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## **The Health Impact Fund:How might it work for novel anticoagulants in atrial fibrillation?**

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## **Abstract**

### ***Background***

Cardiovascular diseases represent the greatest burden of global disease. Spending on cardiovascular diseases is higher than for other diseases, with the majority being spent on drugs. Therefore, these drugs and these diseases are hugely important to health systems, society and pharmaceutical companies. The Health Impact Fund represents a new mechanism by which pharmaceutical innovators would be rewarded on the basis of health impact of their new drugs.

### ***Objective***

To illustrate the concept of the Health Impact Fund using the example of novel anticoagulants for prevention of stroke and thromboembolism in atrial fibrillation.

### ***Discussion***

By considering existing data and the current situation for novel anticoagulants, we suggest that epidemiologic data and modelling techniques can be used to predict future trends in disease and the health impact of new drugs.

### ***Conclusion***

The Health Impact Fund may offer potential benefits to pharmaceutical companies, patients and governments and warrants proper investigation.

**Keywords:** access to medicines, pharmaceutical, equity, epidemiology

## **Abbreviations**

CVD: Cardiovascular disease

HIF: Health Impact Fund

LIMC: Low-Middle Income Country

AF: Atrial fibrillation

NOAC: Novel anticoagulant

GBD: Global Burden of Disease

**Objective** To describe the Health Impact Fund, using the example of novel anticoagulants for prevention of stroke and thromboembolism in atrial fibrillation.

## **Introduction**

Burden of disease due to cardiovascular disease(CVD) is greater than for any other disease globally<sup>1-3</sup>. CVDs are firmly on the global health policy agenda<sup>4-6</sup>. Spending on CVD is greater than for any other disease globally, e.g.hypertension represents over 10% of healthcare expenditure globally<sup>7,8</sup>. Inter-sectoral and inter-disciplinary approaches are essential to reduce global CVD<sup>4,9</sup>.

Most healthcare spending (as in CVD), particularly in low- and middle-income countries(LMICs) and particularly out-of-pocket expenditure, is on drugs<sup>10-12</sup>. Every stage of CVD(primary prevention, secondary prevention and acutely) requires drugs. Efforts to reduce global healthcare costs must involve drugs used to prevent or treat CVD.

Drugs to treat CVD and its risk factors have topped blockbuster charts for over 30 years, whether anti-clotting drugs(e.g.clopidogrel; Plavix™), statins(e.g.simvastatin, Zocor™) or anti-hypertensives(e.g.lisinopril, Carace™)<sup>13-14</sup>. Some of the largest cases of misconduct in trials have occurred in CVDs(e.g.rofecoxib,Vioxx™)<sup>15</sup>. These drugs and diseases are important to health systems, society and pharmaceutical companies and improved drug access may produce the greatest gains.

In this review, implications of intellectual property rights on access to medicines and innovation are examined. Potential solutions are explored. We will define the Health Impact Fund(HIF), a novel proposal to incentivise development and distribution of drugs depending on global health impact. The potential role of the HIF will be considered with respect to novel anticoagulants(NOACs) for stroke prevention in atrial fibrillation(AF).

## **Intellectual property rights**

Until 1994, intellectual property rights were enforced strictly in wealthy countries, whereas LMICs had much weaker patent laws, if any. . Since 1994, LMICs agreed to institute TRIPS(Trade-Related Aspects of Intellectual Property Rights)-compliant

systems<sup>16</sup>. TRIPS became more constraining as increased numbers of countries implement patent exclusivity, shaping all intellectual property rights, including drugs. Although TRIPS implementation and affordability are not the only factors contributing to access, TRIPS has probably widened global health inequalities<sup>17-19</sup>(figure 1).

New technologies, including drugs, have been “produced by companies from high-income countries for high-income markets” <sup>20,21</sup>. The industries and the incentives are not aligned with access, which acts as both determinant and consequence of inequalities in health, income and development<sup>17,19</sup>. Access to drugs is one of global health’s greatest challenges. Even for cheap, generic drugs with proven efficacy, rates of use and access are suboptimal. A recent study of global secondary CVD prevention showed that few individuals took antiplatelet drugs(25·3%), beta-blockers(17·4%), angiotensin converting enzyme-inhibitors(ACEIs), ARBs(angiotensin 2-receptor blockers)(19·5%), or statins(14·6%)<sup>22</sup>. These data suggest that health system improvements are needed to affect drug access. New CVD drugs may not have a major effect when established drugs are so under-used. However, in certain instances, new drugs have transformed disease management(e.g. statins in CVD prevention or ACEIs for hypertension). Intellectual property rights can directly influence affordability,sustainability and rational selection by practitioners by highlighting new drugs with greatest health impact. Indirectly,pharmaceutical companies may be incentivised to improve infrastructure and proper use by health professionals and individuals(figure 1).Therefore, intellectual property rights and new drugs may have wide implications on global health impact.

Ethical and human rights arguments have been used for access to healthcare<sup>4,23,24</sup>, which should guide governments and industries to produce accessible medicines. However, access is not simply based on cost and affordability. If other factors are neglected, benefits of available drugs will not be realised. Even if appropriate, essential medications are available, their correct use is not guaranteed<sup>17,19</sup>. Governments, pharmaceutical companies, society and individuals all have a role to play. However, responsibility for providing access to drugs is in the hands of the stakeholders with greatest capability, namely pharmaceutical companies and governments<sup>19</sup>. Cost of drugs represents a unique opportunity to change the current paradigm(figure 1).

## **Current solutions**

Where cost of medications restricts their provision, several potential solutions have been utilised. First, generic drugs are cheaper than branded versions. Indian companies supply low-cost generics(including CVD drugs), domestically, to other LMICs and increasingly to wealthier countries as well. If generics are used to substitute branded drugs, especially in CVD, economic and public health benefits are likely<sup>25</sup>. Until 2005, India could avoid introducing product patents, although process patents were already available prior to TRIPS<sup>26,27</sup>. However, a recent analysis of new patents filed in India since 2005 suggests no relationship with disease burden or public health priorities<sup>28</sup>.

Second, charitable donations from wealthy countries and pharmaceutical companies are possible. . Since treatments for CVD) are often long-term, if not lifelong, a more sustainable supply is needed.

Proponents of TRIPS state that it contains provisions which allow prioritisation of public health needs. Parallel imports are imports of a patented or trademarked product from a country where it is already marketed<sup>29</sup>. Compulsory licensing is when a government allows someone else to produce the patented product or process without the consent of the patent owner<sup>30</sup>. However, LMICs have not adequately used existing provisions with public health consequences<sup>31</sup>. In summary, CVD drugs are neither available nor affordable in many countries, particularly in the public sector<sup>32</sup>.

## **The Health Impact Fund**

There are no incentives for pharmaceutical companies to develop, market or deliver drugs which will have maximal impact on global health. Such mechanisms would make greatest difference in CVDs, which represent largest disease burden, highest drug spending and greatest number of new drugs in recent years.

The Health Impact Fund (HIF) would reward pharmaceutical companies in proportion to global health impact of their innovation<sup>17</sup>. As a global agency underwritten by governments, it would offer pharmaceutical companies the option to register new

products. Registration would entitle innovators to receive, for a defined period(e.g.10 years), a share of fixed remuneration from a reward pool. The fund would disburse at least US\$6 billion annually, paying each registrant a share corresponding to contribution to global health impact of all registered drugs, as estimated with a global health impact assessment exercise(web appendix 1). In return, the registrant would sell the medicine wherever needed at no more than the lowest feasible cost of production and distribution. After the reward period, free licences would enable generic manufacture and sales<sup>17</sup>.

The HIF has gained momentum<sup>33,34</sup>, but the next challenges are finding PCs willing to license their novel products and credible methodology for health impact assessment to test the HIF.

### **New drugs and new trials**

Atrial fibrillation (AF) is the commonest arrhythmia and is a major cause of stroke and thromboembolism<sup>35</sup>. NOACs are an alternative to warfarin, the mainstay of anticoagulation for over 50 years <sup>36-37</sup>. In the last 3 years, following successful phase 3 clinical trials, three agents(dabigatran, apixaban and rivaroxaban) have been incorporated into guidelines worldwide and more NOACs are in the pipeline<sup>38-40</sup>. As with statins, ACEIs, ARBs and other CVD drug classes, “me-too” agents are anticipated and trials are already underway<sup>41-44</sup>. “Me-too” drugs are expensive and do not serve society well<sup>41-43</sup>. The HIF may combine profits with patient benefit in a mutually beneficial manner.

Imagine that the pharmaceutical companies producing NOACs registered with the HIF. Based on trials or predicted trial outcomes (for edoxaban<sup>44</sup>), the reward for each NOAC would be estimated. Most NOACs have been subject to trials in deep-vein thrombosis(DVT) prior to trials in AF. Potential impact of NOACs could be estimated based on DVT trials if AF trials were not yet completed.

Subgroup analyses are often reported in trials to quantify drug effects in different subpopulations. Ideally, subgroups should be defined before trial initiation, but post-hoc analyses are often reported. Although post-hoc analyses have possible biases

and limitations, they may be useful for modelling. Possible subgroups for NOACs include age, renal function or other cardiovascular risk factors<sup>38-40, 45-46</sup>.

NOACs, like warfarin, and all drugs, have risks(excess bleeding) as well as benefits (prevention of stroke/thromboembolism). Trial data may be used to estimate risks as well as benefits, and to compare different agents. Health impact assessment will aim to model incremental benefit of new drugs versus current “gold-standard” therapy or other new drugs. For anticoagulants, “net clinical benefit” balances risk of bleeding versus benefit of stroke prevention<sup>47</sup> and has been used to compare NOACs and warfarin<sup>48-49</sup>. Similar concepts could be used for health impact assessment of other new drugs.

### **Identifying datasets**

National and local datasets offer invaluable resources from which the target population can be modelled, e.g. the UK’s Clinical Practice Research Datalink<sup>50</sup> and the Danish national healthcare database<sup>48</sup>. Regional variations occur in distribution of risk factors and disease<sup>51</sup>. The more accurately these variations can be incorporated into models, the better the estimation of drug effects. The Global Burden of Disease(GBD) Study has revolutionised knowledge of prevalence, time trends and predictions for disease and risk factors<sup>52,53</sup>. GBD data could be used to model patient populations and drug effects at country level. However, there is variation in missing data and methodologies of data collection across countries; e.g.there is incomplete death registration in many LMICs; with some having no death registration data at all<sup>54-55</sup>.

Registries can be local, regional, national or multi-national<sup>56</sup>. AF registries have highlighted risk associations<sup>57</sup> and have been used to model effects of population-wide implementation of NOACs<sup>58</sup> and differences between “real-world” and “clinical trial” effects<sup>59</sup>. Global registries can be powerful in learning about current risk factor and disease trends, and clinical practice<sup>60-61</sup>. However, registries also have limitations, including variable data selection and data quality due to varying methodologies<sup>62</sup>.

Tools are increasingly used to predict risk of disease outcomes in different populations. In AF, several risk prediction tools for stroke/thromboembolism and bleeding are validated, widely used <sup>63-66</sup>, and have been used to define subgroups

within studies<sup>49</sup>. In individuals, these tools allow trial results to be personalised; e.g. stroke/thromboembolism risk associated with each level of CHA<sub>2</sub>DS<sub>2</sub>-VASc score has been investigated in multiple studies. If the CHA<sub>2</sub>DS<sub>2</sub>-VASc distribution can be estimated in a population, the drug effects at each level of CHA<sub>2</sub>DS<sub>2</sub>-VASc may be modelled, for the health impact assessment.

Optimal data sources will be identified for a particular context (preferably at multiple levels, i.e. local, regional, national)<sup>67</sup>. Growing transparency and public availability of data from trials will benefit the HIF<sup>68-69</sup>.

## **Modelling**

Analyses of population impact, potential cost and comparative analysis of NOACs would be required. The population attributable risk is the proportion of a given disease which can be attributed to a specific risk factor (e.g. AF), whether clinical<sup>70</sup> or subclinical<sup>71</sup> and may be useful for estimating burden of AF and stroke/thromboembolism. The “potentially modifiable burden” of disease (e.g. stroke) may be useful in describing potential benefits of drugs<sup>72</sup>.

The IMPACT model shows how evidence can inform public health policy<sup>73,74</sup>. The “policy effectiveness-feasibility loop” involves: (a) epidemiological modelling; (b) situation analysis; and (c) option appraisal<sup>74</sup>. The first stage can be adapted to include modelling of effects of new drugs so that this same framework can be applied to health impact assessment. The IMPACT model has been used to estimate proportion of change in rates of disease which can be attributed to changes in a particular risk factor<sup>75-76</sup>. The IMPACT model has largely been restricted to CHD, but could be used in other diseases.

Projections of AF burden and representativeness of trial populations for NOACs have been studied<sup>50,76</sup>. Trial data can be used to model different levels of prescription, adherence, cost and other environmental factors. Cost-effectiveness analyses are another data source,<sup>77,78</sup> subject to quality of cost and efficacy data. Incremental cost-effectiveness data are of greatest relevance and value to the HIF but often ignored in favour of “cost-effectiveness thresholds”<sup>79-80</sup>. As with all modelling, limitations and ranges of data must be acknowledged transparently. Different scenarios may be

constructed within models to simulate impact of several competing drugs, e.g.(a) competing drugs have sustained and equal sales;(b)one of the drugs overtakes its competitors; (c) none of the drugs are taken up to an appreciable extent. Several factors such as adherence, side effects of new drugs, indications included in the drug license and ongoing data collection will be considered as the optimal method of health impact assessment is finalised. “Scenario planning” begins by identifying focal issues or decisions(e.g.effect of introduction of a NOAC on use of warfarin, use of NOACs, access to drugs and rates of stroke/thromboembolism) and predicts future environment<sup>81-84</sup>. Four factors shape future scenarios<sup>83</sup>:

### 1. *Social*

Social factors, include: increasing burden of AF and stroke due to ageing populations and demographic transition, values systems(e.g.more demand for equity and corporate social responsibility), lifestyle(e.g.adherence), demand(increasing demand for NOACs from providers and patients), and political energy (to enforce uptake of new drugs).

### 2. *Economic*

Macroeconomic (e.g. “How will international trade flow and exchange rates affect the price of drugs?”; “How will global pharmaceutical companies respond to pharmaceutical companies from LMICs?”) and microeconomic factors(e.g.“How much appetite is there in the system for increased spending on new drugs?”; What financial protections protect patients from catastrophic out-of-pocket expenditures on drugs?”; “How might the structure of pharmaceutical companies change?”; “How much partnership will exist between different producers of NOACs?”) influence uptake and effect of new drugs.

### 3. *Political*

Local(e.g.interpretation of practice guidelines and evidence), regional(e.g.competition between practice in other centres; competition between existing anticoagulation services and new infrastructure for NOACs), national(e.g.implementation of NICE guidelines) and international(e.g.implementation of TRIPS) environments can affect uptake and effectiveness of new drugs. Across all spheres, level of funding within the health sector and for drugs specifically must be considered<sup>85,86</sup>.

#### 4. *Technological*

Direct evidence for effectiveness obviously influences how new drugs are incorporated into clinical practice and health systems. Evidence can change over time, relating to “real-world” effects, side-effects and new clinical indications: e.g. NOACs have proven effectiveness in treatment of DVT<sup>87</sup>. Indirect evidence includes data regarding other competing drugs, new and old. As “me-too” NOACs emerge, their effectiveness and cost-effectiveness may affect and limit uptake and impact of first-generation NOACs. Web appendix 2 highlights an example of scenario modelling.

#### **Reward mechanism**

Health impact assessment should be based on as much high-quality evidence as possible and available. Although models have imperfections and assumptions, any measure of population-based impact will improve on the current paradigm. At present, pharmaceutical company marketing strategies focus on trial data. Health impact assessment requires a longer-term view from both pharmaceutical companies and policymakers. It would be expensive, given the need to assess multiple medicines globally. However, there would also be economies of scale from assessing many medicines at the same time, and efficiencies from assessing the same medicine year after year.

In consultation with stakeholders (including pharmaceutical companies), a reward for a specific health impact threshold will be agreed. If this target is met, then pharmaceutical companies will receive this agreed reward. Health impact assessment by independent assessors would occur annually to estimate actual impact of new drugs and to determine rewards due to pharmaceutical companies. The HIF rewards any company that produces an effective new drug in proportion to how well the drug works, provided that the innovator agrees to sell it at cost price. After the 10-year reward period, the company would also offer free licences to enable generic manufacture and sales. Pharmaceutical companies may be rewarded based on early results and longer-term results may later emerge, showing less benefit or potentially harms associated with the drug. The HIF reward allocated to a drug will be evaluated annually on available evidence and can be changed. Therefore, if a drug actually causes harm, it will not be rewarded. A PC will only receive full reward if the agreed target of impact is met. A consequence of using life-years or disability- or quality-

adjusted life years as the primary health impact assessment modelling outcome may be that highly effective treatments for rare diseases occurring early in life will have a health impact reward similar to a moderately effective treatment for a common disease occurring in adulthood.

Box 1 summarises potential benefits of the HIF for pharmaceutical companies, patients and governments.

## **Conclusions**

The current intellectual property rights regime and the way in which novel drugs are evaluated after proof-of-efficacy in trials are inadequate. The HIF offers an alternative mechanism by which pharmaceutical companies could be rewarded based on global health impact of their novel drugs. Using the example of NOACs for stroke prevention in AF, feasible methods of health impact assessment have been suggested. The same principles apply to other current examples, including antiplatelet agents post-STEMI<sup>89,90</sup>. Trials, registries and other datasets offer potential for modelling future trends in disease burden as well as impact of novel drugs.

Judicious use of available data and scenario modelling represent a significant improvement compared with the status quo where rewards have no association with “real-world” impact of drugs. Feasibility of prospective health impact assessment of novel drugs must now be properly tested using different drugs in different disease areas, in order to take forward the concept of the HIF. There is a growing movement to increase the transparency of pharmaceutical companies and to improve access to their drugs<sup>91</sup>. The HIF may be the most sustainable and feasible solution.

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