

The Future of Cardiac Safety Studies

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Introduction

Across the last several decades, to establish cardiac safety has been a major concern during drug development process. It was found that, many drugs are associated with sudden death and causing fatal arrhythmia. It is difficult identify compound having cardiac toxicity. However, one common effect of these drugs was to prolong QT_c but the challenge is to find whether this problem is related to parent drug or metabolite or due to drug interaction or combination of all three?

Thorough QT/QT_c Study

The objective of “thorough QT/QT_c study” on health human population is to identify whether drug has a threshold pharmacologic effect on cardiac repolarization as it is regulatory concern [1,2]. This is generally detected by QT/QT_c prolongation. Such studies are planned during early phase of drug development which help to provide maximum guidance for the later studies (Figure 1) [3,4].

There are Several Limitations of Thorough QT/QT_c Studies

1. QT_c is not considered to be strong biomarker as there are no consensus on the best suited method of acquiring, measuring, and analysing the QT_c interval during studies as due to poor signal, low frequency, low amplitude and has poor signal-to-noise ratio affected by several confounding factors. In addition, there is poor link between the experimental model of QT_c and clinical events. Many times, it's difficult to establish link between different episodes reported during study [1,5-7].

2. Prolongation of QT internal is also linked with many other factors. It's not always a risk. Marketing approval with “Warning label” was considered for several drugs [8].

3. It's very expensive to conduct “thorough QT/QT_c studies” [9,10].

Conclusion

The most common reason for the drug withdrawal includes QT prolongation and pro-arrhythmias. To prove cardiac safety become extremely difficult for the developers once compound is shown prolong QT during drug development [11].

Refinement in regulations is needed based on earlier experience along with careful planning during pre-clinical stage to review Multiple Ion Channels (MICE), isolated cardiac myocytes, multiple Electrocardiography (ECG) collection, use of computer modelling and

placing a premium on ER relationships [12-14]. The best strategy is to keep ECG as vital data point and establish cardiac safety with the help from preclinical information and early phase human studies keeping several other cardiac biomarkers (heart rate, lipids, CRP, BP, BNP, troponin and imaging) in consideration.

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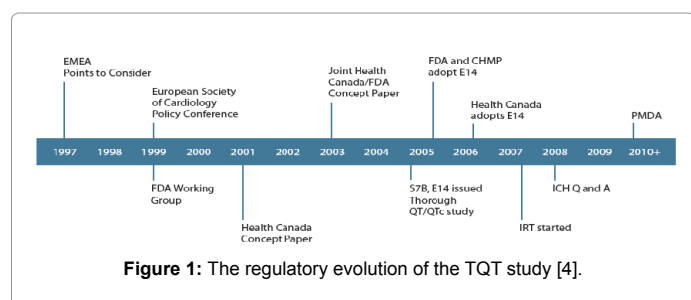


Figure 1: The regulatory evolution of the TQT study [4].

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