The patient pathway in cardiovascular care: a position paper from the International Pharmacists for Anticoagulation Care Taskforce (iPACT)

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Abstract:

This position paper highlights the opportunistic integral role of the pharmacist across the patient pathway utilising cardiovascular care as an example. The paper aims to highlight the potential roles that pharmacists worldwide can have (or already have) to provide efficient patient care in the context of interprofessional collaboration. It results from a literature review and experts seeking advice to identify existing interventions and potential innovative interventions. We developed a conceptual framework highlighting seven critical phases in the patient pathway and for each of those listed some of the initiatives identified by our experts worldwide. Based on the findings, we can argue that much has been done but globally consider that pharmacists are still an untapped resource potentially useful for improved patient care.

Keywords: Cardiovascular Diseases, Anticoagulants, Pharmacists, Interprofessional Relations, Comprehensive Health Care

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Background: The European Heart Rhythm Association (EHRA) White Book is a resource containing extensive information on the status of care provided to cardiac arrhythmia patients in European countries. Some of the information included in this resource mentions the extent of implementation of guidelines in the respective countries. It is a useful resource to annually monitor changes in patient care. However, most of the information here contained is physician-led, therefore information on important interventions provided by other health care professionals, or even by informal carers, for better patient care are missing (1).

The EHRA Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation (AF) defined 15 topics that need to be considered for using these drugs effectively and safely in clinical practice. Some of them include initiation of therapy and subsequent monitoring and ensuring of adherence. This document also recommends the use of specific tools, such as the warfarin alert card or the patient card for Non-vitamin K oral anticoagulants (NOACs) as a means to empower the patient in self-management (2).

The ESC guidelines are a set of recommendations advising health care professionals on how to provide high standard patient care in the various phases of a patient's pathway. These exist for several areas, comprising lipid management, management of atrial fibrillation, to name a few. The recommendations included are anchored to a grading system that informs the reader on the source used to generate the recommendation and the attached classification for evidence generation (*e.g.* meta-analysis *versus* expert opinion). Taking the latter as an example, opportunistic screening of AF is now recommended to be undertaken by pulse palpation or ECG rhythm strip, graded as class I, level B (3). In this same guideline, integrated management of patients is highlighted, where the person living with illness is seen as having a central role in the care process. This is a very important step forward, aside with the recognition that adequate detection should be made at the first point of care with the healthcare system, clearly recognised as most often being the pharmacist, the primary care physician or the community health worker. However, it should be

acknowledged that guidelines do not often get implemented into practice because the health care system structure and functioning is not considered, arguably due to the complexity of healthcare delivery and variability amongst countries. In most European countries, there are insufficient physicians in primary care for timely and adequate patient detection and monitoring (4). The implications are that in real life, the time available for medical appointment is clearly insufficient for patient education, encouragement and empowerment for self-management, for providing advice and education on lifestyle and risk factor management and ultimately for shared decision making (5). The guideline also remarks as a recommendation "An integrated approach with structured organization of care and follow-up should be considered in all patients with AF, aiming to improve guideline adherence and to reduce hospitalizations and mortality", classified as class IIa, level B.

In addition, thinking of the individual's perspective, a patient expectations' and needs are different and often changes in time due to ageing, deterioration of the disease or comorbidities. Therefore, a person cannot be treated as a recipient of various diseases or disease situations and must instead be seen holistically and continuously.

For all these reasons, it is important to consider in each country, which health care professionals are competent, well placed and the most readily accessible in delivering the various steps and subsequently translate guidelines into practice. Pharmacists seem to be the silent or an unnoticed profession, despite the fact that they are a highly regarded profession by both the World Health Organization (WHO) and patients (6). The European Pharmacists Forum has highlighted that community pharmacies are the most accessible healthcare locations (7). Indeed, in most countries of the world pharmacies are spread out geographically favouring community access. Additionally, in most of these countries, citizens do not need to book appointments to see their pharmacist or even pay to seek their professional advice. This is particularly important in the context of public health initiatives, particularly in the area of disease prevention, where a key to success is accessibility and gratuity. International Pharmacists for Anticoagulation Care Taskforce (iPACT) believes it is time to disseminate an overarching strategy paper for pharmacists intervening on patients across their lifetime pathway, using cardiovascular disease as an example.

Aim: This position paper aims to highlight the potential roles within the patients' pathway that pharmacists worldwide can intervene to provide efficient patient care in

the context of interprofessional collaboration. This will be done using cardiovascular disease, particularly atrial fibrillation (AF), as an example. The ultimate aim is to raise awareness, within and beyond the profession, about the pharmacist as an essential partner for better patient care.

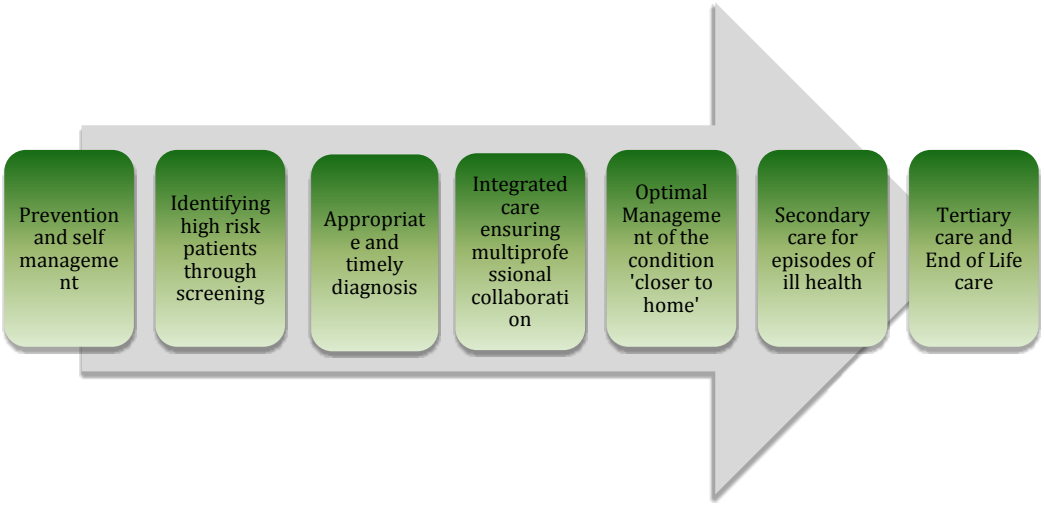
Methods:

This position paper was developed by first mapping the pathway through which a person becomes a patient. This exercise was developed using a selected expert panel (SA, SR and FAC) with experience in hospital, ambulatory, and palliative care who tried to describe graphically this pathway. Subsequently, the panel used cardiovascular disease to populate the sections of the pathway, mainly consisting of the development of high risk characteristics, moving to medical diagnosis initiating treatment and safe-guarding it and then potentially progressing into palliative care. The third step consisted of a narrative literature review seeking to identify experiences along this pathway where interventions involving pharmacists had been developed, regardless of the level of differentiation or evidence gathered. This information was additionally supplemented with searches in the grey literature, mostly published and unpublished documents from pharmacists' organisations, like the Pharmaceutical Group of the European Union (PGEU), the European Pharmacists Forum, the International Pharmaceutical Federation (FIP) and also national associations of iPACT members' respective countries.

Finally, a larger expert panel (iPACT network, which involves expert pharmacists and patient advocates from over 25 countries) was sought to brain storm interventions that highlight opportunities for pharmacists to contribute, such as with the use of innovative technology in point of care testing. In all areas of the patient pathway, iPACT members were used to collect information on pharmacist-led services in their respective countries. All actual and potential interventions are highlighted throughout this pathway, which focuses mainly on primary prevention. Actual interventions reflect the current model of practice for community pharmacy, mainly identified through the literature review (which also included grey literature), while potential interventions reflect innovative experiences for which preliminary results (often only piloted and frequently not yet published) seem promising enough to be adapted elsewhere.

Results: Using pharmacies to identify patients at risk of a certain condition may be an effective way to develop efficient interventions, including early institution of therapy. These interventions may also include the promotion of healthy behaviours, namely through smoking cessation campaigns and immunisation strategies (8) (9). Using group discussions and consensus seeking methods, we have developed a conceptual model that describes the patient pathway in anticoagulation care (figure 1).

Figure 1: Patient care pathway in cardiovascular disease



The seven sequential steps highlighted in this diagram will be subsequently detailed and enriched with selected examples collected worldwide.

1 - Prevention and self-management

Strokes may be preventable by modifying or treating the risk factors. As such, regular evaluation and management of modifiable risk factors is instrumental in disease prevention. Specific interventions in this area include risk stratification for cardiovascular disease and blood pressure and lipid management, to name a few. Health promotion and prevention activities also include disease awareness campaigns and healthy behaviour advice, where a good example of the latter is the smoking cessation service, available in primary care in various locations and delivered through the intervention of various professionals, depending on the country, namely family physicians, psychologists, nurses and pharmacists.

In England, roughly 20% of pharmacies provide smoking cessation service on a regular basis, reaching nearly 150,000 smokers a year. In Scotland, since the widespread implementation of smoking cessation service in 2008, pharmacies now provide 75% of all quit attempts. Wales and Northern Ireland provide similar services (10) (11). In Canada, smoking cessation is also a major task of pharmacists since the launch of the “Pharmacists for smoke free Canada” (12).

These services have been spreading as a result from earlier demonstration that pharmacists can competently deliver tobacco-cessation interventions (13). Reviews of pharmacists interventions in public health have concluded they are effective in regards to smoking cessation, although evidence is still lacking in other areas of behaviour change such as alcohol cessation or weight loss (14). Robust trial designs also led to the demonstration of the associated effectiveness of the service (15). Currently in England this commissioned service is being evaluated for its cost-effectiveness through the use of a pragmatic trial conducted in 60 pharmacies; the service investigated is named "Smoking Treatment Optimisation in Pharmacies (STOP)" and is being compared with the standard smoking cessation service (16). Tobacco is a well-recognised modifiable risk factor for stroke and smoking cessation is regarded as a cornerstone of recurrent stroke prevention (17). So, even if there are is no evidence on the direct impact of pharmacist-led smoking cessation interventions in stroke reduction, the indirect impact seems quite obvious.

A national Know your heart campaign was ran in half the pharmacies of Portugal, where 12,930 patients had blood pressure, body mass index, waist circumference and total cholesterol measured. This campaign allowed the detection of already diagnosed condition and receiving medication but with their condition uncontrolled. A total of 5,600 patients were on antihypertensive medication and 4,700 on lipid lowering medication. The identification of patients with suboptimal therapy occurred in 50% and 53% of individuals in both these groups, respectively. Pharmacists referred 21% of patients to the physician, resulting in the initiation of new therapy in nearly half of them (18).

2 - Identification of High risk patients through screening

AF is responsible for a third of strokes and people with AF have a five-fold more risk of stroke. The 2016 ESC guidelines state opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age, a recommendation classified as class I (evidence or general agreement that a given treatment or procedure is beneficial, useful and effective) level B evidence (*i.e.* data derived from a single clinical trial or large non-randomised studies). Registry data suggests there are a high proportion of undiagnosed patients (19). An important factor contributing to this is the fact that a high proportion of individuals with AF are

asymptomatic. The literature on alternative venues for AF screening has been quickly progressing. Traditionally, such events were held in GP practices, but recently the use of immunisation clinics, nurse-led clinics and community pharmacies has demonstrated added-value in the identification of additional suspects (20) (21) (22). Pulse palpation is the easiest way and is not part of routine clinical practice (23). Studies have highlighted community pharmacies as ideal partners due to their privileged location in the health care system and their easy access, provided adequately trained to undertake this activity. In fact, iPACT in partnership with A-A/AFA has contributed to scale-up pharmacist-led awareness events where pulse palpation, in some cases allied with mobile ECG, is regularly organised in pharmacies around the world (24) (25). Innovative technologies have also been described as a means to increase other allied professionals ability to engage in detection and confidently refer onward to physicians (22) (21). The AF-screen international collaboration has recognised this and extended their collaboration to include allied professionals, namely nurses, pharmacists and patient advocates (26). The benefits of early detection of AF enable early institution of therapy and subsequent reduction in their risk of stroke; moreover, it may also be useful to identify diagnosed patients who are not treated or who are sub optimally treated with antiplatelet therapy instead of anticoagulation.

3 - Appropriate and timely diagnosis

When patients are timely diagnosed, therapy can be initiated early and additional benefits may be gained. In most countries, only physicians' can prescribe but different models of pharmacists prescribing have been described internationally (27). In some countries (e.g. UK, Canada, USA) pharmacists may independently prescribe, although with varying levels of restrictions, implying therapy may be initiated by the pharmacist overcoming the need to refer, further reducing the workload of primary care clinicians. This implies that screening in areas where there are independent pharmacist prescribers, for who advanced competence pharmacotherapy levels are required, could potentially lead to higher detection rates but above all to a higher proportion of individuals correctly initiated on therapy by pharmacists in a timely manner. The challenges associated with this practice vary between and within countries and in some settings, the absence of important information, such as

laboratory data, may restrict the scope of practice. In the UK for instance, prescribing pharmacists may work in hospital, GP practices and in community pharmacies, where the availability of information varies and leads to differential models of collaborative practice, often including physicians and nurses. In all countries, however, the competency is well-established and supported by appropriate education and training.

In countries where the activity of the pharmacist (or nurse) is dependent on the physicians, an efficient referral pathway must be in place so that individuals are not left on their own to take the decision to seek a physician appointment or simply to ignore the pharmacist's advice. The current ESC guideline states that oral anticoagulation therapy to prevent thromboembolism and stroke is recommended for all AF patients with a CHA_2DS_2-VASc score of 2 or more (class I, level A).[3] Studies have shown that when there is early detection, there is the additional opportunity to identify patients meeting these criteria who have been previously diagnosed but yet have not initiated anticoagulant therapy, designated as 'actionable AF' (28).

Even though the market share of NOACs has been progressively increasing worldwide, there are still many countries where VKAs lead the market. The ESC guideline states that when patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored (class I, level A). This implies INR needs to be regularly monitored. However, worldwide there are barriers for timely monitoring, so different solutions are necessary for different health care systems. AF patients already on a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if the patient expresses his preference and has no contra-indications to NOAC (*e.g.* prosthetic valve) (class IIB (usefulness/efficacy is less well established by evidence/opinion), level A). This implies that adherence is monitored and subsequently enabling strategies are developed.

In some countries, INR monitoring is exclusively done in hospital, whereas in others it may be done in primary care. Within primary care, there are also varied solutions that may include the local health care centre, laboratories or pharmacies. Portugal is an example where there was an unmet need in primary care, conditioned by availability and affordability of structures in place, which led to pharmacies to start providing this service. Although it is still currently only available in around 5% of the pharmacies, it has been quickly growing (29).

Adherence encompasses two aspects: a) adherence of healthcare professionals to guidelines and b) adherence of patients to therapy. The first of these will be dealt in this section as we consider it arises immediately upon diagnosis. Patient's medication adherence will be dealt in a different section as it may occur in various phases (see section 5).

3.a) Adherence of healthcare professionals to guidelines:

The evidence suggests the proportion of patients prescribed according to guidelines is suboptimal (30). Up to 25% of patients who are hospitalized and up to one third of ambulatory patients receive an inappropriate dose of DOAC (31) (32). It has been shown that only certain risk criteria justify dose reduction (*e.g.* renal impairment) (33). Under dosing with no renal indication resulted in a nearly five-fold increased risk of stroke without significant difference in major bleeding. Conversely, overdosing in renal impairment doubled the bleeding risk but had no impact on stroke occurrence. (34)

NOAC are most commonly used in lower doses, compared to higher doses (35), perhaps suggesting prescribers tend to be overcautious due to potential adverse drug events or eventually as an indirect result of not having as easy and common laboratory data as when prescribing VKAs.

Predictors for inappropriate dosing vary between studies, but in general the phenomena occurs with all NOACs, whereas decreased renal function is most commonly described as associated with prescribing errors (35). Off label dosing of NOACs has also been described as more common among the elderly, those with higher bleeding and stroke risks (36). This suggests that pharmacists engaging in medication review could focus on dose appropriateness for this specific class. Some have suggested multidisciplinary clinics as a means to ensure safe and effective prescribing and follow-up (35). Within hospital, clinical pharmacists have successfully intervened in patients on inappropriate NOACs prescriptions, either suggesting dose adaption, avoidance of interacting drugs, the need for NOAC monitoring, to name a few, 70% of which accepted by the physician (37). Also in the US, the emergence of pharmacist-led NOAC management services is currently a solution to reduce the risk of incorrect dosing in this class, not only within hospital but also across the healthcare system (38). In some countries, pharmacist-led services

for optimising medicines use have emerged also in the ambulatory setting, namely the polymedication check in Switzerland (39), the New Medicines Service in the UK (40) or the Chat Check Chart in Canada (41). In Belgium for instance, there's a government funded quality improvement program around the safe use of NOAC, focusing on the right dose for the right patient. Within this program, local physicians' and pharmacists can discuss cases, analyse their current prescribing and dispensing profile and advise dose changings (42).

Choosing the right therapy may be quite complex and various studies have highlighted that inappropriate medications are frequently overprescribed and that pharmacists engaging in various forms of medication review have a key role in minimising the problem (43).

4 - Integrated care ensuring multiprofessional collaboration

One recommendation that is consistent in every guideline is that AF patients on OAC therapy should receive an integrated approach, with structured personalized care and follow-up. In many countries, if not in the majority, this aspect may be considered as the major flaw of the healthcare system. There are anecdotal descriptions of lack of integrated care where citizens receive defragmented advice from various providers, sometimes inconsistent, and also where there is no appropriate means created for data sharing or information flow (44). The consequences are immense, not only for the system, where often duplicate diagnostic tests may occur, leading to avoidable costs, but also for the individual, who finds himself lost in an intricate and siloed health system, where barriers are profuse. For the individual in particular, the consequences may include contradicting information about diagnosis, duplicate diagnostic testing, or interacting therapy leading to potential health threats, time wasted on avoidable consultations, with the corresponding work absence and loss of productivity. Although some of these examples may appear unrelated to pharmacy, in many countries pharmacists are involved (*e.g.* in the execution and interpretation of diagnostic tests), This implies that if information systems were more intelligently planned, a test undertaken in any of these settings should immediately become associated with the patient ID, leading other healthcare professionals involved not to require their repetition, unless borderline values or other reasons for uncertainty were identified. However, there are good examples worldwide how these barriers are being

transposed. In New Zealand for example, there is an instituted program directly linking community pharmacies and GP practices so that information is shared and both professionals are constantly up-to-date with the way the patient is managing his therapy (45). In Portugal, a shared information system between all medical practices has been developing, where it is possible to continuously monitor the tests and treatments instituted, as well as episodes of hospital admission. The citizen is responsible for deciding who has access to his/hers information and it is expected that this will include pharmacists. In Flandres there is an electronic platform that allows pharmacists and GPs to share medical information like the vaccination status, medication overview, and population screening if applicable. The latest data from 2018 indicate over 6.7 million inhabitants (from a total of 11.5 M in the country) have their data shared on this platform (46).

Information transferred at discharge tends to be poor, as shown by a recent study where complete medication data was only available in 5% of individuals discharged (47). However, it has also been shown that simple interventions focusing on better information transfer, mostly across the healthcare interfaces, have positive impacts on patient safety. A meta-analysis has shown that single medication reconciliation at transitions of care, which are the most common interventions reduce medication discrepancies in 66% (48).

New ways of working are being discussed and tested worldwide and it seems today undisputable that working harder using the same hospital-centred model will not improve the lives of our community-dwelling citizens (49). Efficiency needs to arise from different delivery models, more centred on the communities, the mobility of individuals and their empowerment and willingness for self-management.

Refer-to-Pharmacy is an example of an electronic referral-system under development in the UK, through which hospital pharmacists refer patients directly to their community pharmacist for medication support (50). Another example from the UK are the one stop clinics have been emerging also for cardiovascular treatments (51), following the successful examples from oncology (52). The main idea behind these clinics is to increase and expedite access to preventive care and then to ensure an adequate onward referral is made so that care is fully integrated. For pharmacists it is obviously important to be part of this structure fully integrated in the primary care team and also being responsible for medicines' timely access and for ensuring medicines optimisation.

More recently, a national initiative in the UK has focused on the transfer of care around medicines following data whereby following electronic referral from hospital to community pharmacy, there were statistically significant lower rates of readmissions amongst those that received a community pharmacist follow up consultation that those without a follow up consultation (53). In terms of multiprofessional collaboration, the role of technologies is extremely important, and there are only a few examples identified where the pharmacist has full read and write access to the patient medication record, namely in Valencia (54). Of course, this aspect is not only related to technology ability but also to law, data protection and ethics and frequently the arguments used to prevent full integration of information between all intervenient parties are related to confidentiality. Interestingly, there are recent cases where patient representative associations created fora to raise awareness about the need to use and share patient data (e.g. usemydata.org), whilst other created digital tools to collect information on medicines use and subsequently shared it with the European regulatory agency. This suggests that perhaps those claimed to need protection, are those who better understand the full benefits of information technology used securely.

5 - Optimal Management of the condition 'closer to home'

The health care paradigm has progressively been shifting from a care centred on the treatment of illness to care directed at illness prevention. However, in many countries, this is still not fully achieved for many reasons, a frequently cited reason being finances, which are mainly directed at treatment rather than prevention. However, as systems evolve, it is expected that the care is provided as close as possible to the individual's home. This will enable much more frequent monitoring with lower interference in the person's daily life aligned with the theology of primary care. However, even within primary care there are many countries where systems are defragmented and the full potential of existing structures is not reached. A traditional dichotomy between public and private entities exists in many Beveridge countries and this extends to ensured and uninsured entities in Bismark models. This constitutes a major barrier mainly for community pharmacists aiming to supplement the services provided by others, in areas where there is an expressed need. Again, there are cases of success in some countries where pharmacist-led services have been remunerated

(National Health Service/insurance co-payment), which may be seen as recognition of value and need.

5.a) Adherence of patients to treatment:

Evidence-based medicine guides prescribing and it is universally recognised that the highest level of evidence arises from RCTs, systematic reviews and meta-analysis (55) (56) (57). However, in trials two basic assumptions are made: 1) that individuals included in the trial represent the person in front of you requiring therapy, which is not always the case recognising all clinical trials have strict inclusion and exclusion criteria; and that the patient takes the drug as prescribed, also known to be untrue. The first issue is dealt in papers looking at the efficacy/effectiveness gap (58), which have greatly contributed to raise the awareness on the need for real-world evidence, currently driving most of the observational studies being done in various areas (59). Others have shown that there are differences in the medicine use patterns of real-life patients, namely in primary adherence, in secondary adherence but also in persistence (60) (61). These issues, often forgotten, will greatly impact on the outcome of therapy, both in terms of stroke prevention but also on haemorrhagic events.

In primary prevention, the communication terms used by health care professionals to describe medication are important as these may influence the perceived need. The use of the word therapy instead of treatment has been recently advocated by patient representatives and in fact the reason seems quite logical. If you refer to treatment, it implies the person is ill and is expecting recovery, therefore is likely to discontinue medication when asymptomatic. When the word therapy is used, this means that it may include preventive care, like it is the case of anticoagulants which mainly are used to prevent stroke, whereas other medications may be used to manage the eventually existing symptoms of disease.

There is extensive evidence on the impact of medication adherence in secondary cardiovascular prevention on Major Adverse Cerebral and Cardiovascular Events (MACCE) (62). The positive impact of treatment simplification has been demonstrated (63). However, complexity of treatment depends not only on the number of doses taken per day, but also on the pharmaceutical formulation (powder versus pills), need for dose adjustment and additional requirements (*e.g.* splitting pills; taking one pill every other day), and the total number of medicines. Treatment

simplification is already undertaken by hospital and community pharmacists, normally as a component of a broader service, namely medication reconciliation, medication review or certain forms of adherence enabling services. Medication adherence interventions should be tailored to the specific patient's needs and also to the phase of the person-medication relationship (64). The NMS service for example is particularly suited to enhance medication adherence in the initial phase of treatment. The service is designed to have an initial consultation and a follow-up visit and the evaluation of this service has shown a 10% increase in adherence (40). However, the sustainability of the effects has yet to be demonstrated. Other interventions may be more useful during the implementation phase for instance, which may include simple interventions (*e.g.* reminder cards or dose-administration aids) (65) (66) and expand to complex interventions (67).

In the concept of care closer to home, patient empowerment is central. This implies raising health literacy of the population to provide them with the necessary means to manage their condition. A service recently developed in France consists of two or three interviews between pharmacists and patients over the course of one year, which aims to instruct patients on their anticoagulant medication (warfarin), to ensure patients understand the directions of use and know how to deal with side-effects and drug interactions (68).

The role of the community pharmacist in the management of drug-drug interactions (DDIs) is also of utmost importance and it is an intervention that must precede any adherence enabling strategy developed. A study analysing over 250,000 prescriptions in community pharmacy identified DDIs in over 10% of them and highlighted warfarin as one of the two drugs classified as at highest risk for causing potentially serious interactions (the highest severity; class D). This is an area with enormous potential and with clear benefits for patient safety and better use of medical resources available, surely resulting on cost-savings (69). Interesting technological solutions in this area are being developed to help pharmacists in this role. The "Check for Medication Appropriateness" (CMA) is a system integrating clinical rules to identify four main types of high-risk situations involving medication use: drug use in renal insufficiency, use of QTc interval prolonging drugs, use of drugs with a restricted indication or dosing and use of very severe drug-drug interactions. Early data from using this system highlighted anticoagulants as the drug class leading to more

frequent interventions, clearly confirming the need for additional monitoring systems and collaborative efforts in anticoagulation medication management in ambulatory care (70).

In Belgium, drug dispensing data can be shared amongst pharmacists through the shared pharmaceutical file, enabling additional opportunities for detecting drug-drug interactions, including those acquired in other pharmacies (71).

Technology in general has enormous potential for the management of individuals at home these are used in an intelligent manner. In the UK for example, there are currently virtual clinics being developed so that patients discharged from hospital following a myocardial infraction are managed remotely (72). This includes having the ability to have access to laboratory and clinical data (*e.g.* blood pressure readings and LDL levels) entered periodically by the patient, but also access to patient reported experiences and outcomes (PREs and PROs), such as experienced side-effects and perceived quality of life. Another interesting example recently emerged in Belgium where a cloud based medication profile is made available for the patient to access using his ID card. The details are entered by the physician or the pharmacist but there the notion of a shared responsibility in this medication record. The "Personal Health Viewer" enables the patient to see his own detailed information, including medical reports, lab results, registration as organ donor, end-of-life decision, nursing files, among others. This system considers the citizen is the holder of all information, as foreseen by the current legislation, and as such enables the citizen to choose who can access his data (73).

6 - Secondary care for episodes of ill health

When instances of the care pathway fail, eventually the patient may have a reason for admission to hospital. In this phase, there are important roles for both community and hospital pharmacists, in sharing information about medication in both ways. This allows the pharmacists to undertake medication reviews and optimisation of medicines. Using the example of OAC, several studies have illustrated that inappropriate prescribing, monitoring, and administration of OAC occur frequently. Oral anticoagulants are often under dosed, inadequately monitored, contributing to increased risk for DRPs (74) (75) (76).

Anti-coagulants have been identified among the top medication classes leading to hospital admissions, regardless of the investigated country (77) (78) (79). Some

studies have even evidenced the causality associated, highlighting warfarin as a "definite" responsible for GI bleeds (80). However, it has been shown that services like the integrated medicines management is effective in reducing the risk of hospital re-admissions, a service where pharmacists play a key role (81).

5-20% of hospital admissions are caused by medication misuse and that more than half of these are avoidable. Medication non-adherence is one of the areas for concern, as it is estimated that 11-22% of hospital admissions for exacerbations of chronic disease are a direct result of it (82). However, potential interventions in this area seem more indicated for pharmacists influencing ambulatory care. In fact, the hospital pharmacist has a key role in pharmacokinetics monitoring because it has been shown that the frequency of bleeding correlates most closely with the minimum steady state plasma drug concentration. This is illustrated in a study where edoxaban was administered 30 mg twice daily led to significantly more bleeding events than the same drug administered as 60 mg once daily (83).

Although none of the RCTs leading to market entry of NOACs directly compared efficacy and safety of standard and low doses, there seems to be an overuse of the reduced dose in the absence of renal indication for dose adaption. This is an observation applicable to all NOACs, albeit more market in dabigatran, likely to result from the different mechanism of action (84). In routine clinical practice, prescribed NOAC doses are often inconsistent with drug labelling. These prescribing patterns may be associated with worse safety with no benefit in effectiveness in patients with severe kidney disease and worse effectiveness with no benefit in safety in apixaban-treated patients with normal or mildly impaired renal function (34).

Some studies have even demonstrated that a proportion as high as 30% of patients were receiving a dose of dabigatran inappropriately low, after taking into account creatinine clearance, age and bleeding risk (85).

The predictors for dose reduction, other than dabigatran treatment, include advanced age, high CHA_2DS_2-VASc score, and high HAS-BLED score (86).

The role of the hospital pharmacist in medicines optimisation goes obviously beyond OAC and studies undertaken in Brazil have shown that even in venous thromboembolism prevention, there is wide room for improvement as around 40% of hospitalised patients were found to receive inappropriate treatment (87).

Dose adaptation in the presence of renal impairment is also a key role for hospital pharmacists. With the more recent introduction of NOACs, all of which are partially eliminated via the kidney, the assessment of kidney function is important to estimate their clearance and ensuring appropriate dosing. However, a study conducted in Denmark with the purpose to describe the severity of adverse medication incidents caused by oral anticoagulants in hospitals showed that all fatal and almost all serious adverse medication incidents were associated with the prescribing phase of the medication process. In addition, during admission and surgery, prescribing excess anticoagulant was the most frequent problem and, on the other side, during discharge, prescribing insufficient anticoagulant was the most frequent problem (88). As more drugs to improve patient outcomes enter the health care system, potential new interactions become apparent. These interactions can impact on a drug's absorption, distribution, metabolism, excretion, or actual clinical effect. Drugs with a narrow therapeutic range or low therapeutic index are more likely to be the objects for serious drug interactions and as pharmacists, monitoring and altering doses to mitigate is part of our everyday process in reviewing patients. A Swedish study investigating the role of computerized medical records showed that over one fifth of ADR induced hospital admissions resulted from drug-drug interactions (DDIs) and frequently associated with polypharmacy (89), hence possible to manage and prevent by pharmacists' interventions. Another study in Bogota found that over 84% of hospitalized patients had one DDI, with the second more frequent involving anticoagulants (90). A systematic review additionally showed that NSAIDs were more commonly involved in DDIs leading to hospital admissions whereas warfarin was more frequently identified at emergencies or at outpatient hospital visits (91). This information could be important to better target the allocation of pharmacist workforce.

With initiatives aiming to reduce length of hospital stay, and with reports of approximately 60% of patients having three or more medicines changed during their hospital stay, the need to counsel patients on medicines at discharge but also the need to ensure adequate transfer around medicines has been communicated (92). Even when the patient uses the hospital as an unplanned admission, there have been initiatives emerging where patients are transferred home as soon as possible, while ensuring adequate hospital care is provided during a limited period of time until full recovery is achieved. Domiciliary hospitalisation is a relatively new concept that is

now implemented in some countries, namely Australia, UK, Spain and Portugal, which fits this purpose (93).

Improving the transfer of information about medicines across all care settings would help to reduce incidents of avoidable harm to patients and contribute to a reduction avoidable medicines-related admissions and re-admissions to hospital. In the UK, the continuity of patient care when transitioning from one healthcare setting to another is a national priority (94).

A recent systematic review highlighted how community pharmacists could help identify and rectify medication errors, thus providing a significant impact on improving outcomes (95). In 2012, the Royal Pharmaceutical Society (RPS) issued professional guidance in its publication 'Keeping patients safe when they transfer between care providers—getting the medicines right' on the core principles that underpin the safe transfer of information related to medicines for a patient transferring between care providers in any setting (96).

Effective interventions for minimising medication interactions and keeping patients out of hospital have long been shown to be cost-effective, with the PINCER trial evidencing important reductions in medication misuse in various therapeutic areas, including antihypertensive medication. This study was conducted across a sample of 72 GP practices and in this particular case evidenced a reduction in the long-term prescription of angiotensin converting enzyme (ACE) inhibitor or loop diuretics to those 75 years or older without assessment of urea and electrolytes in the preceding 15 months (97). Currently, with the recent investment in pharmacists working collaborative within GP practices, surely the impact of such initiatives will see a quick boost.

7 - Tertiary care and End of Life care – domiciliary support

Prescribing of medicines for older people who live in nursing homes is a very common intervention. Prescribing is one of the most common medical interventions experienced by older people resident in nursing homes (98).

Residents are often the frailest old and take up to four times as many medications than their age-matched community-dwelling nonfragile older counterparts in addition to age-related changes in pharmacokinetics and pharmacodynamics, nursing-home residents are at high risk of adverse drug events (99).

The US experience of using consultant pharmacists to carry out medication review represents one practice model that has been in place for some time. Indeed, this role is mandatory in all US nursing homes which receive funding from major federal government health programmes (100).

A number of studies have been conducted in Australia involving pharmacists either as the main professional delivering the intervention, or as part of a multidisciplinary team. Roberts and colleagues implemented a programme which focussed on establishing professional relationships between pharmacists and nursing home staff, educating nurses on common issues in geriatric pharmacotherapy, and medication reviews prepared by the pharmacists. These reviews were considered by a geriatrician and showed a reduction in the number of prescribed and administered drugs, some reductions in prescribing costs (101).

Deprescribing in general has become quite popular as a multidisciplinary team intervention, arising as a counter response to the rise of polypharmacy. More recently, other initiatives, such as "Choosing wisely" highlight not only the notion of evidence-based medicine but rationality (and sometimes also rationing) related to decision making. A good example is the paradox evidenced in a study that has demonstrated that in the last year of life, the number of medications prescribed rises, not only as a result of symptomatic medications but also as result of using long-term preventive treatments, for which the benefit is obviously intangible at this stage of life (102). One quite common example of therapy within this category is lipid—lowering medications, reported to be used by nearly 10% of individuals in their last month of life (103).

Discussion

In most countries worldwide, health care system is developed in siloed structures, perhaps ignoring that an individual can move from one to the other care site and receive duplicate or contradictory care. The development of a collaborative pathway is essential to provide better care in a holistic manner. Taking some examples from services marketing, the idea transmitted in the 4C's, can perfectly be adapted to health care. Today there is vast information available on the use of healthcare resources, which enables us to analyse past events and time-trends and use that information for clairvoyance, ie, anticipate the needs of the population in real time. The WHO has long stated that if nothing is reversed in the way people live (including lifestyle

options and environmental factors), chronic obstructive pulmonary disease will be the third leading cause of death in 2030. This is one example, but there are many others that may be used to anticipate future needs of our society; obesity in the industrialised countries is also one important factor which directly contributes to the burden of cardiovascular disease. If we anticipate we will have rising burden of obesity, we need to develop effective collaboration across sectors that may have an impact on obesity and this is the principle of Policy in all policies. If we simply focus on healthcare treatment, ignoring the role of preventive care, perhaps all investment will be directed to the structure and workforce needed to provide more bariatric surgeries. However, if we think broader, there will be a role to play also in the education, environment, trade and health sectors. Schools must be places incentivising sports and healthy eating, there must be equal conditions for children and adults of all socio economic strata to exercise, and economic capacity cannot be barriers to healthy eating. Within the health sector, the collaboration also needs to be organised to accompany the person's lifecycle. The health champions' programme in the UK is a public health initiative set up to invest in prevention, but seems to focus mainly in adult individuals, losing its full potential. Pharmacists and allied HCPs must move out of their comfort zone and engage with local schools, as they are currently doing to administer HPV vaccines. But, there is more to preventive care. The role of technologies is also important and while apple and other giants are developing applications to count steps and monitor blood pressure, healthcare seems to be the passive recipient, not being able to incorporate technology as a means to communicate with healthy individuals and contribute to disease prevention. Why not developing a public health app, through which the individual is motivated with gaming and other powerful tools to engage into healthy living? Also, this app should then be able to collect data that can intelligently be used to provide information to a health care hub, indicating if the individual should seek preventive care and favour integration of primary care providers; in other phases, perhaps direct him to urgent or hospital care and in the last instance to palliative care. This system must be powerful enough to break the silos and connect the pathway horizontally to go along the individual's lifecycle. Most workspaces are currently physically set up in a way that does not favour collaboration. This needs urgent solving and surely architects and engineers can come up with solutions for health care equally functional as they have been able to do for other sectors. Once an efficient pathway is established, then it

should be customized and national upscaling will follow. Finally, for people to be able to use it efficiently, communication about its functions must be made freely available to all, including the providers and the public. Communication with the public is often not maximised in healthcare and again in this area, experts in the filed should be sought so that flexible solutions exist to reach the low literate, the media excluded but also the highly educated.

This position paper tried to set the scene by identifying areas along the patient pathway where pharmacists are present, although their full potential is currently underused. Next steps will need to focus on the identification of effective ways to make pharmacists useful and efficient resources for integrated cardiovascular care.

Limitations: Literature review was mostly narrative, to support some of the thoughts and to foster additional idea exchange. We did not aim for a systematic review, so there is surely relevant literature missing. This position paper results from the personal perspectives of a group of individuals with shared common interests, namely the fact that all authors are pharmacists and are therefore likely to have strong beliefs in the power of this workforce. Nonetheless, we have tried to support the views conveyed with evidence generated from various countries.

Conclusion:

Pharmacists are located in various steps across the patient care pathway, close to the community, in hospitals and in tertiary care, with no barriers to access driven by the need to book or pay for appointments, and in some areas being the only health service in that area. We have highlighted various areas where pharmacists seem to be an untapped resource for the implementation of a person-centred care pathway in the area of anticoagulation.

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Conflict of interest statement:

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Figure 1: Patient care pathway in cardiovascular disease

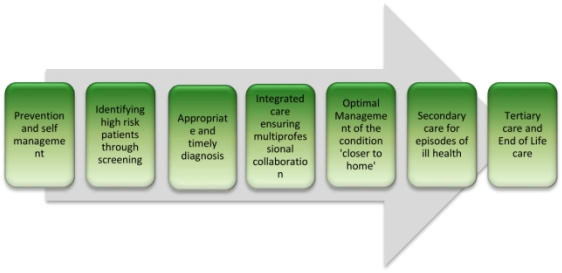

Figure 1: Patient care pathway in cardiovascular disease

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