mean (SD)	22.29 (17.156)	25.82 (25.538)
	Median	18.00	21.30
	Q1, Q3	10.40, 36.00	12.00, 26.00
	Min, max	4.2, 60.0	1.0, 97.2
N for placebo/control arm	*n*	28	15
	Mean (SD)	293.3 (435.50)	4135.4 (4312.29)
	Median	190.0	2104.0
	Q1, Q3	122.5, 246.5	258.0, 7988.0
	Min, max	38, 2405	151, 13780

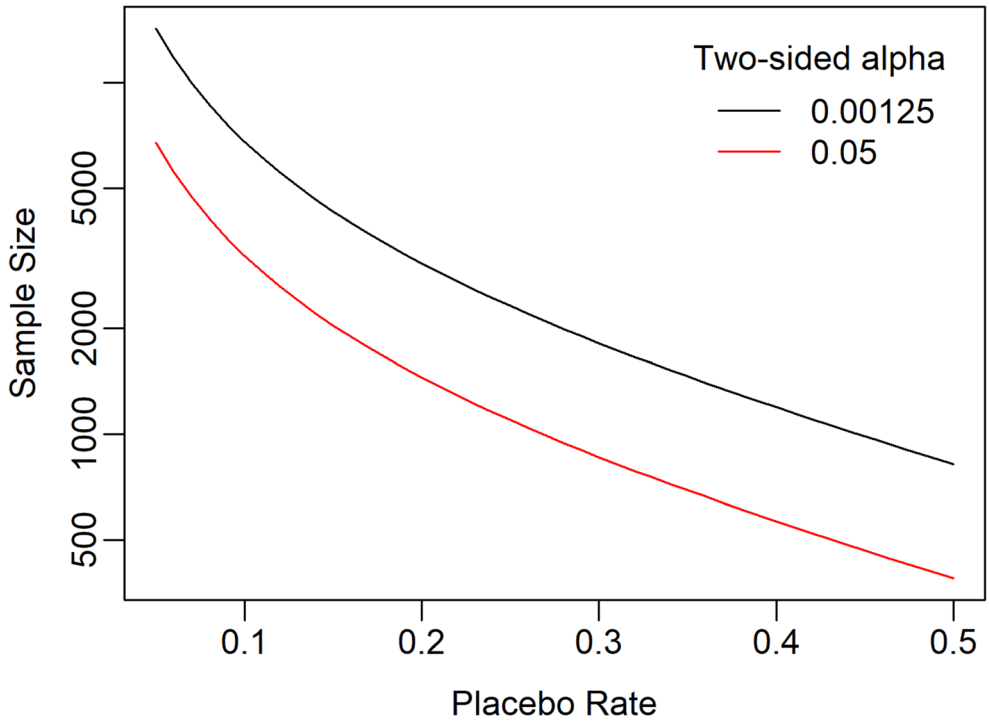

Fig. 1 Total sample size with equal allocation to two groups needed for 80% power to detect a relative risk of 0.8 at two-sided significance levels of 0.05 and 0.00125 as a function of the event rate in the control group

free of major neurological and cardiovascular events being more than 85% in the device-implanted group alone. The same medical device was granted a CE mark in 2014 on the basis of 6 months follow-up in 146 patients. Similar endpoints and patients' numbers were used in most device approvals, making device approvals in HF more similar to approval of oncological drugs than HF drugs.

Can the "mega-trial" be the culprit?

We performed a meta-regression using the R package "metafor" [14] to examine the potential modifying effect of the study size on the estimated treatment effect for the 43 oncology and cardiology studies identified. Weighted least squares with inverse variance weighting was used, and non-linearity of the associations was assessed by examining the statistical significance of a quadratic term added to the model. The effective sample size for studies with unequal allocation to treatment groups was taken as the size of a study with equal allocation that would have provided the same power [15]. Results suggest that estimated treatment effects decrease with increasing study size (Fig. 2).

Although lower projected control event rates drive larger sample sizes, so do smaller projected treatment effects. Some clinical trials may be designed to detect some minimum beneficial drug effect, smaller than that observed in earlier phase trials, with the common wisdom that treatment effects in larger trials can be expected to be smaller than in smaller, earlier studies. But this may be a self-fulfilling prophecy. The enrolled patient population in these large studies may be more appropriately heterogenous—lending results more generalizable to the target patient population—but under pressure to enroll a large number of patients in a fixed timeframe may also be more inappropriately heterogenous, as discussed below.

First, the large number of sites needed to enroll a very large trial efficiently pushes the study's operational management to seek multiple high enrolling sites, which are often found in poorer countries [16]. Patients enrolled in such sites may differ in terms of background therapy, not only for the disease of interest but also other medical conditions the patients may have. Although this may have an advantage in determining the efficacy of new drugs in a more diverse patient population, the generalizability of the result to patients who are treated according to current international guidelines is uncertain, and poorly controlled comorbidities may result in clinical outcomes that are not modifiable by the drug under study. It is extremely important that patients are enrolled in clonal studies only if and when background therapy has been fully optimized—both procedures and medical therapy, including reaching recommended doses of available therapies before attempts to introduce a new experimental therapy are undertaken.

Second, such "mega-trials" may be difficult to oversee leading to enrollment of marginally appropriate or even frankly inappropriate patients. We assume when designing studies that for any given condition, an endless pool of appropriate patients who meet the study's eligibility criteria is at the disposal of each and every investigator, and that by increasing the

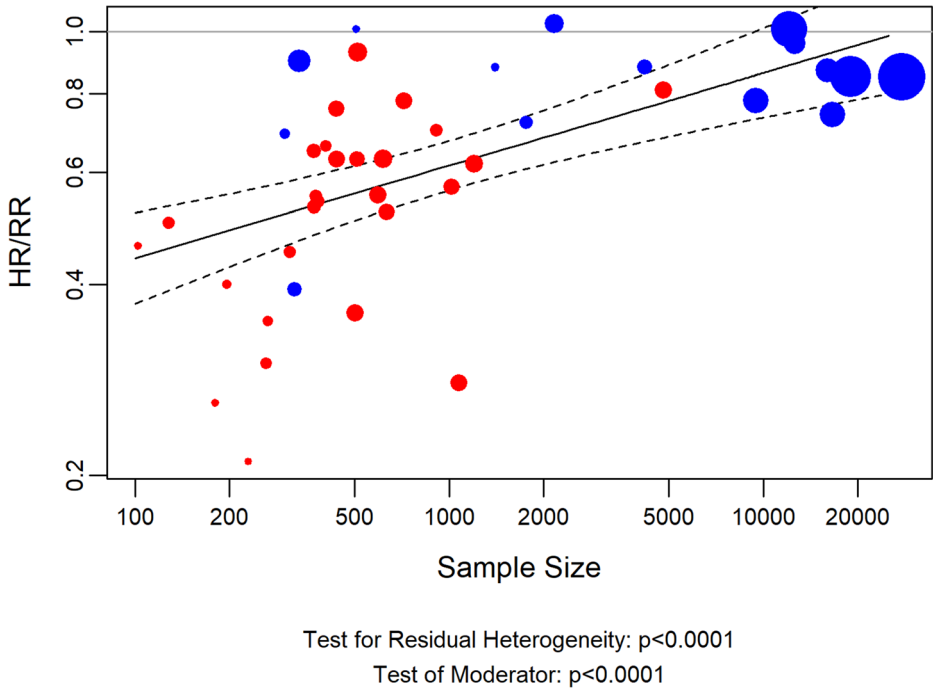

Fig. 2 Meta-regression of log sample size as a moderator of treatment effect. Cardiology trials in blue, oncology trials in red

study size, we are simply pulling a larger number of these patients from this pool. Thus, the estimated treatment effect should remain the same but estimated with increased precision. However, in an effort to enroll patients in the trial in a reasonable timeframe, patients may be pulled from some larger pool that is not the intended target, and who may be at more or less risk of the outcome and less responsive to the study drug. For example, patients with stable severe heart failure that is not acute may be enrolled into an acute heart failure study, or patients enrolled into HFPEF studies may have combination of hypertension (leading to some left ventricular hypertrophy) and chronic lung diseases leading to shortness of breath but not significant heart failure. From the other hand, as suggested above, enrolling patients who are not appropriately treated with multiple severe comorbidities may lead to a high event rate which may not be modifiable by any therapy [17]. Enrolment of both low-risk patients and high-risk patients, whose risk may be unmodifiable, may lead to reduction of the treatment effect if the intervention tested is less effective in patients who are at substantially higher or lower risk of the outcomes than the intended patient population. This issue may be larger in some disease states where the disease definition is less objective—something that has been observed in particular in acute heart failure and heart failure with preserved ejection fraction [18].

Finally, conducting mega-trials such as the ones most commonly undertaken in cardiovascular diseases is prohibitively expensive (usually > $100 million). As a result, contrary to the smaller studies conducted in oncology, only a handful very large pharma companies can conduct the pivotal mega-trials needed in cardiology. In addition, the need to drive enrollment in large scale studies and the movement of these trials to poorer countries have resulted in the recruitment of patients with substantially lower risk for the pivotal endpoints of the trials as noted in TOPCAT and COMMANDER [19, 20] and less stringent oversight of patients that results in questionable compliance to the study medication being tested as occurred in TOPCAT [21].

Possible solutions

The FDA has released recently a new draft guidance describing endpoints appropriate for the development of HF drugs [22]. Following the draft guidance's issuance, an open meeting was conducted where potential new pathways for HF drug development were discussed [23]. Both the guidance and the discussion focused on using patient-reported outcomes describing symptoms as well as measures of functional capacity to enable approval of new therapies for HF. These endpoints are in line with FDA's traditional acceptance of direct measures (observed by the investigator or reported by the patient) of improved symptoms, function, or survival as evidence of efficacy. The acceptance of measures other than the traditional "hard" endpoints of rehospitalizations and deaths will undoubtably help stir the HF field towards more research and innovation. However, although quality of life measures were discussed as viable endpoints during the open meeting and are accepted by EMA (for chronic heart failure) and the FDA's Center for Devices and Radiologic Health, FDA's draft guidance document for HF drug development failed to mention quality of life measures.

As noted in the approval process of drugs used to treat cancer, the FDA accepts validated surrogate endpoints as proof of efficacy, and "reasonably likely" surrogate endpoints may support accelerated approval. At this time, however, no validated or "reasonably likely" surrogate endpoints have been accepted in cardiology including heart failure.[24] Thus, none of the cardiology drugs approved by the FDA in the last 15 years has been approved under an accelerated approval pathway and only five of those drugs were approved for HF in the last 15 years, all were for HFrEF. In order to advance the HF field, we believe that endpoints should be assessed by the scientific community and regulators to allow accelerated approval where the unmet need is most significant—HFpEF and AHF. Such endpoints can include not only symptom relief and functional capacity measures but also measures of disease progression, such as structural cardiac changes on imaging or biomarkers that quantify end organ damage. Such endpoints—inclusive of biomarkers and echocardiographic changes of left ventricular size and mass—have been associated with outcomes in HF, and some of them have been found to be predictive of treatment effects of new therapies, making them ideal endpoints for studies [25]. The new draft guidance mentions the possibility of accelerated approval of drugs for HF based on reasonably likely surrogates, and we believe the scientific community and industry should respond by identifying appropriate endpoints and engaging with regulators to move the field forward. Such a shift may enable smaller studies to be conducted leading to accelerated approval. Such surrogate endpoints would especially be important to advance development of new therapies for HFPEF and AHF where no effective therapies are available. In these disease states, well-validated endpoints that can be shown to predict treatment effects on longer term outcomes may facilitate development of effective therapies where such therapies are not existent. In patients with HFREF where effective therapies are in existence, the feasibility of surrogate endpoints may be limited. Which surrogate endpoints can be used in AHF and HFPEF studies has not been agreed upon as of yet. One can assume that those may include measures of cardiac damage (such as Tn used in ACS studies), measures of quality of life (such as EQ5D), and measures of echocardiographic disease progression (especially for HFPEF). We believe that such endpoints can be easily developed and validated. Those which are not validated (such as natriuretic peptides) should not be used. Importantly, when such surrogate or symptomatic endpoints are defined, efforts should be undertaken to define what are not only statistically but also clinically meaningful difference.

At the same time, scientists developing new therapies for HF and especially HFpEF and AHF should adopt a more proactive approach to drug development. In the last 20 years progression of HF therapy through drug development has been heavily reliant on appropriation of therapies developed for other indications such as ACEi (initially developed as vasodilators to treat hypertension), beta blockers (developed for blood pressure and ischemia treatment), or SGLT2s developed as anti-diabetic and found to have effects on HF due to the requirement to conduct CV outcomes studies assessing safety of new therapies for diabetes. If HF therapy is to be improved, smaller studies should be utilized to assess targeted therapies in more narrowly phenotypically defined patients' populations, possibly by adopting approaches known as "basket" studies. Although, it is not likely that we will find genetic targets for HF drug therapy as is the case in oncology, we should explore other approaches for targeted therapy in HF addressing core pathophysiological mechanisms such as inflation, cell ischemia, and vascular or end organ damage.

These smaller studies should be closely followed by the requirement to complete larger ones assessing, as proposed in the draft FDA guidance, longer term outcomes including important side effects that are uncommon and may not be detected in smaller studies or which may become evident only over time. We believe that enabling smaller studies prior to initial approval will unleash a substantial wave of innovation, as seen in other disease states such as oncology. Similar measures are not necessarily a priority in types of HF such as HFrEF where progress has been made and life-saving drugs are available for patients.

Many problems exist in the process of developing therapies for patients with AHF and HFPEF. Those include definition of the disease—for both AHF and HFPEF, an objective agreed upon definition does not exist, leading as suggested above to enrolment of patients who may not have the disease in question, classification, and targets to therapies that are more precisely defined via phenotypical profiles, or proteinomic or genetic targets. However, we believe that smaller studies that are better targeted can help resolve many of those issues through better patient definition of the desired patient population and outcomes of interest.

Authors contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Stefanie Senger, Gad Cotter and Beth Davison. The first draft of the manuscript was written by Beth Davison and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and material The analysis was done based on published data from the literature—no specific data was collected for this manuscript and analysis.

Compliance with ethical standards

Conflict of interest Beth A. Davison and Gad Cotter report personal fees from Novartis Pharma AG, grants from Novartis Pharmaceutical Corp; grants from Amgen Inc., grants from Celyad, grants from Cirius Therapeutics Inc, grants from Laguna Pharmaceuticals, grants from Sanofi, grants from Roche Diagnostics Inc., grants from Trevena Inc., grants from NIH, grants from Ventrix, outside the submitted work.

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Code availability The analysis was done using commonly used code which has been identified in the statistical methods.

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