**Patient pathways in cardiology: Should pharmaceutical and medical device companies care?**

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**Abstract**

A shared goal of patients, providers and the companies that produce new therapies is to have these therapies used according to guidelines. Health services specialize in patient care and may lack the capabilities to take a product from conception through to everyday use. This results in a mutually beneficial relationship between health services and industry. The market for cardiovascular drugs is significant which results in competition between companies. While traditional methods of observational analysis may be able to determine to what extent drugs and devices are being prescribed or implanted by health providers, there is less real-world patient level insight as to why patients are taking (or not taking) these treatments and why one agent is chosen over another. Considering patient pathways is a novel approach which can be utilized to understand real-world patient activities. This approach focuses on the patient flow across the healthcare system and barriers at each stage including identification of patients, diagnostic testing, the decisions on treatment, and prescribing can help identify ways of improving the utilization based on guidelines. It overcomes several assumptions related to patient and clinician decision making and practical considerations such as geography and availability of health services. In this manuscript, we introduce the concept of patient pathways and why considering them maybe of interest to companies. As significant resources are invested to bring a product to market, this approach can help define if there are missed opportunities for their products to be utilized and potential barriers to implementation.

**Keywords:** patient pathways; companies;missed opportunities

*Companies and health services*

A shared goal of patients, providers and the companies that produce new therapies is to have these therapies used according to guidelines. Although not the sole objective for every organization, one of the main objectives of most companies is to generate profit. To achieve this aim, pharmaceutical and medical device companies sell products to health providers. It has been suggested that the pharmaceutical industry has a number of unusual characteristics in terms of its operations that influence the process of bring new pharmaceuticals to patients.[[1]](#endnote-1) These practices enable large pharmaceutical companies to augment profitability significantly compared to other large public companies.[[2]](#endnote-2) The focus on profit is necessary as the time and cost required to develop new products is significant, for example DiMasi et al’s study of the cost of compounds that were abandoned during testing estimated that the average out of pocket cost per new drug was $403 million.[[3]](#endnote-3) Additionally, new drug or device approval in the United States can take an average of 12 and 7 years respectively from pre-clinical testing to approval together which means that costs rise to in excess of $1 billion.[[4]](#endnote-4) The expertise of companies is therefore the development and optimization of products and guiding them through the regulatory and manufacturing processes. This includes research, development and patenting with multiple stages of approvals including review by medical and scientific experts, rigorous testing in clinical trials, country specific marketing approvals and cost-effectiveness analysis in order to ensure that the drug has both efficacy and safety.[[5]](#endnote-5) There are also additional tasks and costs of related activities such as formulations[[6]](#endnote-6) and marketing.[[7]](#endnote-7) Therefore, even though the original idea for a medication or device may come from clinical practice via a clinician or academic clinician, it can be challenging for these professionals and health services alone to navigate these complex processes without input from business experts. This is a consequence of the well-described disconnect between academia and companies resulting in an academic researchers’ inability to integrate into the world of entrepreneurship and business management as they often lack the business training to build a healthy and sustainable model.[[8]](#endnote-8)

Health services rely on pharmaceutical and device companies to develop products that are used in daily practice for cardiovascular disease. Pharmaceutical companies produce, for example, cardiovascular medications that are used such as antithrombotic medications, lipid-lowering medications, antihypertensive drugs, medications for heart failure and medications for heart rhythm control which are used in everyday care of patients with cardiovascular disease. Devices such as pacemakers and defibrillators are used to prevent bradycardias and other life threatening arrhythmias. As cardiovascular diseases are common, this creates a significant market (The global cardiovascular drugs market is estimated to be $47 billion in 2018 and is projected to be nearly $64 billion by 2026[[9]](#endnote-9)) and so there is great interest from companies to produce these medications. As previously stated, most health services specialize in patient care and lack the organizational capacity or expertise to take a product from conception through to the regulatory and manufacturing phases required for requirements for everyday use. This results in a mutually beneficial relationship between health services and industry.

*Competitive cardiovascular market*

Many pharmaceutical and device companies are large corporations with the infrastructure, resources and employees who can navigate all the stages to bring product from conception to everyday use. In the United States, the pharmaceutical market generated $484 billion and it spent $6.4 billion on direct-to-customer advertisement and $60 billion yearly on medical research and development.[[10]](#endnote-10) When an area of potential profit is identified by one company often other companies will attempt to penetrate that market through cost leadership (by producing similar agents at a lower price) or product differentiation (by developing better agents that offer enhanced benefits). The huge market for cardiovascular drugs can result in competition between companies. For example, warfarin, heparin and low-molecular weight heparin are well-established anticoagulants used for thromboprophylaxis, stroke prevention and treatment of thrombus. However, these medications have limitations including the need for regular blood monitoring for warfarin, intravenous administration of heparin and daily injections for low-molecular weight heparin. The introduction of direct oral anticoagulants as alternatives represents a major advance in anticoagulation.[[11]](#endnote-11) The market for these drugs is significant as Medicare spending in the United States on these agents has increased 16-fold since 2011 to more than $7 billion annually in 2019.[[12]](#endnote-12) The first medication direct oral anticoagulant successful introduced into clinical practice was dabigatran, a direct thrombin inhibitor, and the next drug developed was rivaroxaban, a factor Xa inhibitor. Now there are also apixaban and edoxaban which are also routinely used for anticoagulation. Particularly in non-valvular atrial fibrillation where anticoagulation can be near lifelong treatment there is great interest for companies producing these agents to understand why these drugs are or are not being prescribed and how influences the choice of one drug over another. While traditional methods of observational analysis may be able to determine to what extent drugs and devices are being prescribed or implanted, there is less understanding of real-world patient level sequence of activities and detailed understanding of treatment such as why patients are on or not on certain therapies and why one agent is chosen over another.

*Events that happen to patients and assumptions*

In order to appreciate what and why events take place greater focus should be on the patient and what happens to them. Patients transition from being in a healthy state to developing cardiovascular disease in a sequence of events typically starting with the predisposition for disease and development of risk factors which progresses to the onset of disease and associated consequences. This is followed by detection of the illness in an asymptomatic stage found incidentally or following symptoms and presentation to healthcare professionals. At presentation or identification, ideally the correct diagnosis is made which is confirmed on investigations and the appropriate treatments are instigated. While the whole process would be of interest to pharmaceutical companies, the choice of therapy in actual practice and whether patients stay on these therapies is of high value as it can directly influence profits.

In this best case scenario, the pathway for patients contains several assumptions. First, a patient may recognize there is something not right when symptoms occur but the reality is that patients may ignore symptoms or fail to recognize their significance. Second, there is the assumption that the patient knows where to seek help and how to find the appropriate clinician who can make the appropriate diagnosis. For example, patients can see family doctor or general practitioner for chest pain or call an ambulance, however, choosing the incorrect path (such as seeing a community practitioner for a patient with ST-elevation myocardial infarction) may result in delays which can be catastrophic as every 10 minute treatment delay resulted in 3.3 deaths in 100 PCI-treated patients with cardiogenic shock.[[13]](#endnote-13) Third, there may be health service provision delays such as a patient who lives in a rural area where no appropriate services are proximate and so increased travel times creates delay. It has been reported that patients that live in urban areas have a 14% less risk of dying from acute myocardial infarction compared to those living in rural areas.[[14]](#endnote-14) Fourth, it is presumed that clinicians reviewing a patient would make the correct diagnosis and order the right tests but the reality is that misdiagnosis is part of everyday practice which has been observed in acute myocardial infarction,[[15]](#endnote-15) heart failure[[16]](#endnote-16) and aortic dissection.[[17]](#endnote-17) Finally, it is expected that the right treatment is started and it is very different the treatment started by an expert versus non-expert in the area as well as an inexperienced trainee compared to an experienced specialist.

*What are patient pathways?*

Patient pathways are a sequence of clinically relevant events.[[18]](#endnote-18) The patient is at the center of the patient pathway and events that happen to them are tracked across time. Based on the question or area of interest a starting point is defined. From the starting point, what happens temporally before or after a starting point in the patient journey is determined that is relevant. This starting point can vary from onset of disease to after it is identified and it really depends what is relevant to the question of interest. The sequence of events may include care that has taken place in different settings as well as initial and revised diagnoses which may be correct or incorrect. Of interest is not just what journeys that take place for patients but the relative proportion of patients on the more or less favorable pathways. Ideally, the desirable and undesirable patient pathways will be defined and then intervention be implemented to hopefully move patients from less favorable to more favorable pathways. Patient pathways can also be considered in terms of the pathway leading to diagnosis, pathways after diagnosis and the eventual outcomes for patients and pathways to treatment. A predefined question may be in place and the patient pathway is then relevant to the particular question.

*Patient pathways to increase use of products*

 The patient pathway approach considering the patient flow across the healthcare system and barriers at each stage can help identify ways of improving the utilization of new therapies based on guidelines. The information regarding patient pathways is valuable to pharmaceutical and device companies because the information may be used to persuade those involved in the process of care to use their treatment. From a patient perspective, if a new treatment is demonstrated to be associated with a patient pathway that has better symptom control and quality of life, the patient may prompt those caring for their health to consider instigating the treatment. This is particularly important in countries where individuals are able to pay privately to receive treatments as patients can directly influence what care they receive. In these countries the role of advertisement may be important to increase uptake of therapies. Next, clinicians may be persuaded to adopt new therapies based on demonstration that the therapy is associated with desirable patient pathways. Understanding real-world activities through patient pathways could strengthen existing evidence and support of the incorporation of new therapies into guidelines that would directly influence implementation in clinical practice. It is unequivocal that if a new drug or device is better in terms of efficacy and safety compared to existing products without a substantial increase in cost, it should be used in everyday practice which could have impact the on local commissioning of treatments. However, even if the product is non-inferior to existing products, if a new device can result in a patient pathway that results in easier delivery of care or patient monitoring without additional cost a clinician may choose this treatment over alternatives. An example of this may be a clinician’s choice to use a cardiac implantable device such as pacemaker or defibrillator that has remote monitoring capabilities to reduce face-to-face appointments as information about patient physiology can be detected remotely. Finally, healthcare resources are limited so there is great interest in the health services itself to be cost-effective. If a new treatment can alter patient pathways to result in fewer costly interventions, shorter lengths of stay and fewer readmissions there may be interest in adopting the new treatment. This is particularly important in countries with public healthcare where there are only finite resources so the use of new treatments must be associated with some form of benefit.

*Patient pathways to aid in earlier diagnosis*

 The other important consideration for companies regarding patient pathways is how the management of patients could be altered in order to both improve health of patients and increase uptake of their products.

Medicines and device are licensed and regulated for use in particular conditions. The key point is that the diagnosis needs to have taken place in the patient pathway before any chance for the patient to have treatment. Understanding the patient pathways is critical to understand what opportunities there are for more patients to be on treatment. This is particularly important where patients may develop a condition that may be asymptomatic or the patient may have atypical symptoms. For example, there are a spectrum of presentations for patients who are identified with atrial fibrillation. Some patients may develop symptoms of palpitations and it is detected on electrocardiogram. Other patients may have no symptoms and are incidentally found to have the arrhythmia. Other patients present with a stroke secondary to thromboembolism due to undiagnosed atrial fibrillation. These different patient pathways are not only important in terms of what pathways exist but what the relative proportions are of patients in each pathway. A company developing drugs for anticoagulation and stroke prevention in atrial fibrillation for example may be interested to know how to promote pathways for earlier diagnosis of the condition so that more patients may be considered for treatment.

*Patient pathways to reduced missed opportunities for treatment*

The second significant consideration is whether there are missed opportunities for earlier treatment related to delayed diagnosis and misdiagnosis. Delayed diagnosis and misdiagnosis are a reality of everyday clinical practice which is often not given enough attention because it can damage the patient-health provider trust, lead to poor patient outcomes and medical litigation. Missed acute myocardial infarction has been reported to be an underrecognized and significant problem that leads to poor outcomes[[19]](#endnote-19) and misdiagnoses has been reported for patients with acute myocardial infarction15 and heart failure.16 For instance, hereditary amyloidosis is a rare condition that can affect the heart and causing cardiac amyloidosis. Among patients with transthyretin amyloidosis it has been reported that there is a 22 month delay in diagnosis and this delay has a negative impact on cardiac function.[[20]](#endnote-20) A company who develops treatment for cardiac amyloidosis might be interested to know what happens to these patients from birth and how some patients end up on the treatment while others never have the treatment including those that die without treatment. The pathway of patients who receive the drug may be very different from those who do not receive the drug. Furthermore, there may be patients that end up on the drug for longer period of time while others receive the drug at a later stage of their illness and die shortly after treatment. This may be of interest to the company to know if there were actually patient pathways with missed opportunities for their drug to be initiated at an earlier stage and how to create interventions so that patients get the benefit from the medications they produce.

If all clinicians treated patients according to guidelines, patients who have a diagnosis of a condition should have been tried on recommended treatments. Unfortunately, real world clinical practices includes different levels of knowledge and awareness of treatments among clinicians. Consequently, the reality is that not all patients that are eligible have the treatments. This creates missed opportunities which refer to incidences where different actions by those involved could have resulted in more desirable outcomes.[[21]](#endnote-21) For example, there are many agents used for patients with chronic heart failure and reduced ejection fraction including beta-blocker, angiotensin receptor neprilysin inhibitor, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, SGLT2 inhibitor, vasodilators and ivabradine.[[22]](#endnote-22) While it can be expected that most cardiac specialists would be comfortable to initiate these treatments, there are also patients that are managed by their general practitioner/family physician or other medical specialist such as geriatrician or acute medical physician who may be less experienced or comfortable with these treatments. Moreover, patients may have been tried on these treatments but some they may not be able to tolerate and this is not always captured in routine patient records. The traditional epidemiological approach of identifying the population with heart failure with reduced ejection fraction and the proportion that are on treatment fails to determine why patients are or are not on therapy. This is where consideration of the patient pathway can be useful to know not only whether patients had been tried on what treatment but also who looked after their care and whether there could have been earlier opportunities to start these treatments. For a company producing these medications, considering the patient pathways may show that there are professionals that do not know about the benefits of these therapies and an educational intervention may be the best way to inform these clinicians who may look after patients with heart failure and improve the proportion of patients on treatment. Furthermore, if there is low proportion of patients on treatment it may warrant investigation as to whether patients were tried and could not tolerate treatment which is not a missed opportunity compared to patients who were never tried on treatment which is a missed opportunity for therapy.

*Why are patient pathways not considered by industry?*

 Patient pathways are a novel concept. The basic elements of the current methods of observational research involves considering one or more exposure variables and how it may be associated with an outcome of interest. The patient pathway transforms the exposure variable into a series of events that happen to a patient or a path and how it is associated with an outcome or considers how a variable is associated with a series of events that happens to a patient. This adds a level of complexity which has not been considered before but the real world data derived knowledge can enable better predictions and decisions about interventions. This may be of interest to companies so they can better market their products or gain an intellectual advantage over competitors.

 The complexity of patient pathways requires high quality data and expertise which may create barriers widespread consideration of the concept. The growth of routinely collected data from hospital and community health records has resulted an abundance of research. However, it can be challenging to link records across different settings and there is not guarantee that the records have a reliable and sufficient information that is of value for the question of interest. Furthermore, there may be important considerations in the patient pathway that are not captured such as a patient deciding to ignore their symptoms and delay seeking a healthcare professional or which healthcare professional the patient decides to see. These variables about patient choosing to delay presenting to healthcare professional and the patient’s choice of who they present do may ultimately impact the care they receive. If these variables are not captured in the data, they cannot be shown to have any significance. As companies make key decision such as product development and marketing strategy, they be willing to invest resources to generate this high quality data to better understand why their products are used or not used.

*What are the limitations of the patient pathway?*

 There are a few limitations of considering patient pathways. First, the requirement of high quality data requires investment of resources as there is cost associated with guiding a study through ethics and regulatory approval, training those involved to collect data, physically carrying out the data collection and carrying out the analysis. Second, the findings of considering pathways are mainly generalizable to the settings to which the data is derived as what happens to patients in different countries are likely to vary due to the type of healthcare service available. For example, in private healthcare settings patients may be reluctant to seek medical attention because of the cost while in public healthcare settings patients may be more likely to seek help as there is no financial implications. However, the knowledge obtained from understanding local pathways can help develop targeted interventions. Third, the person carrying out the work must be skilled to not make assumptions and consider not only what happens to patients but why it is happening. For example, a company invest resources to market a product to clinicians with promotional sessions and educational events. However, this may be wasted efforts if the product is not available at the healthcare site or is not part of the local guidelines. A targeted approach may mean working first with the site and regulators before considering further marketing actions. Similarly there may be complex events happening in real world practice such as patients being started on treatment in hospital and the medications being changed to alternatives in the community under their family doctor.

*Conclusions*

 Considering patient pathways is a powerful new way for pharmaceutical and device companies to gain insight into real-world activities. As significant resources are invested to bring a product to market, this approach can help define if there are missed opportunities for products to be utilized. By considering the sequence of events that happen to patients in detail, it is possible to define the patient pathways and determine how their intervention is used or not used in actual practice.

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