



Review article

A critical analysis of the COMPASS trial with respect to benefit-risk assessment using the numbers needed to treat: Applicability and relevance in Indian patients with stable cardiovascular disease



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ABSTRACT

The recently published Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial evaluated the hypothesis that rivaroxaban alone or in combination with aspirin would be more effective than aspirin alone for secondary prevention. In India, stable cardiovascular disease occurs in a much younger age group relative to the rest of the world.

Our critical analysis of COMPASS trial showed that the younger age group appeared to derive greater benefit from the rivaroxaban + aspirin combination (relative to aspirin alone) as seen with number needed to treat metrics as compared to the older age group.

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1. Introduction

Rivaroxaban is a direct factor Xa inhibitor that is currently licensed for use in a wide variety of indications. These include deep vein thrombosis (DVT), pulmonary embolism (PE), prevention of recurrent DVT and PE in patients with a previous DVT, prevention of venous thrombo-embolism (VTE) in patients undergoing elective hip and knee replacements, prevention of stroke in patients with non-valvular atrial fibrillation (AF) (with one or more risk factors for stroke) and prevention of thromboembolic events following acute coronary syndrome (ACS) (this indication is approved only by European Medicines Agency).¹ The Drugs Controller General of India (DCGI), the United States Food and Drug Administration (USFDA) and Health Canada have also accorded approval to rivaroxaban for these indications. All regulatory approvals are based on studies that have compared rivaroxaban with warfarin.^{2–8}

In recent years, the use of rivaroxaban is being expanded and one potential area where it can be used is in secondary prevention in patients with stable cardiovascular disease (CVD). This is based on the hypothesis that it may have benefits (with acceptable

safety) when added to aspirin as seen with its addition to aspirin in ACS.⁹ The recently published Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial evaluated this very hypothesis. The trial studied rivaroxaban in combination with aspirin versus rivaroxaban alone in the setting of patients with stable atherosclerotic disease.¹⁰ The study found that those who received the combination (5 mg/d dose of rivaroxaban) had better cardiovascular outcomes (as assessed by a composite of cardiovascular death, stroke, or myocardial infarction (MI) but also more major bleeding events relative to those who received aspirin alone. Rivaroxaban (10 mg/d) alone did not result in better cardiovascular outcomes relative to aspirin alone and was also associated with a similar risk of major bleeding events. The decision, thus, to prescribe rivaroxaban like any anticoagulant therapy must finely balance the reduction in risk of thrombo-embolic events with the increased risk of bleeding.

India as a country has a high burden of CVD and this tends to affect the productive work force in the age group of 35–65 years due to ACS.¹¹ The median age at which MI occurs in the country is 53 years and 5–10% cases are seen in men and women under the age of 40 years. Kaul U et al in their analysis of n = 709 Indian patients (with stable coronary artery disease) from the CLARIFY registry showed the mean age of the Indian patients to be 59.6 ± 10.9 vs 64.3 ± 10.4 years for the rest of the world.¹² Against this backdrop, we thought it was prudent to dissect the COMPASS trial to assess the benefit-risk of

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using rivaroxaban in the younger age group (less than 65 years) relative to the older age group.

For the purpose of benefit-risk evaluation, a commonly used metric for anti-thrombotic therapy is net clinical benefit (NCB). This is a composite endpoint comprising individual efficacy and safety endpoints.¹³ In COMPASS trial, the NCB outcome analysis showed a beneficial effect with rivaroxaban plus aspirin relative to aspirin monotherapy, irrespective of age.

Yet another metric that can be used for this purpose is the Number Needed to Treat (NNT) (for both benefit and harm; NNT-B and NNT-H, respectively) as well as the Likelihood of Being Helped or Harmed [LHH]. These metrics are relatively easier to understand as well as to calculate. Since the COMPASS trial did not provide a sub group analysis of benefit and risk of rivaroxaban plus aspirin combination therapy in young patients (who represent the major proportion of stable coronary disease patients in India), we carried out this analysis using the NNT metric.

2. Understanding the concept of NNT (NNT-B and NNT-H) and LHH

The concept of NNT was first introduced in 1988 by Laupacis et al.¹⁴ who defined it as “the number of patients a clinician should treat in order to prevent one adverse outcome” and its original intended use was for benefit. The concept of NNT is based on noting the frequency/proportion of occurrence of an outcome (either benefit or harm). It is estimated as a cumulative incidence of that outcome (numerator) per number of patients followed up over a given time period of time (denominator).¹⁵ This will result in a percentage of patients with the outcome over time (out of the total number followed up). The metric is thus a proportion. It is mathematically expressed as 1/Absolute risk reduction (for both benefit (NNT B) and harm (NNT H)). Both of these can then be used to calculate a single metric the LHH. Table 1 gives the detailed description of NNT-B, NNT-H and LHH, including their concepts and what it means to the practicing clinician. These calculations for the COMPASS trial are described in the next section and also presented in Tables 2 and 3.

3. Data collection, and extraction risk benefit calculations – COMPASS trial – NNT-B, NNT-H and LHH

3.1. Locating, selecting and extracting the data

The COMPASS paper and its supplementary appendix published in the New England Journal of Medicine [NEJM] were used as primary data sources.¹⁰ Variables included were – primary efficacy outcome (cardiovascular death or stroke, or MI; Major Adverse

Cardiovascular Outcomes or MACE] and safety outcome (major bleeding events). These were then tabulated for the two age groups-less than 65 and more than 65 years. The NNT-B and NNT-H were calculated as a reciprocal of the absolute risk difference between rivaroxaban + aspirin and aspirin alone for both groups. The LHH was calculated as the ratio of NNT-H/NNT-B and the two groups were then compared. The data and calculations are presented in Tables 2 and 3. We did not carry out calculations for rivaroxaban alone versus aspirin alone as the between group difference was not statistically significant.

4. Benefit-risk calculations – COMPASS trial – NNT-B, NNT-H and LHH

4.1. Analysis irrespective of age and its interpretation

When rivaroxaban + aspirin [N = 9152] was compared to aspirin (N = 9126) alone (without subgroups being divided according to age), the NNT-B was 76 indicating that a total of 76 patients would need to be treated with rivaroxaban + aspirin (rather than aspirin alone) for one additional patient to achieve benefit over a 23-month period. The NNT-H was 83, indicating that a total of 83 patients would need to be treated with rivaroxaban + aspirin (rather than aspirin alone) for one additional patient to be harmed over the 23-month period. The LHH was 1.1. This LHH indicates that every time one patient is treated with rivaroxaban + aspirin (rather than aspirin alone), one patient experience benefit and one patient will experience harm.

4.2. Analysis of benefit risk in the under 65 years (N = 4334) group and its interpretation

When rivaroxaban + aspirin (N = 2150) was compared to aspirin (N = 2184) alone, the NNT-B was 48 indicating that a total of 48 patients would need to be treated with rivaroxaban + aspirin (rather than aspirin alone) for one patient to achieve benefit over a 23-month period. The NNT-H was 500, indicating that a total of 500 patients would need to be treated with rivaroxaban + aspirin (rather than aspirin alone) for one patient to be harmed over the 23-month period. The LHH was 11. This LHH indicates that every time eleven patients are treated with rivaroxaban + aspirin (rather than aspirin alone), one patient experience benefit and one patient will experience harm.

4.3. Analysis of benefit risk in the more than 65 years (N = 13,944) group and its interpretation

When rivaroxaban + aspirin (N = 7002) was compared to aspirin (N = 6942) alone, the NNT-B was 91 indicating that a total of 91

Table 1
Number Needed to treat [For Benefit and Harm] (NNT-B and NNT-H) and the Likelihood of Being Helped or Harmed [LHH].

Metrics	Definition	Formula	Interpretation	Characteristics
NNT-B	Single number which tells the practicing clinician about the number of patients he would need to treat with one intervention rather than another, to prevent one additional adverse outcome [cardiovascular death, myocardial infarction or stroke] ¹⁶	1/ARR	An ideal NNT-B would be 1, indicating that every time one patient is treated with one rather than another intervention, one patient derives benefit	An ideal NNT-B should be as close to 1 as possible.
NNT-H	Number of patients who need to be treated with one intervention [rather than another] for one patient to be harmed or for one patient to have an adverse outcome [major bleeding events]	1/ARI	Every time one patient is treated with one rather than another intervention, one patient derives benefit	The higher the NNT-H the better is the intervention because this indicates lesser likelihood of harm relative to the comparator. It should be as far away from 1 as possible.
LHH	Number of patients who stand to benefit from treatment for one patient being harmed	NNT-H/ NNT-B	If NNT-H/NNT-B is 10:1 then for every 10 patients who receive any given benefit because of the drug, one patient will experience harm because of the drug	The value of LHH should be greater than 1 and the further away from 1 that the value is, greater is the likelihood that the intervention produces more benefit than harm

ARR = Absolute Risk Reduction, ARI = Absolute Risk Increase.

Table 2

Overall benefit-risk analysis of data from the COMPASS trial-calculation of NNT-B, NNT-H and LHH; regardless of age.

Variable	Efficacy endpoints (MACE outcome)		NNT-B	Safety endpoints (Major bleedings)		NNT-H	LHH ^d
	Event rate (%)	Absolute risk difference ^c (%)		Event rate (%)	Absolute risk difference ^c (%)		
R + A ^a [N = 9152]	4.1	-1.3	76	3.1	1.2	83	1.1
A ^b [N = 9126]	5.4			1.9			

^a Rivaroxaban Plus Aspirin.^b Aspirin Monotherapy.^c Differences in event rates.^d Ratio of NNT-H and NNT-B.**Table 3**

Benefit risk analysis from COMPASS trial of two different age groups – <65 years and >65 years, using NNT-B, NNT-H and LHH.

Variable	Efficacy endpoints (MACE outcome)			NNT-B	Safety endpoints (Major Bleedings)			NNT-H	LHH ^d
	Event rate (%)	Absolute risk difference ^c (%)			Event rate (%)	Absolute risk difference ^c (%)			
<65 yrs [N = 4334]	R + A ^a	A ^b	-2.1	48	R + A ^a	A ^b	0.2	500	11
	[N = 2150]	[N = 2184]			[N = 2150]	[N = 2184]			
> 65 yrs [N = 13,944]	R + A ^a	A ^b	-1.1	91	R + A ^a	A ^b	1.6	63	0.7
	[N = 7002]	[N = 6942]			[N = 7002]	[N = 6942]			
	4.2	5.3			3.6	2.0			

^a Rivaroxaban + aspirin.^b Aspirin Monotherapy.^c Differences in event rates.^d Ratio of NNT-H and NNT-B.

patients would need to be treated with rivaroxaban + aspirin (rather than aspirin alone) for one patient to achieve benefit over a 23-month period. The NNT-H was 63, indicating that a total of 63 patients would need to be treated with rivaroxaban + aspirin (rather than aspirin alone) for one patient to be harmed over the 23-month period. The LHH was 0.7. This LHH indicates that every time less than one patient is treated with rivaroxaban + aspirin (rather than aspirin alone), one patient experiences benefit, and one patient will experience harm.

5. Understanding the implications of the benefit-risk calculations in the COMPASS trial

At the end of the COMPASS paper, the authors have made the following statement “The risk of MACE was significantly lower with the combination of rivaroxaban + aspirin than with aspirin alone, and the risk of major bleeding was significantly higher.⁹ This indicated that the benefit seen is achieved at the cost of increased risk of major bleeding. However, our analysis shows that the benefit-risk is disparate in the two groups studied with the <65 years group appearing to derive greater benefit from the rivaroxaban + aspirin combination. This is reflected in the NNT-B of 48 relative to the NNT-B of 91 in the >65 years age group. Similarly, the younger age group, also has a lower risk of harm as indicated by the NNT-H of 500 relative to the NNT-H of 63 seen in the >65 years age group. The values of LHH in the two groups were 11 and 0.7, respectively. The value of 0.7 which is lower than 1, indicates that in the older age group, the rivaroxaban + aspirin combination is causing more harm than benefit.

6. Takeaway from the COMPASS trial-our perspective

In India, warfarin remains the anti-coagulant of choice due to physician comfort that in turn derives from several decades of experience with using the drug.¹⁷ However, in the last few years, four

Non-vitamin K oral anticoagulants (NOACs) have become available as alternatives to warfarin-these include dabigatran etexilate [approved in India on 12 December, 2011 for prevention of stroke, systemic embolism, and reduction of vascular mortality in adult patients with AF], apixaban (approved in India on 3 August, 2012 for prevention of VTE in patients undergoing elective hip or knee replacement surgery), edoxaban (not yet approved in India) and rivaroxaban (approved in India on 30 January, 2010, for prevention of VTE in patients undergoing elective hip or knee replacement surgery). The advantage of NOACs is that unlike warfarin, they have a more predictable therapeutic effect, do not require routine monitoring, have fewer potential drug-drug interactions and no restriction on dietary consumption of vitamin K-containing food. The downside is the lack of specific antidotes until recently to address bleeding side effects associated with them and also lack of measurement assays for these antidotes.

The COMPASS trial evaluated a very low dose of rivaroxaban, for an indication yet to be approved in India-secondary prevention in patients with stable atherosclerotic vascular disease. The major takeaway for the country from this trial is the favorable benefit-risk profile (as assessed by using three NNT metrics) of the combination of rivaroxaban with aspirin among patients aged less than 65 years (relative to those more than 65 years). The combination in fact, appears to produce more harm than good in the older age group. The CREATE registry¹⁰ shows that a majority of the patients with ischemic heart disease in the country belong to the age group of 40–60 years. Thus, from an Indian perspective, the relatively favorable benefit-risk profile of the combination will help strengthen the available treatment options for Indian clinicians for their younger patients, once the drug receives regulatory approval for this indication.

At the present moment, all NOACs are significantly more expensive than warfarin. The patent of dabigatran has expired (February 2018), while the patents for remaining NOACs will expire by 2022 with the rivaroxaban patent expiring in 2024. This will make generic versions of rivaroxaban available in India, which will be

cheaper. Until such time, the use of rivaroxaban regardless of the indication will continue to remain expensive. Studies on pharmacoeconomic evaluations with rivaroxaban to date have included VTE where the comparator was low molecular weight heparin.^{18,19} and stroke prevention in AF²⁰ where the comparator was warfarin. The studies (two of which included modeling) showed rivaroxaban to be cost effective. The decision to prescribe rivaroxaban (in combination with aspirin) in India, to patients aged <65 years can be considered as an option as the disease is seen a decade earlier in the country. However, this needs to be strengthened through evidence that can be generated in a randomized controlled trial (where the comparator would be the older age group) with pharmacoeconomic evaluations of its benefit-risk as also assessments of quality of life.

Conflict of interest

None declared.

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None.

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