Improving medical decision making: Stroke prevention in atrial fibrillation
Arts, D.L.

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Chapter 1

General introduction and thesis outline
INTRODUCTION

In this thesis we address the problem of low guideline adherence in general, and specifically for atrial fibrillation (part A), as well as the potential of decision support systems for improving it (part B). Furthermore, we investigate the use of complex prediction models for improving stroke prevention in patients with atrial fibrillation (part C). Figure 1 displays an outline of the thesis and the topic of each chapter.

PRELIMINARIES

In the late 1900s, the medical community started to doubt their reliance on accumulated personal experiences for medical decision making. Archibald Cochrane (1909-1988) first criticized our practice of medicine in his 1972 book Effectiveness and Efficiency: Random Reflections on Health Services [1]. He noted that many medical practices that were presumed to be effective lacked evidence from controlled trials. Shortly thereafter, researchers began publishing about the variation in treatment practices and documenting errors in clinical reasoning.

In 1990, the term “evidence-based medicine” was formally introduced and by 2000 it was well known throughout the medical community [2]. Currently, evidence-based medicine (EBM) is defined as “an approach to medical practice intended to optimize decision-making by emphasizing the use of evidence from well designed and conducted research” with the intention to provide the best possible care for individual patients [3].
Chapter 1

EBM is now considered the gold standard for clinical practice, as treatment strategies can be based on results from large groups of patients, as opposed to one physician’s opinion. The most common implementation of EBM involves evidence-based clinical practice guidelines (CPGs): “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances” [4].

Young doctors are educated on the importance of applying EBM and the role of evidence therein during internships [5]. But, are physicians, young and old, really using evidence-based medicine in daily practice? Are we applying the best available evidence to make decisions in relation to patients’ circumstances and preferences?

Guideline overload

Today, we have no shortage of CPGs. Medical societies are constantly creating and updating guidelines for specific diseases, with more than 1000 guidelines being created annually [6]. However, the mere provision of guidelines does not ensure doctors adhere to them. It has consistently been shown that guideline adherence varies greatly, but rarely exceeds 80% and is on average 55% [7, 8]. Why would physicians not follow guidelines that often? Cabana et al. [9] describe possible reasons for non-adherence in their systematic review (e.g., Lack of Awareness, Lack of Outcome Expectancy, and Guidelines Factors) and divide these into three different categories: Knowledge, Attitudes, and Behavior. Other studies found barriers in similar categories [10, 11]. Knowledge of these barriers to guideline adherence allows us to look for solutions that target specific issues in guideline implementation and adherence.

Decision support

Making good use of guidelines requires a high-quality guideline, a willing doctor and patient, the right tools, circumstances, and time. Part of the medical community has long known that there are other methods to support clinicians besides (paper) guidelines. Some turned to computers to help implement clinical practice guidelines even before the term “evidence-based medicine” was introduced. These systems, which supported healthcare workers in making clinical decisions, were aptly named “Clinician Decision Support Systems” (CDSSs). One of the first of these systems was "MYCIN," a 1976 rule-based system that was designed to help doctors diagnose blood infections and select the right treatment [12]. It used IF-THEN rules (e.g., IF patient has fever THEN recommend antibiotics) to guide physicians to the right endpoint. Many, if not most, CDSSs still use these basic IF-THEN rules to make recommendations today.

Parts A and B of this thesis relate to guideline adherence and decision support. What specific reasons do physicians have for guideline non-adherence? Can we improve
guideline adherence by supporting physicians with clinical decision support systems? We attempted to answer these questions in the field of atrial fibrillation (AF), specifically stroke prevention in AF, as guideline non-adherence is prevalent in this domain and the potential for improving patient health is large (Box 1).

**Box 1. Atrial Fibrillation**

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia (abnormal heart rhythm), characterized by rapid and irregular beating. Its prevalence has increased over the last 30 years [13]. In 2006 it ranged from 0.7% (age 55-59) to 17.8% (age > 85). On average, 2% to 3% of the population is affected in Europe and North America [14]. Patients with AF are at high risk for stroke, with up to a five-fold risk compared to patients without AF [15]. Apart from the increased risk, stroke severity also is increased [16]. Therefore, most patients with AF need to be treated with antithrombotic medication to reduce stroke risk. Oral anticoagulation (OAC), such as warfarin and the new oral anticoagulants (NOACs), can reduce risk of stroke by 60% [17, 18].

Most recent guidelines recommend prescribing OAC for all but the lowest risk categories to allow for easy implementation and optimal stroke risk reduction. To determine which patients should receive OAC, stroke risk scores are used to predict individual risk of stroke for each patient. In doing so, net benefit is balanced against possible side effects, mainly increased bleeding risk. Several such risk-prediction schemes have been developed in the past and are used in international guidelines [19, 20]. Currently, the CHA$_2$DS$_2$-VASc is the most widely used stroke risk score: it consists of 7 variables that can add up to a total of 9 points [19]. Due to the high net benefit of treatment with OAC, the stroke risk cut off for this treatment has been lowered over the past few years [21]. The most recent European Society for Cardiology (ESC) guidelines recommend treatment for patients scoring 1 point or more. This means that most patients over 65 years old with AF should be receiving antithrombotic medication. For this thesis we focused on the Revised Dutch GP guideline for atrial fibrillation, authored by the Dutch College of General Practitioners (NHG). It introduced the CHA$_2$DS$_2$-VASc, but did not yet recommend treating all patients with 1 point. Instead, it recommended weighing risk and benefit with the patient [22].

**PART A: CURRENT PRACTICE: GUIDELINE ADHERENCE**

Adherence to stroke prevention guidelines in AF is poor [23-25]. This non-adherence is mainly related to underuse of OAC in patients with medium to high stroke risk. Two important reasons for OAC underuse are: 1) the complexity of the decision rules used, and 2) physicians’ concerns with the bleeding risk associated with OAC. However, the benefit of stroke prevention greatly outweighs the risk of bleeding due to OAC, and OAC should therefore not be withheld when indicated [26].

To determine if guideline non-adherence in AF stroke prevention was as prevalent in the Netherlands as it was in other countries [27, 28], we evaluate guideline adherence amongst general practitioners (GPs) using a national database in Chapter 2. We investigate to what extent Dutch GPs appropriately prescribe anticoagulants to protect their patients from stroke, and balance medication-related adverse event risk against poten-
tial benefit. Next, we investigate potential barriers to guideline adherence. Some barriers relate to the guideline itself: recommendations may not be clearly defined, making them hard to implement. Likewise, the level of the evidence might be missing from recommendations, allowing for uncertainty regarding their importance [9, 29]. Lugtenberg et al. reported that suboptimal guideline features may have acted as a barrier for adherence to the Dutch AF guideline [30]. To establish what specific features might limit guideline adherence, we perform a thorough appraisal of the guideline in Chapter 3. Using established methods of evaluating guidelines, we assess how optimization might improve its implementation in daily practice.

Another guideline-related barrier to adherence is often mentioned by critics of guidelines: they argue that Randomized Controlled Trials are not representative of real-world populations, and thus guideline recommendations are not applicable to their individual patients [31]. To determine if physicians indeed have valid reasons for guideline non-adherence, we set out to discover what intentional reasons they have for not acting according to guideline recommendations in Chapter 4. We perform a systematic review of studies on guideline adherence, and categorize reasons for non-adherence.

PART B: IMPROVING GUIDELINE ADHERENCE WITH CLINICAL DECISION SUPPORT SYSTEMS

Can clinical decision support systems help improve guideline adherence? Over the past years, many trials have tried to answer this question. Studies often focus on indirect measures for quality of care and results indicate that usage of CDSSs can lead to improvements in clinical practice and guideline implementation [32-34]. However, evidence for direct improvement on patient health is lacking: the overall effectiveness of CDSS on mortality has not been established, but a recent review did find a moderate improvement in morbidity outcomes [35]. Therefore, CDSSs hold promise for the future of healthcare, but can they help us apply guidelines in the best way possible? Current evidence is not universally in favor of decision support, as negative side effects can occur when implementing these systems, such as reducing the perceived need for human verification of medication, providing inaccurate recommendations, or interruption of workflow [36]. Furthermore, there is no clear consensus on what makes decision support successful. Studies have identified many possible factors for lack of effectiveness. These include: lack of usability, lack of integration with host systems, lack of time to effectuate advice, inapplicability to the patient, lack of integration with current workflow, and alert fatigue [33, 37]. However, due to a lack of homogeneity in methodology and implementations across a wide range of medical specialties, we have yet to definitively determine features of effective decision support [38].
To help answer questions regarding CDSS effectiveness and factors pertaining to effectiveness, we began the Expert-AF project. Our goal was to investigate whether a CDSS can improve adherence to stroke prevention guidelines in the Netherlands. Chapter 5 contains the trial protocol for the Expert-AF project, a cluster randomized controlled trial that was run amongst Dutch GPs. We created our own clinical decision support system for a widely used GP electronic health record system. Chapter 6 describes the effectiveness of the system we implemented as measured by the change in the proportion of patients treated according to the guideline. Furthermore, we collected reasons for non-adherence to gain insight into why GPs would withhold a treatment with such high net benefit from their patients. In Chapter 7 we use focus groups and surveys to evaluate the system we created. We investigate how GPs experienced our system and what factors promoted or limited use. By doing so, it provides a clear overview of the challenges one faces when trying to implement a new system in an existing, busy workflow.

PART C: IMPROVING DISEASE PREDICTION

While the topic of how to implement decision support is intriguing, we have thus far only attempted to use computers to help with implementing pre-existing guidelines. These guidelines are usually developed by multidisciplinary groups of experts who summarize current literature and define an easy-to-use overview of best practices for specific health conditions [39]. After a guideline has been completed, it is up to researchers or electronic health record (EHR) vendors to “translate” a guideline into a decision rule. This usually results in a simple IF-THEN rule, just like those used in MYCIN in 1976. The average smartphone can run these rules in a split second and its resources will not be used to their full capacity.

Can we use more complex methods that may improve disease prediction, regardless of implementation? Can we do more with the computational power modern computers offer? The answer is yes. There are more complex methods for making predictions that might be more effective than traditional methods. It is important to note that this does not necessarily involve computers, but in practice these methods are so complex that only the computational power of a modern computer can solve the math involved. An example is Artificial Neural Networks (ANNs). These networks, which mimic the mammal brain by using connected neurons in order to learn, are often used by large web companies such as Google and Facebook. ANNs have been around in medicine for a long time. For example, ANNs are currently used for the prediction of breast cancer and analysis of MRI images [40, 41]. They are trained using a process called “supervised learning” and can automatically model complex non-linear relationships between risk factors. We currently break these relationships down into formulas to make them usable in daily clinical
practice. This results in a loss of information about the subtleties of the relationships between risk factors. Can we use computers to leverage these subtleties and improve predictions? In Chapter 8 we try to improve stroke prediction in atrial fibrillation using logistic regression and neural networks. We investigate whether these techniques are better at predicting stroke than the established stroke risk stratification schemes and determine how patients could benefit from these predictions.

**The future of medical decision making**

The medical community will continue to strive for the effective use of evidence in healthcare. In this thesis we investigate whether guidelines and computers can facilitate the ongoing transition to evidence-based medicine in years to come. Are they the future of medical decision making?
REFERENCES


