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Μη Παρεμβατικές Μελέτες (Non-Interventional Studies - NIS) Προδιαγραφές Ευρωπαϊκών Κρατών

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ΕΙΣΑΓΩΓΗ

Οι Μη Παρεμβατικές Μελέτες (ΜΠΜ) είναι μελέτες μετεγκριτικής φάσεως και αποτελούν την εναλλακτική επιλογή στις Παρεμβατικές Κλινικές Μελέτες μετά την κυκλοφορία του σκευάσματος, οι οποίες παρέχουν πληροφορίες για την χρήση του σκευάσματος και να επιβεβαιώσουν το πρότυπο ασφαλείας του, στον πραγματικό πληθυσμό (Real World Data). Οι Μη Παρεμβατικές Μελέτες (Non-Interventional Studies) αποτελούν τμήμα της διαχείρισης του κύκλου ζωής του φαρμάκου (Product Life Cycle Management). Ο σκοπός διεξαγωγής τους είναι η συλλογή επιπρόσθετων δεδομένων για την αποτελεσματικότητα και την ασφάλεια του φαρμάκου και η παρακολούθηση της ορθής χρήσης του. Τέτοιες μελέτες μπορούν να αυξήσουν τα επιστημονικά δεδομένα, τόσο σε διεθνές (Global studies) όσο και σε τοπικό επίπεδο (Local studies), ανάλογα με το σχεδιασμό τους και το στόχο τους.

ΟΡΙΣΜΟΣ

Ως Μη Παρεμβατική Μελέτη ή Δοκιμή (ΜΠΜ) ορίζεται η μελέτη κατά την οποία το ή τα υπό μελέτη φαρμακευτικά προϊόντα συνταγογραφούνται ως συνήθως, σύμφωνα με τους όρους που προβλέπονται στην άδεια κυκλοφορίας του ιδιοσκευάσματος. Η ένταξη του ασθενούς σε μια συγκεκριμένη θεραπευτική στρατηγική δεν αποφασίζεται εκ των προτέρων από πρωτόκολλο δοκιμής. Ο ασθενής εντάσσεται στην μελέτη με βάση την τρέχουσα ιατρική πρακτική. Η απόφαση χορήγησης φαρμάκου διαχωρίζεται σαφώς από την απόφαση συμμετοχής του ασθενή στη μελέτη. Στους ασθενείς δεν πρέπει να εφαρμόζονται επιπρόσθετες διαδικασίες διάγνωσης ή παρακολούθησης για τους σκοπούς της μελετης. Για την ανάλυση των συλλεγομένων δεδομένων πρέπει να εφαρμόζονται επιδημιολογικές μέθοδοι. (Άρθρο 21 Directive 2001/20/EC)

Οι μη παρεμβατικές μελέτες ορίζονται από τη μεθοδολογική προσέγγιση που χρησιμοποιείται και όχι από τους επιστημονικούς στόχους. Περιλαμβάνουν την έρευνα της βάσης δεδομένων ή την αναθεώρηση των αρχείων, όπου όλες οι εκδηλώσεις ενδιαφέροντος έχουν ήδη συμβεί. Τέτοιες μελέτες μπορεί να είναι :

- Μετεγκριτικές Μελέτες Ασφάλειας (Post Authorization Safety Studies - PASS).
- Μελέτες Cohort (προοπτικές και αναδρομικές).
- Μελέτες παρακολούθησης περιστατικού (Case Surveillance).
- Μελέτες σύγκρισης περιστατικού-μάρτυρα (Case-Control Studies).
- Διασταυρούμενες Μελέτες (Cross-Sectional Studies).

Μη παρεμβατικές μελέτες είναι επίσης εκείνες που περιλαμβάνουν πρωτογενή συλλογή δεδομένων (π.χ. μελέτες από τα αρχεία/μητρώα των ασθενών στα οποία τα δεδομένα που συλλέγονται προέρχονται από τη συνήθη κλινική πρακτική), υπό τον όρο ότι πληρούνται οι προϋποθέσεις που αναφέρονται ανωτέρω. Σε αυτές τις μελέτες, οι συνεντεύξεις, τα ερωτηματολόγια και τα δείγματα αίματος πρέπει να πραγματοποιούνται ως η συνήθης κλινική πρακτική ορίζει και όχι για τους σκοπούς της μελέτης.

Οι αναδρομικές μελέτες είναι χρήσιμες σε περιπτώσεις που διαφαίνεται από τα αρχεία των ασθενών η εξαγωγή χρήσιμων συμπερασμάτων όσον αφορά την αποτελεσματικότητα, την ασφάλεια ή την μεταβολή των δοσολογικών σχημάτων σε συγκεκριμένους υποπληθυσμούς ή σε περιπτώσεις κατά τις οποίες μια προοπτική προσέγγιση θα έπαιρνε πολύ χρόνο για να συγκεντρωθούν επαρκή δεδομένα. Οι αναδρομικές μελέτες είναι επίσης χρήσιμες όταν υπάρχει μια σημαντική χρονική καθυστέρηση μεταξύ έκθεσης σε έναν

παράγοντα κινδύνου και την ανάπτυξη μιας νόσου. Οι αναδρομικές μελέτες έχουν σχετικά χαμηλό κόστος και μπορούν να χρησιμοποιήσουν τις υπάρχουσες βάσεις δεδομένων και μητρώων/αρχείων ασθενών.

ΣΚΟΠΟΣ

Οι μη παρεμβατικές μελέτες διεξάγονται με σκοπό την παρατήρηση, καταγραφή και συλλογή δεδομένων προάγοντας έτσι την επιστημονική γνώση και κατάρτιση. Η αξία και συνεισφορά τους στην έρευνα είναι σημαντική καθώς τα προσδοκώμενα οφέλη ποικίλουν. Μερικά από αυτά είναι τα εξής :

- Καλύτερη γνώση του φαρμάκου σε χορήγηση σε ευρύ πληθυσμιακό δείγμα, σε συνθήκες πραγματικής κλινικής πρακτικής, εκτός των «ελεγχόμενων» ορίων των παρεμβατικών μελετών.
- Μικρότερο κόστος από τις παρεμβατικές κλινικές μελέτες.
- Προώθηση και υποστήριξη της επιστημονικής έρευνας
- Εντοπισμός σπάνιων ανεπιθύμητων αντιδράσεων ή αλληλεπιδράσεων με άλλα σκευάσματα.
- Αναγνώριση υποδιαγνωσμένων νοσημάτων.
- Η προσθήκη νέων δεδομένων για το προϊόν, τα οποία πιθανόν να οδηγήσουν στη διερεύνηση νέων ενδείξεων.
- Δυνατότητα συσχέτισης με "πολιτιστικούς", "κοινωνικούς" παράγοντες και εντοπισμός διαφορών μεταξύ ομάδων πληθυσμού.
- Δημιουργία μεγάλων βάσεων δεδομένων σχετικά με το φάρμακο, τη νόσο, φαρμακοοικονομικά στοιχεία.
- Μακροχρόνια αποτελέσματα ασφάλειας.
- Μελέτη υπό-ομάδων πληθυσμού.
- Συγκέντρωση δεδομένων για την εμφάνιση, τη διασπορά και μετάδοση μίας νόσου στον άνθρωπο.
- Συγκέντρωση δεδομένων για την εξέλιξη διαφόρων νοσημάτων, καθώς και για την πρόληψή τους μέσω κατάλληλων θεραπευτικών παρεμβάσεων.
- Συγκέντρωση δεδομένων για την ποιότητα ζωής των ασθενών.
- Συγκέντρωση δεδομένων της συμμόρφωσης των ασθενών ως προς την συνταγογραφούμενη θεραπευτική αγωγή.

ΕΙΔΗ ΜΗ ΠΑΡΕΜΒΑΤΙΚΩΝ ΜΕΛΕΤΩΝ

1. ΜΕΛΕΤΕΣ PASS
Post-Authorization Safety Studies

Σύμφωνα με την οδηγία 2001/83/EC (DIR) Art 1(15) ως μελέτη PASS (Μη Παρεμβατική Μετεγκριτική Μελέτη Ασφάλειας ή Αποτελεσματικότητας) ορίζεται η μελέτη η οποία διεξάγεται με σκοπό την ανακάλυψη, το χαρακτηρισμό και την εκτίμηση του κινδύνου ασφαλείας ενός θεραπευτικού σκευάσματος, επιβεβαιώνοντας το επίπεδο ασφαλείας του, ή το επικαιροποιημένο Σχέδιο Διαχείρισης Κινδύνου ή μετρώντας την αποτελεσματικότητά του. Στην Ελλάδα, για τον ΕΟΦ αποδεκτές για κατάθεση και έγκριση είναι μόνο οι Μετεγκριτικές Μελέτες Ασφάλειας σύμφωνα με την εγκύκλιο 82798 της 22/11/2012.

2. ΣΥΓΚΡΙΤΙΚΕΣ ΜΕΛΕΤΕΣ ΠΑΡΑΤΗΡΗΣΗΣ
Comparative Observational Studies

Οι παραδοσιακές επιδημιολογικές μέθοδοι είναι το στοιχείο κλειδί στην αξιολόγηση των ανεπιθύμητων ενεργειών. Υπάρχει μια σειρά από μελέτες

παρατήρησης που είναι χρήσιμες στην επικύρωση συμβάντων από άμεσες αναφορές και σειρές περιστατικών. Σημαντικές μελέτες αυτής της κατηγορίας είναι οι συγχρονικές μελέτες (cross-sectional studies), οι μελέτες ασθενών-μαρτύρων (case-control studies) και οι μελέτες cohort (αναδρομικές και προοπτικές).

- **ΣΥΓΧΡΟΝΙΚΕΣ ΜΕΛΕΤΕΣ (ή ΔΙΑΣΤΑΥΡΟΥΜΕΝΕΣ ΣΕ ΤΟΜΕΙΣ) Cross-sectional (survey) Studies**

Εξετάζεται είτε ένα τυχαίο δείγμα ή το σύνολο των υποκειμένων σε ένα καλά καθορισμένο υπό μελέτη πληθυσμό προκειμένου να ληφθεί απάντηση σε ένα συγκεκριμένο κλινικό ερώτημα. Τα δεδομένα συλλέγονται από έναν πληθυσμό ασθενών σε ένα συγκεκριμένο χρονικό σημείο (ή χρονικό διάστημα), ανεξάρτητα από την έκθεση στο φάρμακο ή την κατάσταση της νόσου. Αυτός ο τύπος των μελετών χρησιμοποιείται κατά προτίμηση για να εξετασθεί η επικράτηση μιας ασθένειας σε ένα χρονικό σημείο ή για να εξετασθούν οι τάσεις με την πάροδο του χρόνου, όταν μπορούν να συλλεχθούν δεδομένα για μια σειρά χρονικών σημείων. Τέτοιου είδους μελέτες μπορούν επίσης να χρησιμοποιηθούν για να εξετασθεί η πρωταρχική σχέση μεταξύ της έκθεσης και της έκβασης σε συγκεκριμένους πληθυσμούς. Μείζον μειονέκτημα των μελετών αυτών είναι ότι η χρονική σχέση μεταξύ της έκθεσης και των αποτελεσμάτων. Πολλές φορές δεν είναι δυνατόν να εντοπισθεί άμεσα η σχέση, γεγονός που περιορίζει τη χρήση τους για αιτιολογικές έρευνες εκτός και αν τα ευρήματα δε μεταβάλλονται με την πάροδο του χρόνου.

- **ΜΕΛΕΤΕΣ CASE CONTROL**

Αποτελούν συγκριτικές κλινικές μελέτες χωρίς τυχαιοποίηση, οι οποίες μοιάζουν με τις προοπτικές και αναδρομικές έρευνες της επαγωγικής επιδημιολογίας με τη διαφορά ότι στη θέση του αιτιολογικού παράγοντα υπάρχει το θεραπευτικό μέτρο και στη θέση του νοσολογικού αποτελέσματος το θεραπευτικό αποτέλεσμα (ίαση, βελτίωση, έκβαση κλπ). Οι μελέτες αυτές διεξάγονται συνήθως αναδρομικώς και επιδιώκουν να καθορίσουν τις διαφορές των υποπληθυσμών. Οι ασθενείς με μια συγκεκριμένη νόσο ή κατάσταση επιλέγονται και συγκεντρώνονται σε μια ομάδα ελέγχου. Παράλληλα επιλέγεται και μια παρόμοια ομάδα, η οποία δε φέρει τη νόσο (controls). Κατόπιν, οι περιπτώσεις (cases) και οι μάρτυρες (controls) συγκρίνονται για πιθανούς παράγοντες κινδύνου ή παράγοντες που πιθανώς εμπλέκονται στην αιτιολογία της νόσου. Στις μελέτες αυτές είναι εξαιρετικά δύσκολη η διάκριση και εξουδετέρωση των συγχυτικών παραγόντων καθώς συχνά παρατηρείται άνιση κατανομή των περιπτώσεων μέσα στην ομάδα ελέγχου, εφόσον τα υποκείμενα δεν πληρούν συγκεκριμένα διαγνωστικά κριτήρια που ορίζονται από τον ερευνητή.

- **ΜΕΛΕΤΕΣ COHORT**

Οι μελέτες Cohort αποτελούν διαχρονικές πληθυσμιακές συγκρίσεις ως προς την κλινική έκβαση σε συνάρτηση με την εφαρμογή ή όχι ενός θεραπευτικού μέτρου. Επειδή οι διαχρονικές εξελίξεις ενός περιστατικού εξαρτώνται από πολλούς παράγοντες, τα ευρήματα αυτών των μελετών μπορούν να αξιολογηθούν μόνον όταν η αποτελεσματικότητα της εξεταζόμενης μεθόδου είναι πολύ μεγάλη. Οι μελέτες Cohort περιλαμβάνουν την επιλογή δύο ή περισσότερων ομάδων και προοπτική παρακολούθησή τους επί σειρά ετών. Οι ομάδες επιλέγονται με βάση τις διαφορές στην έκθεσή τους σε ένα συγκεκριμένο παράγοντα και οι ασθενείς παρακολουθούνται μέχρι να διαπιστωθεί ποιος αναπτύσσει την πιθανή ασθένεια. Η επιλογή μιας συγκρίσιμης ομάδας είναι ένα από τα πιο δύσκολα σημεία των μελετών αυτών. Συχνά γίνονται πολύπλοκες στατιστικές προσαρμογές στο στάδιο ανάλυσης, προκειμένου να διορθωθούν διαφορές μεταξύ των δύο ομάδων κατά την έναρξη. Ο πληθυσμός

σε κίνδυνο για την εμφάνιση ενός συμβάντος παρακολουθείται σε βάθος χρόνου για την καταγραφή και ανάλυση του συμβάντος αυτού. Πληροφορίες σχετικά με την κατάσταση έκθεσης γνωστοποιούνται καθ' όλη την περίοδο παρακολούθησης για κάθε ασθενή.

Στις προοπτικές μελέτες Cohort πρόβλημα αποτελεί το γεγονός ότι συνήθως απαιτούνται αρκετά έτη παρακολούθησης, έτσι ώστε να είναι δυνατή η εξαγωγή ασφαλών συμπερασμάτων, με αποτέλεσμα να αυξάνεται σημαντικά το κόστος διεξαγωγής. Οι αναδρομικές μελέτες Cohort μπορούν να μειώσουν σημαντικά τόσο το χρονικό διάστημα όσο και το κόστος διεξαγωγής, αλλά δεν είναι πάντοτε εφικτή η πραγματοποίησή τους. Οι μελέτες cohort αποτελούν τις πλέον κατάλληλες, μη παρεμβατικές μελέτες στην αιτιογνωστική επιδημιολογία για τη διερεύνηση της ύπαρξης σχέσης μεταξύ προσδιοριστών και συχνότητας εμφάνισης των παθήσεων. Μεγάλο πλεονέκτημα των μελετών cohort είναι το γεγονός ότι μπορούν να υπολογιστούν απ' ευθείας τα μέτρα συχνότητας των εκβάσεων στα εκτεθειμένα και τα μη εκτεθειμένα άτομα. Επισημαίνεται όμως ότι οι μελέτες Cohort θα πρέπει να διεξάγονται εφ' όσον υπάρχουν ενδείξεις από άλλα είδη μελετών (Case-Control Studies) ότι υπάρχει σχέση μεταξύ ενός προσδιοριστή και μιας έκβασης.

3. CASE-SURVEILLANCE STUDIES

Σκοπός της έρευνας αυτής είναι να μελετήσει τους ασθενείς με συγκεκριμένες παθήσεις, όπου σε ορισμένες περιπτώσεις είναι πιθανό να σχετίζονται με το προϊόν και να εξακριβώσει την έκθεση στο προϊόν αυτό. Αποτελεί μελέτη απλής κλινικής παρακολούθησης χωρίς συγκριτικό δείγμα, γεγονός που αποτελεί σημαντικό μειονέκτημα καθώς η απουσία συγκριτικής ομάδος μπορεί να έχει ως συνέπεια να αποδοθεί στο υπό εξέταση γεγονός/συμβάν μέτρο μια κλινική δράση (π.χ. βελτίωση) που θα εμφανιζόταν στο πλαίσιο της φυσικής εξέλιξης της νόσου ή που σχετίζεται με γνωστούς/άγνωστους παράγοντες οι οποίοι δημιουργούν σημαντική μεταβλητότητα και ασάφεια στην πρόγνωση. Η κύρια μεθοδολογική ανησυχία στις μελέτες αυτές έγκειται στην εξουδετέρωση των συγχυτικών παραγόντων (παράγοντες κινδύνου, συνοδά νοσήματα, συγχορηγούμενα φάρμακα κλπ.) πράγμα που μπορεί με τον κατάλληλο προοπτικό σχεδιασμό, την κατάλληλη επιλογή μαρτύρων, του μεγάλου δείγματος αλλά και με την πρέπουσα πολυπαραγοντική ανάλυση παλινδρόμησης να αποτελέσουν σημαντικά εργαλεία επιδημιολογικής φύσεως για την εκτίμηση της ασφάλειας των φαρμάκων.

4. ΜΕΛΕΤΕΣ REGISTRY

Ένα μητρώο ή βάση δεδομένων για τις μελέτες Registry, είναι ένας κατάλογος αρχείων ασθενών οι οποίοι εμφανίζουν τα ίδια χαρακτηριστικό/ά. Αυτό το χαρακτηριστικό μπορεί να είναι το νόσημα ή το αποτέλεσμα της νόσου (μητρώο νοσήματος-Disease Registry) ή η εξειδικευμένη έκθεση (μητρώο έκθεσης στο φάρμακο ή μητρώο φαρμάκου-Exposure or Drug Registry). Και οι δύο κατηγορίες μητρώων, οι οποίες διαφέρουν μόνο στον τύπο των στοιχείων των ασθενών που παρουσιάζουν ενδιαφέρον, είναι δυνατόν να οδηγήσουν στη συλλογή μιας ομάδας πληροφοριών με τη χρήση τυποποιημένων ερωτηματολογίων σε μακροπρόθεσμο πλαίσιο.

5. OUTCOME STUDIES

Είναι οι μελέτες που αξιολογούν δοσολογικά σχήματα, διαφόρους τρόπους χορήγησης (ακόμη και χρήση ιδιοσκευασμάτων εκτός των εγκεκριμένων ενδείξεων), μετρώντας την αποτελεσματικότητα ή το Σχέδιο Διαχείρισης Κινδύνου στην συνήθη πρακτική σε σχέση με συγκεκριμένη κατάσταση υγείας του ασθενή (Health Outcome).

6. DRUG UTILIZATON STUDIES (DUS)

Οι μελέτες DUS περιγράφουν τον τρόπο με τον οποίο ένα φαρμακευτικό προϊόν εισέρχεται στην αγορά, συνταγογραφείται και χορηγείται σε έναν πληθυσμό, και πώς οι παράγοντες αυτοί επηρεάζουν τα αποτελέσματα, συμπεριλαμβανομένων των κλινικών, κοινωνικών και οικονομικών αποτελεσμάτων. Μελέτες αυτής της κατηγορίας παρέχουν στοιχεία για συγκεκριμένες πληθυσμιακές ομάδες, όπως οι ηλικιωμένοι, τα παιδιά, οι ασθενείς με ηπατική ή νεφρική δυσλειτουργία, οι οποίοι συχνά κατηγοριοποιούνται κατά ηλικία, φύλο, παράλληλη φαρμακευτική αγωγή καθώς επίσης και άλλα παρόμοια χαρακτηριστικά.

ΠΡΟΔΙΑΓΡΑΦΕΣ ΚΑΙ ΕΓΚΡΙΤΙΚΕΣ ΔΙΑΔΙΚΑΣΙΕΣ ΕΥΡΩΠΑΙΚΩΝ ΚΡΑΤΩΝ ΣΤΙΣ ΜΗ ΠΑΡΕΜΒΑΤΙΚΕΣ ΜΕΛΕΤΕΣ

Ο σχεδιασμός, η διεξαγωγή και η αξιολόγηση των αποτελεσμάτων των κλινικών μελετών στον άνθρωπο, διέπεται από ένα σύνολο ηθικών, μεθοδολογικών και επιστημονικών προδιαγραφών που περιγράφονται ως ICH/GCP (International Conference of Harmonization / Good Clinical Practice). Ως ορθή κλινική πρακτική νοείται ένα σύνολο διεθνώς αναγνωρισμένων ποιοτικών απαιτήσεων δεοντολογικού και επιστημονικού χαρακτήρα, που πρέπει να τηρούνται κατά το σχεδιασμό, τη διεξαγωγή, την καταγραφή των δεδομένων και τη δημοσιοποίηση των αποτελεσμάτων των κλινικών μελετών στις οποίες συμμετέχουν άνθρωποι. Η τήρηση της ορθής κλινικής πρακτικής εξασφαλίζει την προστασία των δικαιωμάτων, της ασφάλειας και της ακεραιότητας των υποκειμένων, καθώς και την αξιοπιστία των αποτελεσμάτων των μελετών. Εκτός των οδηγιών της Ορθής Κλινικής Πρακτικής (GCP) έχουν εκδοθεί και κατευθυντήριες οδηγίες όσον αφορά τον σχεδιασμό και εκτέλεση των μη παρεμβατικών κλινικών μελετών και ειδικότερα των PASS μελετών με τους κανόνες της Ορθής Πρακτικής Φαρμακοεπαγρύπνησης (GVP) και συγκεκριμένα στο Module VIII και Module VIII-Appendix 1 της οδηγίας EMA/813938/2011 Rev 1.

Στα πλαίσια της νομοθεσίας αυτής εμπίπτουν και η βάση δεδομένων Eudravigilance για την Φαρμακοεπαγρύπνηση στον Ευρωπαϊκό Οργανι-σμό Φαρμάκων. Αποτέλεσμα της εφαρμογής αυτής της βάσης δεδομένων είναι να υπάρχει απόλυτη διαφάνεια ως προς την διεξαγωγή των μελετών καθώς και έλεγχος των στοιχείων που δημοσιεύονται και προκύπτουν από τις μελέτες PASS. Η Ευρωπαϊκή Ένωση απαιτεί μια αποτελεσματικότερη ανάλυση των δεδομένων ασφάλειας από αυτή που συνέβαινε πριν από την εφαρμογή της οδηγίας. Σκοπός αυτής της λεπτομερειακής απαίτησης αναφοράς των ανεπιθύμητων ενεργειών είναι η όσο το δυνατόν καλύτερη καταγραφή του προφίλ ανεπιθύμητων ενεργειών των φαρμάκων μετά την εισαγωγή τους στην κλινική χρήση.

Πίνακας 1. National Authorities

	BE	CZ	FR	GER	AUS	BG	CYP	DNK	IT	SP	NL	UK	SL	EST	LITH	HUN	TUR
EC approval	?	X	?	X	?	√	X	?	√	√	X	X	√	X	√	X	√
CA Notification	X	√	X	√	X	X	√	√	X	X	X	X	√	X	X	X	X
CA Approval	X	X	X	X	X	√	X	X	√	√	√	√	X	X	X	X	√
NEC Fav. Opinion	√	?	X	√	?	√	√	X	X	X	√	√	X	√	√	√	X

Μη Παρεμβατικές Μελέτες (Non-Interventional Studies - NIS) Προδιαγραφές Ευρωπαϊκών Κρατών

Στον πίνακα που παρατίθεται παραπάνω αναφέρονται οι εγκριτικές διαδικασίες οι οποίες εφαρμόζονται στα διάφορα κράτη-μέλη της Ευρωπαϊκής Ένωσης (και όχι μόνον) σχετικά με τη διεξαγωγή των μη παρεμβατικών κλινικών μελετών[1].

Οι μη παρεμβατικές κλινικές μελέτες στην Ευρώπη, θα πρέπει να κατατίθενται προς ενημέρωση η προς έγκριση είτε στις Επιτροπές Δεοντολογίας ή στις Ρυθμιστικές Αρχές ανάλογα με το κράτος. Ο ερευνητής θα πρέπει να συμμορφώνεται με τη νομοθεσία περί προστασίας των προσωπικών δεδομένων . Το έντυπο πληροφόρησης του ασθενή θα πρέπει να είναι σε θέση να παρέχει λεπτομερή περιγραφή των δεδομένων που αναμένονται να συλλεχθούν από τους ερευνητές.

Τα αποτελέσματα της μελέτης και οι ανακοινώσεις, αναφορές, δοκίμια και οι πιθανές επιστημονικές παρουσιάσεις θα πρέπει να υποβληθούν στις αντίστοιχες αρχές μέσα σε εύλογο χρονικό διάστημα. Ο κάτοχος της άδειας κυκλοφορίας του σκευάσματος υποχρεούται να αποστείλει περίληψη των αποτελεσμάτων της μελέτης σε όλους τους ερευνητές που συμμετείχαν σε αυτή. Η μελέτη σε καμία περίπτωση δε θα πρέπει να αποτελέσει κίνητρο για την προώθηση ή τη συνταγογράφηση ενός συγκεκριμένου φαρμάκου.

Πίνακας 2. EU Regulatory Status Table

	GER	FR	CZ	IT	TUR	BE	BG	NL	ROM
BfArM (CA) The Federal Institute for Drugs and Medical Devices	X								
Federal Panel Doctors' Association	X								
Central Federal Association	X								
CCTIRS (Ministry of Higher Education and Research)		X							
CNIL (National Commission on Informatics and Liberties)		X							
CNOM (National College of Physicians)		X							
Pharmaceutical Industry Self Regulating Body			X						
AIFA (Italian Drug Agency)				X					
Ethics Committees				X	X			X	
MoH (Ministry of Health)					X				
Pharma.be						X			
Bulgarian Drug Agency (BDA)							X		
Competent Authority (CA)								X	
NDA									X
NEC									X

Στον παραπάνω πίνακα φαίνονται οι Κανονιστικές Διατάξεις οι οποίες ισχύουν σε κράτη-μέλη της Ευρωπαϊκής Ένωσης σχετικά με τις εγκρίσεις και τα

1. EC: Ethics Committee – Επιτροπή Δεοντολογίας
CA: Competent Authority – Αρμόδια (Ρυθμιστική) Αρχή
NEC: Fav. Opinion : Θετική Γνωμοδότηση Εθνικής Επιτροπής Δεοντολογίας.

νομικά καθεστώτα που διέπουν τη διαδικασία πραγματοποίησης μιας μη παρεμβατικής κλινικής μελέτης. Ενδεικτικά αναφέρεται ότι στη Γαλλία η μελέτη θα πρέπει να εγκριθεί από το Υπουργείο Ανώτατης Εκπαίδευσης και Έρευνας (CCTIRS), από την Εθνική Επιτροπή Πληροφορικής και Ελευθεριών (CNIL) και να λάβει θετική γνωμοδότηση από τον Εθνικό Ιατρικό Σύλλογο (CNOM). Τα ανεπιθύμητα συμβάντα τα οποία καταγράφονται σε μη παρεμβατικές μελέτες για τα σκευάσματα που χρησιμοποιούνται σε αυτές θα πρέπει να αναφέρονται στις Υπηρεσίες Φαρμακοεπαγρύπνησης εκάστης χώρας και να καταγράφονται στο Eudravigilance.

Στη Γερμανία παράλληλα με τη γνωστοποίηση στην Αρμόδια Ρυθμιστική Αρχή, ο χορηγός της μελέτης θα πρέπει να τη γνωστοποιήσει στον Ιατρικό Σύλλογο και στο φορέα της Δημόσιας Ασφάλισης Υγείας. Πληροφορίες σχετικά με τη σχεδιαζόμενη μελέτη πρέπει να εισαχθούν σε δημόσια προσβάσιμο μητρώο εντός 21 ημερών από την έναρξή της. Η εταιρεία θα πρέπει να κοινοποιήσει περίληψη των αποτελεσμάτων σε όλους τους επαγγελματίες υγείας που συμμετείχαν στη μελέτη εντός 12 μηνών από την ολοκλήρωσή της (τελευταίο ασθενή/τελευταία επίσκεψη). Η περίληψη των αποτελεσμάτων της μελέτης θα πρέπει να δημοσιοποιείται το αργότερο 12 μήνες μετά την ολοκλήρωση (π.χ. μέσω του Διαδικτύου).

ΣΥΖΗΤΗΣΗ

Στην Ελλάδα οι Κανονιστικές Διατάξεις και η τήρησή τους, όπως ορίζονται από τη Διεθνή Διακήρυξη του Helsinki, την Ευρωπαϊκή Νομοθεσία 2001/20EC και την Ελληνική Νομοθεσία (ΦΕΚ 1973/30-12-2003 και ΦΕΚ 886Β'/20-12-84, Υπ. Απόφαση Α6/10983/1984) για τη διεξαγωγή κλινικών δοκιμών φαρμάκων και την προστασία του ανθρώπου αποτελούν κοινή υποχρέωση ερευνητών, χορηγών, επιτροπών Ηθικής και Δεοντολογίας και Αρχών Υγείας και Φαρμάκων. Συγκεκριμένα οι ευθύνες των ιατρών ερευνητών καθορίζονται από τον Κώδικα Ιατρικής Δεοντολογίας ΦΕΚ 287/2005 Άρθρο 25 και την Νομοθεσία του Εθνικού Συστήματος Υγείας καθώς και τη Φαρμακευτική Νομοθεσία ΦΕΚ 59 24/01/2006. Παράλληλα οι ευθύνες των χορηγών και των Εθνικών Αρχών καθορίζονται από τη Φαρμακευτική Νομοθεσία αλλά και την ειδική νομοθεσία περί κλινικών μελετών. Σύμφωνα με το άρθρο 7 της Υπ. Απόφασης Α6/10983/1984 η κλινική δοκιμή μπορεί να διεξαχθεί μόνο μετά από τη χορήγηση σχετικής άδειας από τον ΕΟΦ, εκτός αν πρόκειται για φάρμακα, για τα οποία έχει ήδη χορηγηθεί άδεια κυκλοφορίας και τα φάρμακα αυτά δεν προορίζονται να ελεγχθούν σε νέες ενδείξεις ή σε νέα υψηλότερη δοσολόγηση ή σε παρατεταμένη χορήγηση σε μεγάλο αριθμό αρρώστων ή αν η κλινική δοκιμή δεν αποσκοπεί στην έρευνα ανεπιθύμητων ενεργειών.

Οι μη παρεμβατικές μελέτες οι οποίες δεν εμπίπτουν στην κατηγορία των μελετών PASS κατατίθενται προς έγκριση/ενημέρωση στις Επιστημονικές Επιτροπές των νοσοκομείων οι οποίες εγκρίνουν την διεξαγωγή τους από τον συντονιστή ερευνητή, το κέντρο του οποίου συνεργάζεται/συντονίζει από κανένα έως 15 ιδιώτες ιατρούς συνήθως. Αυτή η διαδικασία δεν υποστηρίζεται νομοθετικά, αλλά αποτελεί εθιμική εφαρμογή του προηγούμενου καθεστώτος κατά το οποίον ο ΕΟΦ ενέκρινε όλες τις μη παρεμβατικές μελέτες.

Σημαντικοί περιορισμοί της ορθής εγκριτικής διαδικασίας των μη παρεμβατικών μελετών στην Ελλάδα είναι οι ακόλουθοι:

1. Οι Επιστημονικές Επιτροπές των νοσοκομείων δεν πληρούν τις προϋποθέσεις των Επιτροπών Δεοντολογίας.
2. Δεν είναι δυνατόν να πραγματοποιηθούν μη παρεμβατικές μελέτες σε ιδιώτες ιατρούς μόνον.
3. Οι διάφοροι διοργανωτές των μη παρεμβατικών μελετών (εκτός των

PASS) ερμηνεύουν την υφιστάμενη νομοθεσία κατά το δοκούν, με αποτέλεσμα άλλοι να χρησιμοποιούν την παλαιά διαδικασία των συντονιστικών κέντρων και άλλοι ουδεμία διαδικασία έγκρισης/γνωστοποίησης.

ΣΥΜΠΕΡΑΣΜΑ

Εκ των ανωτέρω τεκμαίρεται ότι η συμπλήρωση της υφιστάμενης νομοθεσίας στην Ελλάδα όσον αφορά την έγκριση, γνωστοποίηση, διεξαγωγή και ανακοίνωση των αποτελεσμάτων των μη παρεμβατικών μελετών είναι επιτακτική.

ΕΥΧΑΡΙΣΤΗΡΙΑ

Τέλος θα ήθελα να ευχαριστήσω όλους όσους βοήθησαν στην συγγραφή αυτού του άρθρου, την Πρόεδρο της ΕΛΕΦΙ την κα Αικατερίνη ΠΑΠΑΘΩΜΑ, την κα Βαρβάρα ΜΠΑΡΟΥΤΣΟΥ για τα είδη των μη παρεμβατικών μελετών, την κα Τίνα ΑΝΤΑΧΟΠΟΥΛΟΥ για την παρουσίαση του υφιστάμενου νομοθετικού πλαισίου για τις μη παρεμβατικές μελέτες, την κα Ιωάννα ΚΟΥΚΛΗ για τους σκοπούς των μη παρεμβατικών μελετών, την κα Δέσποινα ΚΩΝΣΤΑΝΤΑΚΗ και τον κο Παναγιώτη ΜΠΕΡΕΤΣΟ για τη έρευνα των εγκριτικών διαδικασιών στα Ευρωπαϊκά κράτη και τέλος την κα Kamila NOVAK για την έρευνά της στο διαδίκτυο και την συλλογή της βιβλιογραφίας.

Λέξεις Κλειδιά :

μη παρεμβατική κλινική μελέτη, αναδρομικές, προοπτικές, αξία, σκοπός, προδιαγραφές

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Και το όνομα αυτού Δήλον!

Αντώνης Κυριακάκης,
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AbbVie
Τίνα Ανταχοπούλου,
Medical Director, AbbVie

Ξεκινά επιτέλους η πιλοτική φάση χρήσης του νέου Μητρώου Καταγραφής Μη Παρεμβατικών Μελετών του ΣΦΕΕ. Σε ανοιχτή συνάντηση που έγινε στο αμφιθέατρο του Αμερικανικού Κολλεγίου Deree, στις 19 Ιουνίου 2013, παρουσιάστηκε η σχεδόν οριστικοποιημένη πλατφόρμα του Μητρώου Καταγραφής, το όνομα του οποίου είναι «*Δήλον*».

Όπως φαίνεται και από το όνομά του (Δήλον: το φανερό, το εμφανές), με το Μητρώο αυτό ο ΣΦΕΕ φιλοδοξεί να αποδείξει και στην πράξη τη δέσμευση όλων μας για διαφάνεια και στον τομέα διεξαγωγής των Μη Παρεμβατικών Κλινικών Μελετών. Σε μια εποχή που η επιχειρηματικότητα και οι ιδιωτικές πρωτοβουλίες, στην συνείδηση των πολλών, ταυτίζονται με την προσοδοθηρία, που η έρευνα με προϊόντα που κυκλοφορούν ή ακόμα και χωρίς προϊόντα (π.χ. επιδημιολογικές μελέτες) θεωρείται προωθητική ενέργεια, και τα δημοσιεύματα για αδιαφανείς διαδικασίες, πειράματα εις βάρος των ασθενών και οι συναλλαγές κάτω από το τραπέζι σημειώνουν εξάρσεις και υφέσεις, η ανάγκη για καταγραφή και αποτύπωση από την πλευρά της Φαρμακευτικής Βιομηχανίας καθίσταται αδήριτη. Αυτή την ανάγκη έρχεται να καλύψει το Μητρώο, τόσο ως μια προσπάθεια αυτορρύθμισης, όπως αυτή άλλωστε προβάλλεται ξεκάθαρα και στον ανανεωμένο Κώδικα Δεοντολογίας για την Προώθηση των Συνταγογραφούμενων Φαρμάκων, όσο και ως μια προσπάθεια καταγραφής της δραστηριότητας και προσφοράς της Φαρμακευτικής Βιομηχανίας στην έρευνα σε περίοδο οικονομικής ύφεσης στη χώρα μας.

Γι' αυτό, επιβάλλεται όλοι μας να ξεπεράσουμε τους αρχικούς μας δισταγμούς και να αγκαλιάσουμε την προσπάθεια αυτή του ΣΦΕΕ, συνεισφέροντας στην επιτυχία του Μητρώου και συμβάλλοντας στην επιπλέον απομόνωση των κακών πρακτικών, που ενδεχομένως μεν εφαρμόζονταν από μικρή μερίδα του χώρου μας, δημιουργούν όμως δυσανάλογα μεγάλη αρνητική επίπτωση.

Ποια θα είναι η διαδικασία;

Προβλέπεται να γίνεται καταχώρηση κάθε μη παρεμβατικής μελέτης που διεξάγεται στη χώρα, με φάρμακο ή χωρίς, προοπτική ή αναδρομική, διεθνής ή τοπική. Κάθε μελέτη που δεν είναι παρεμβατική, όποιο σχεδιασμό και αν έχει, πρέπει να καταγραφεί στο Μητρώο. Η πιλοτική φάση χρήσης του θα διαρκέσει μέχρι το τέλος του χρόνου, δίνοντας αρκετό χρόνο για να διαπιστωθούν τυχόν δυσλειτουργίες ή παραλείψεις, αλλά και για να γίνουν προτάσεις βελτίωσης, ενώ η κύρια φάση χρήσης του Μητρώου θα ξεκινήσει από 1η Ιανουαρίου 2014. Η προσπάθεια που έγινε για την κατανάλωση του ελάχιστου δυνατού χρόνου από τους χρήστες, μάλλον απέδωσε καρπούς, δεδομένου ότι πρόκειται για μια αρκετά απλή και εύχρηστη πλατφόρμα με ομαδοποιημένα πεδία. Το μόνο που τελικά ζητείται, από όλους εμάς που ασχολούμαστε με τις κλινικές μελέτες, εκτός της πίστης στον επιστημονικό σκοπό που εξυπηρετούν οι μη παρεμβατικές μελέτες, είναι η προσήλωση στη διαφάνεια που υπηρετεί το *Δήλον* και, βεβαίως, υπομονή για να ξεπεραστούν οι πρώτες δυσκολίες.

Evolution of Market Access in Greece under austerity measures and thresholds on healthcare and pharmaceutical spending*

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Preface

This paper describes and attempts to evaluate pharmaceutical policies in Greece in relation to Market Access of medicinal products under austerity measures and thresholds on healthcare and pharmaceutical spending.

The paper reports the policies implemented in Greece to control the rational use of medicinal products and corresponding public expenditure.

There is a bundle of pricing and reimbursement policies as well as prescribing guidelines, directed at pharmaceutical Industry, health care providers and patients that have been put in place to establish considerable savings of public pharmaceutical expenditure.

Given the fiscal impact of the unprecedented economic and financial crisis and the existing high healthcare expenditure in Greece these policies were of great interest to TROIKA and the public healthcare payers.

1. Introduction

Greece is confronted with severe fiscal problems due to high public debt and deficit that necessitated financial assistance from IMF, EU and ECB – the so called Troika.

The major challenge is to reduce public sector expenditure with the health care expenditure being a significant portion of this target.

Health care expenditure in Greece accounted for a considerable part of GDP -10,6% and contribution of pharmaceutical expenditure was estimated to be at the level of 24,8% of total expenditure with its public share mounting to 79%.(2007 figures) [1,2]

Reduction of healthcare expenditure is targeted through remarkable cost cutting and health care system modernization aiming at increasing efficiencies and preventing adverse health outcomes.

The Government pursues to implement the comprehensive health sector reform with the objective of stabilizing public health expenditure at, or below 6% of GDP, while declaring that Ministry of Health is maintaining universal access without major compromises on the quality of care delivery. Policy measures include reducing the fragmented governance structure, reinforcing and integrating the primary healthcare network, streamlining the hospital network, strengthening central procurement and developing a strong monitoring and assessment capability and e-health capacity. However the expedited pace of change and resistance to the immense pressure put on the health care system and providers along with deficiencies and gaps in the new policies and measures create critical patient access inequality issues to health care services and medicinal products.[3]

The program measures aim at achieving savings in the purchasing (accrual basis) of outpatient medicines of about 1 billion Euros in 2012 compared to 2011 and to reach spending of about 2.440 billion Euros in 2013 (accrual

* Summary of the discussions at SFEE MD Committee Market Access Forum Seminar at American College of Greece February 2013

basis). The goal is to bring public spending on outpatient pharmaceuticals to about 1 percent of GDP i.e. around 2 billion Euros (in line with the EU average) in 2014. Total (outpatient plus inpatient) public expenditure on pharmaceuticals should be no more than 1.5 per cent in 2013 and 1.3 per cent in 2014.[3]

This paper focuses on the impact of recent policy changes in pharmaceutical market access in Greece as part of austerity measures applied since the beginning of 2010.

Furthermore will attempt to examine the consequences of application of GDP threshold to health and pharmaceutical expenditure in Greece.

2. Public Pharmaceutical spending in EU and Greece – Evolution and current status

In the 5 year period preceding 2008 financial crisis total pharmaceutical expenditure in Greece nearly doubled from 4.329 billion euros in 2004 to 7.788 billion euros in 2008. Spending on outpatient public pharmaceutical expenditure increased from 2,4 billion in 2004 to 4,53 billion in 2008 and reached 5,1 billion euros in 2009. [4]

Per capita public pharmaceutical expenditure in Greece in 2008 reached almost 700 euros, repre-

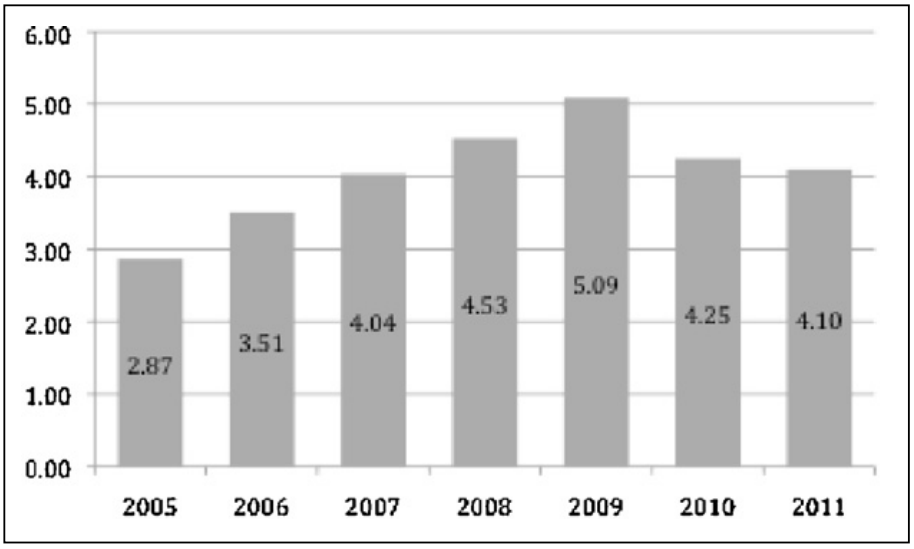

Figure 1:

Annual pharmaceutical expenditure of the Greek Public Health Insurance Funds, 2005–2011 (billion Euros).

Source: Final Report of IOBE Nov 2011& Data from the General Secretariat of Social Insurance Febr 2012.

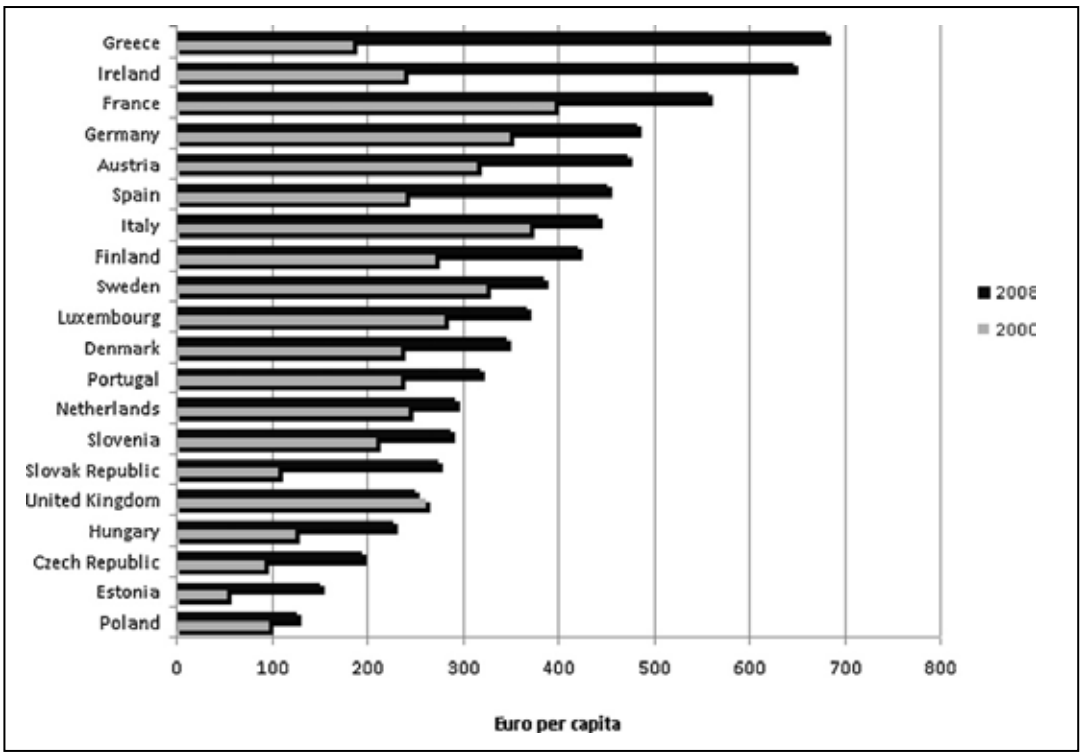

Figure 2:

Per capita public pharmaceutical expenditure in the EU. Source: Kanavos P, Vandoros S, Nicod E, Irwin R, Casson M. European Parliament

Report: differences in costs of and access to pharmaceutical products in the EU.

Brussels: Policy Department, Economic and Scientific Committee A DG Internal Policies;2011.

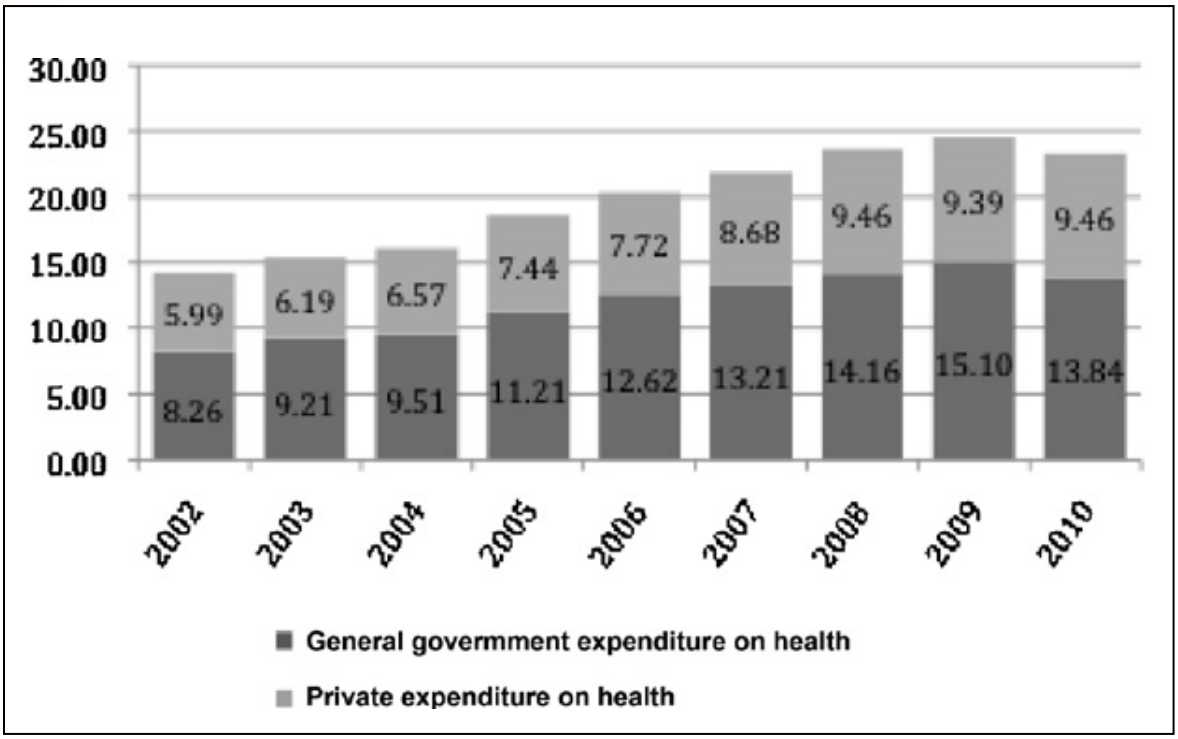

Figure 3:

Annual public and private expenditure on health in Greece, 2002–2010 (billion Euros).

Source: S. Vandoros, T. Stargardt, from the WHO Global Health Expenditure Database; 2012.S.

senting the highest among EU countries in 2008 according to OECD data (figure 1).

The high per capita pharmaceutical expenditure can be attributed to lack of cost containment measures, mainly abolishment of the positive reimbursement list in 2006 and lack of Health Technology Assessment (HTA) as well as several other reasons including [5]

1. OTC medication reimbursement, if prescribed as concomitant treatment
2. High prescription volumes due to lack of prescribing monitoring systems and audits
3. Lack of generic prescription policies
4. Relatively high generic prices - maximum at 80% of originator price, as a national strategy to support national pharmaceutical generic manufacturers
5. Originators prices were calculated at the average of 3 lower European price. Repricing was made only once per year till end 2009 for the first 4 years after marketing.
6. Prescribing behavior related to easiness of prescribing for minor ailments, excess pharmaceutical influence on prescribing choices for originals or generics,
7. Substitution of older cheaper drugs by newer more expensive ones due to high pharmacy and wholesaler profits and a large number of pharmacies (11.500) and wholesalers (130)
8. Prescribing by brand name only –no substitution at the pharmacy level
9. Corruption has also contributed to high outpatient pharmaceutical spending. There are claims about physicians incentivized to unnecessary prescribing of particular medicines. There were cases of abusive prescribing detected and reported by General Inspector of Public Administration because of ministry of vignets authenticity stickers.
10. Decision making of Ministry of Health did not apply health care system monitoring for efficiencies and poor management allowed waste of resources.

11. Health Care System fragmentation with great inefficiencies in resources allocation and effectiveness, inducing non rational use of services and non control of funds and expenditure.
12. Lack of primary health care service within National health Care system(NHS) with free access to specialty physicians and tertiary care NHS settings
13. High number of physicians on private sector ,contracted by Social Insurance creating high false demand for services
14. Tax evasion and Social Insurance evasion due to lack of monitoring systems to ensure proper collection , legitimate registration of workers and overall compliance
15. Low cost sensitivity among citizens, patients, health care providers and political leadership may be associated with the ethos of securing their individual interest and not being concerned for the common good and future sustainability of the NHS.
16. Something about the large number of emigrants and the surcharge upon the Social Security Institute due to social politics.

3. Understanding variation and comparison in expenditure as per cent of GDP

The fundamental question is if it is appropriate to implement austerity measures in crisis countries , by imposing thresholds on healthcare and pharmaceutical expenditure as a percentage of GDP and particularly in Greece, where GDP contracts continuously over 5 years and has reached almost a total of minus 25% (-10% in 2011 and -13 % in 2012).[6]

From a theoretical perspective, it might be hypothesized that there is a linear relationship between pharmaceutical spending and per capita income but there is no reason to expect that it should be a fixed percent of GDP across countries and over the years.

As pharmaceutical sector is subject to fluctuations in terms of innovation output this may bring peaks and troughs in prices, number of patients on innovative treatments and spending consequently.

Moreover healthcare policies and healthcare system organization changes may also contribute to variation in GDP.

In addition differences in demographics (i.e. high elderly population size), in disease incidence, morbidity and mortality (i.e. obesity, smoking, dyslipidemia, hypertension and consequently high Cardiovascular risk &diabetes or rising incidence/prevalence of HIV), in healthcare system priorities (i.e. low importance to prevention, diagnosis and screening) in unexpected health crises (i.e. flu, cold winter, hot summer) in deep economic recession with extremely high and long unemployment (i.e. many uninsured people, very limited capacity for out of pocket patient payments) may require additional spending because of higher consumption burdens on the health care system and for securing public health of society.

In addition the comparison of pharmaceutical spending across countries is not straightforward as its includes a plethora of different elements, taxes, compulsory discounts, rebates, VAT, profits to distributors (wholesalers and retailers) plus the cost of medicines which differ significantly. [7,8]

4. Overview of the pharmaceutical reforms In Greece

Following debt crisis and the initial Memorandum of Understanding with Troika several cost containment measures have been introduced.

There were measures targeting pricing, volume of prescriptions as well as statutory changes.

PRICING	VOLUME	STATUTORY
New pricing rules	**Prescriptions' check >150€**	Hospital Discounts &Tenders
Rebates & Clawback	**Electronic prescription / handling**	EOPYY-Primary Care Setting for 9mil Greeks
Catalogue L 3816 for serious diseases treatments (highly priced)	**Negative Reimbursement List / OTC LIST**	Single Regulation for coverage of patients benefits for all SSF s
Targets for generics' use	**Off label restrictions**	Negotiations with Social Sick Funds
VAT reduction	**Therapeutic Protocols**	Closed Budgets
Reduction % of wholesalers and pharmacists' profit		Hospital Restructuring
Positive Reimbursement List		

Table 1:
Cost containment Measures

The first measure applied was the reduction of prices. According to Market Decree of April 27th 2010 the price cuts were in the range of 0-27% with a weighted average of 21,5% and they were followed by a second reduction of about 10,2 % on July 2011. [9,10]

Furthermore generics pricing cap was reduced from 80% to 70% then 63% and lately to 40 % of the originator's price before patent expiry.

It is worthwhile to mention that originator prices upon patent expiry are reduced at 50 % of their value (at first generic entry)[11]

Another important reform was related to reintroduction of the positive reimbursement list (PRL).[10]

The PRL was not incorporating HTA, neither budget impact nor cost effectiveness measures.

The PRL introduced a 4% rebate as a ticket entry fee into the PRL, which was then increased to a 9% and established as an annual rebate fee to SSF.

The PRL had established a reference price per therapeutic cluster at ATC4 level mainly with some cases on ATC5 level by including generics as well in the clusters.

According to latest PRL criteria a new drug is entered in the list based on its ATC4 cluster.

If to be subclustered at ATC 5 it needs to have either an accelerated review or

fast track review by EMA or FDA, or ATC5 clustering in Germany or ASMR 1 02 in France or NICE positive assessment& approval in UK or a specific indication that is different form the other drugs in the respective cluster. This methodology accounts cost effectiveness indirectly and only for new drugs.[13]

The PRL is not based on efficiencies but is focusing on cash flows rather on budget impact or effectiveness.

The SSF reimburse the treatments at the level or reference price and the difference to a prescribed treatment is to be paid by the patient in addition to his treatment copayment.

Copayment levels were redefined according to FEK/B'/ 1814 8-6-2012 &FEK 43/15-1-2013 and are at 25% with some diseases at 10% and very few at 0% (neoplastic diseases, hematology malignancies, Multiple Sclerosis, psychiatric disorders, Alzheimer disease)

The 3rd Memorandum of Understanding has been signed between the Greek Government and the Troica in Nov 2012. The targets for public outpatient and Hospital inpatient are:

	2012	2013	2014
Public outpatient expenditure	Target set at €2.88bn	€2.44bn or 1,2% of GDP	€2bn or 1% of GDP
Hospital inpatient expenditure	€ 760 mn	0.3% of GDP	0.3% of GDP
Total (outpatient & inpatient) expenditure	€3.640 bn	1.5% of GDP	1.3% of GDP

Table 2:

3rd Memorandum of Understanding Pharmaceutical expenditure in 2013 &2014

Financial assistance in EU Member S 26-27 November 2012 Third Review Mission to Greece available at http//.ec.europa.eu/

PRICING

A new price bulletin recosting all pharmaceuticals has been finally published on 22/10/2012 (no new products included since year 2011). The rules used for this recosting as described in various new Ministerial Decrees published are presented below:

- On-patent: Average of the 3 lowest EU countries
- Off-patent: After the verification by any appropriate method of the expiry of the 10-year or 11-year, as appropriate, protection period the wholesale prices of a reference medicinal products are reduced by 50%, without an application by the marketing authorization holder. For products with a retail price between €5 and €10, a price reduction of 5% on the retail price in force is applied, while respectively for products with a retail price lower than €5 a 3% reduction is applied.
- Generics: The wholesale prices of generic medicinal products are reduced to 40% of the latest price of the reference product under protection of the patent for products with a Retail price under 10€, a proportional price reduction applied as above. Generic products cannot have a price higher than 80% of the price of the reference products after the expiry of their protection period.
- By an application submitted at the competent service, the marketing au-

thorization holder may request a lower price, without any restriction; such lower price shall be approved immediately through a supplementary/corrective Price Bulletin

The new price bulletin, as reported by Greek Pharmaceutical Association, SFEE, had many mistakes in the calculation of the prices and there are many objections filed by companies pending to be corrected in an updated Price Bulletin in the near future.[14]

REIMBURSEMENT

On 28/09/2012 SSF- EOPYY issued a circular regarding Guidance on e-prescribing, announcing that from 01/10/2012 onwards medicinal products will be reimbursed by EOPYY at a reference price for their respective category. The new Reference prices shall be based on the cheapest marketed generic per molecule, strength and dosage form. According to the circular:

Physicians have the option, once they have determined the active substance, to prescribe by brand any of the corresponding medicinal products. If they prescribe a medicinal product with a higher price than the reference price in its category, they must notify it to the patient that, in addition to the statutory co-payment rate, he/she will be charged with the difference between the retail price of the medicinal product and the reference price. A message on the printed slip of the electronic prescription will indicate the amount of the additional cost to the insured due to the prescription of a medicine in excess of the reference price, plus the amount of the statutory patient co-payment. The pharmacist will dispense normally the prescription through the electronic system, as provided for by legislation. The withholding of the additional amount shall be effected automatically by the system, so that the pharmacist will receive from the insured the statutory co-payment plus any difference between the retail price and the reference price.

Regarding the above development, on 01/10/2012 SFEE sent a letter to the Deputy Minister of Health (and on 04/10/2012 to the President of EOPYY on the same subject) stating that the change of the prescribing system, as implemented today, will directly cause huge problems both to the operation of the pharmaceutical market and to Greek patients and highlighting a number of issues that need to be resolved:

1) To exempt from the implementation of this measure specific fragile patient groups, such as patients with mental disorders, etc (FEK 3057/B/18-11-2012.

2) Medicinal products for very serious diseases that currently have zero patients' co-payment (eg diabetes, oncology, products of Law 3816/2010) should be excluded from the expansion of this system and they should be administered to patients with zero co-payment, as it happens today.

3) A low but fair and sustainable for patients and companies reimbursement price should be introduced, which will operate as a threshold, beyond which the reimbursement price cannot be reduced

4) The uploaded list contains many errors and inaccuracies regarding the prices (eg co-marketing products) but also other kinds of errors. Therefore, the Ministry of Health should immediately allow the access of pharmaceutical companies to the system in order to proceed with the necessary corrections.

Following the publication of OJ 2912/30.10.2012 regarding the new mechanism for reimbursement, EOF on 14/11/2012 (www.eof.gr), has published on its website the positive Reimbursement List per ATC 4 including the Reference Price per cluster as well as the updated Negative List. According to the draft Ministerial Decree circulated on 15/11/2012, the new Lists shall

be effective 5 days after the publication of a corrective Price Bulletin.

However Positive Reimbursement list is on hold due to erroneous medicines prices that affect reference price and copayment.

Hospital tenders

"Unofficial " tenders per hospital rather of offer/discount sort represent a barrier to access that is not very formal & transparent .They should develop into a more formal process under the regional peripheral Health Care System (so called YPE –covering a number of Hospitals) or executed under the National Procurement Committee (so called EPY) ,as done for Medical Devices. The EPY statutory framework is not straightforward and many tenders fail to be legally finalized and executed because of long objections processes.

eRx and Therapeutic protocols

Electronic prescribing is totally applied despite technical pitfalls and system failures happening from time to time.

Therapeutic protocols have been finalized and recommended from 30 Scientific Committees are uploaded on EOF website and on eRx system (HDIKA)since end 2011 .The therapeutic protocols are under update with the aim to become more practical as a prescribing algorithm application (1st line, 2nd line,3rd line, etc) with the appropriate level of evidence.

The project is coordinated by the Athens Medical Society that is developing the standard web template and dialogue with all stakeholders ,so by diagnosis per ICD 10 and Therapeutic protocols guidance as regards sequence of treatment (1st,2nd etc line) and in connection with the Positive Reimbursement List appropriate choices of treatment option and duration will lead prescription volume control.

Figure 2: Per capita public pharmaceutical expenditure in the EU. Source: Kana E, Irwin R, Casson M. European Parliament Report: differences in costs of and products in the EU. Brussels: Policy Department, Economic and Scientific Com Policies;2011.

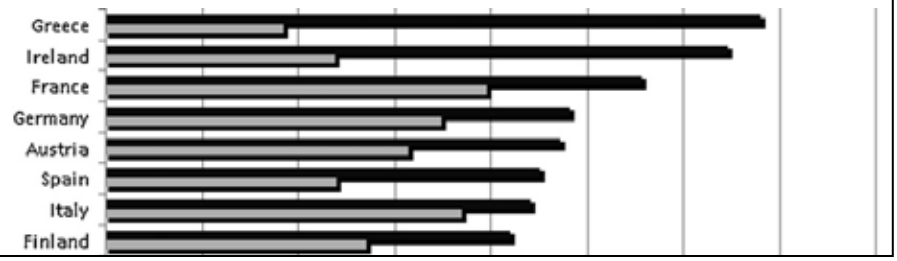

Diagram 1:

Athens Medical Society (www.mednet.gr) proposal on the standard of http://server.e-bi.gr/kenicdv4/ as used already for DRGs in Hospitals (KEN) and Application Programming Interface-API on ICD -10 coding of Diagnosis and Medicines ATC number.

5. The consequences of imposing a GDP threshold on health and pharmaceutical expenditure and GDP.

The relationship between spending on health and medicinal products and income is complex. The European Commission has recognized that spending on health increases the productivity potential of the society and contributes to economic growth, raising per capita income[15]. Consequently, lowering health expenditure may reduce economic performance, increasing spending as a percentage of GDP in the long term.

Under mitigating circumstances in Greece with the deepest economic recession(GDP drop by -25%), highest societal unrest due to unemployment

of 25% and significant reduction in healthcare spending as percentage of hugely contracted GDP ,negative health care outcomes are to be expected.

There is also a variety of technical issues why expenditure varies between countries. Attempting to impose a cap may be detrimental for a number of reasons.

Imposing caps may shift towards private healthcare provision which pose social access barriers for unemployed people, pensioners, poor people and disadvantaged population groups.

As the lack of access to healthcare services will deteriorate the health indices this will require greater spending in future ie for hospital terminal care, hospital procedures, or hospital facilities use and or building.

The use of arbitrary caps to determine cost containment activity is not new. It has been applied to Italy for same time and has been subject of scientific studies. Maintenance of thresholds was conducted by recurrent price cuts, reference drug prices of products, reduction of pharmacists and wholesalers margins, increased copayments, delisting of less essential drugs, as almost done recently in Greece.

The actual effect of ceilings has apparently helped to reduce pharmaceutical expenditure in Greece by 2 billion euros in 2 years' time, however they have distorted society cohesion pushing social deinsure, with violent and uncoordinated policies of cost containment.

The definition of pharmaceutical expenditure as a percentage of GDP varies significantly depending on the components included. For example in Greece total pharmaceutical expenditure is 2,4% of GDP, whilst public is 1,9% and if taxes, and payments to distributors are excluded is 1,2%.

The comparison of the levels of expenditure as a percentage of GDP between countries may vary because of its definition, over time and for different other reasons as health needs, structure of healthcare system and pattern of GDP evolution.

Using GDP threshold on health and pharmaceutical expenditure, may in shortterm lead to cost saving however it is not in the long run an effective policy tool and can lead to poor health outcomes.

For sustainability of public funds the focus should on assessment and remediation of inefficiencies on the basis of cost benefit analyses of alternatives.

6. Efficiency of reform policies

Given that Greek originators prices are already relatively low, as the average of the 3 lower EU 22 prices, one of the main goals should be to increase the efficiency of generics market.

As generic prices in Greece are relatively high with an 80% cap maximum price versus the originator off patent price are leading to less competition.

In addition the therapeutic reference pricing per ATC 4 classification in the positive reimbursement list including on patent ,off patent and generics has a negative effect on the degree of competition in relevant off patent prices preventing them from falling as they would and therefore increasing cost to taxpayers[16].

The relatively high generic prices keep the generics volume and market share at about 17% of the total market significantly falling short of the Government target of 30%.

The government and MoU reimbursement of the cheapest generic per ATC4 or ATC5 was introduced as a measure to increase generics penetration and

relevant savings. The substitution takes place at pharmacy level, provided that pharmacist informs the patient and he accepts.

This measure increased the level of out of pocket payments by the patients whose capacity to pay has been reduced dramatically by the financial crisis.

In addition cheapest drug is not necessarily the cheapest treatment and may not be the best medical option for the patient, who may be forced to change repeatedly , due to prices reductions and or availability issues ,from one generic to the other ,which may lead to medication errors, lack of efficacy or tolerance issues and adverse events.

The compulsory INN prescribing was introduced as a key tool for prescribing behavior mainly for preventing physicians to prescribe particular brands and for refraining them from interacting with pharmaceutical industry.

Again INN prescribing is added to the mix for increasing generic use, on top of generic substitution by pharmacies.

INN prescribing is compulsory in the Hospital setting as well where cost containment is pursued as well by discounts and tenders.

Compulsory INN prescribing is challenging physicians' freedom to prescribe what they judge clinically to be the most beneficial medicine for the patient. The physicians' professional bodies are in great disagreement and they have advised their members to prescribe by brand name and declare on the Rx that they do not bare any responsibility for any adverse outcomes in the event of substitution of treatment.

INN compulsory prescribing it discriminates in favor of generics, distorts market conditions, undermines trademark value and may even maintain prices at a higher level than they would be if true competition would be allowed.

To the generic substitution, INN prescribing and therapeutic reference price in the Positive Reimbursement List, additional price erosion measures as extra rebates and clawbacks are also in effect.

However since in Greece in the past there have been safety and quality concerns with the generics use, a prerequisite for an increase in generic market share is the strict enforcement of regular controls at production sites and to market to ensure high quality of generics and perform additional quality assurance well defined and systematically executed in terms of frequency, level, location and methods.

Regarding prescription volume, which is a considerable factor contributing to increased expenditure drug budgets at national level has been set to help control costs. In addition prescribing guidelines and targets e.g compulsory INN Rx of 85% among all prescriptions by a physician are adopted and are mandatory by law for shaping Rx patterns and to manage the budget.

Monthly caps on pharmaceutical expenditure have been published on a national level and any excess will have to be returned as extra rebate on a scale relevant to volume of sales (scaled rebate) and Market share (clawback).

The implementation of all these approaches would necessitate enforcement mechanisms and credible monitoring.

Health Technology Assessment is not directly applied in Greece to divert funding from less cost effective products towards higher therapeutic value medicines. Cost effectiveness data are optional for inclusion in the Positive Reimbursement list while NICE positive assessment, as well as ASMR 1, or 2 rating, or Germany ATC 5 classification, or accelerated review status by EMA, or FDA fast track review may allow subcluster classification and no therapeutic reference pricing.

7. Pharmaceutical policies impact

Pharmaceutical spending in Greece was very inefficient for a long time and the waste involved in public expenditure contributed significantly to the Greek public debt crisis.

A steep rising of pharmaceutical expenditure in the years of 2006-2009 led to a peak per capita consumption without any prevention policies being in place to avoid this development.

As cost containment measures in Greece led to consecutive price cuts and as 11 out of the EU 27 countries have Greece as reference price country, there were some companies that heave threatened to withdraw their products. Actually withdrawals was limited to few products while parallel exports resulted in local shortages that led Health Authorities to ban particular products exports for ensuring proper local demand coverage. Government must supervise proactively the market supply and enact measures before shortages are observed.

The main focus of the policy reforms was on the need to manage budget and almost nothing about managing uncertainty about outcomes.

Apart from designing and publishing reforms implementation and enforcement were not so successful to achieving the goals .Mainly delays, errors and lack of synergies had an impact on quality healthcare and public health.

As the spending goals seem to have been achieved mainly by cost saving, due to reduced consumption due pharmacists strikes, reduced willingness for out of pocket, noncompliance or discontinuation of treatment, no patient access to EOPYY physicians as part of strikes and EOPYY debts to pharmaceutical companies that stopped selling on credit.

As now originators prices are low the focus should be on volume of prescriptions and generic update and generic prices.

Considerable care should be exercised so that public cost saving is not converted to private spending especially for the population groups that cannot bear additional private expenditure.

Policy makers should reexamine measures that have compromised patient access to public healthcare and pharmaceuticals particularly for the vulnerable groups and low income patients. There are great concerns about the level of quality of health care services provided due to the reduction of healthcare personnel, the increase of demand for services within Hospitals of NHS, the lack of disposables ,devices and medicines due to reduced budgets and hospital debts. On top of all these shortages and lack of resources Health care professionals remain unpaid for more than 6 months for their duty shifts and quite often go on strikes which aggravates the patient access to surgeries and diagnostic or therapeutic interventions.

They have also to prevent further public health disaster due to high number of unsecured jobless people, which for the time being cannot receive primary or hospital care within NHS.

These disadvantaged population groups are in need of social healthcare for humanitarian reasons.

Non Governmental Organizations and Archidiose are temporally taking care of them through Social Voluntary work of Healthcare professionals and donations of medicines by pharmaceutical companies.

8. Summary & Conclusions

In conclusion great savings have been achieved with regard to pharmaceutical spending mainly because of price erosion measures as well as increased patient copayment and shift of public expenditure to private spending.

Prescribing volumes have been mildly reduced and generics uptake lag behind targets.

No new medicines have been entered in Greece in the last 2 years because of no new medicines pricing by the Government as an additional cost containment leading to a major inequality to patient access to new and innovative treatment despite clawback option.

There is generic substitution at pharmacy level introduced in Sept 2012 and compulsory INN prescribing established by law in Nov 2012 and therapeutic reference pricing as part of positive reimbursement list that is anticipated to be implemented later on is reshaping the contracted pharmaceutical market.

There are considerable imperfections in reprising mechanism of medicines that led to numerous erroneous price bulletins and while their final corrections are still pending, market is distorted, serious shortages are experienced and patient access has been compromised creating warranted concerns for adverse health outcomes.

The non-favorable environment and the disproportional cost containment for pharmaceutical R&D enterprises and particularly the lack of recognition of innovation and new medicines is leading to loss of employment and shrinkage of R&D pharma companies in the country.

The Government has to reassess policies reforms on a cost benefit analysis for alternatives that may increase efficiencies and to convince Troika that pharmaceutical expenses thresholds as a fixed percentage of GDP that is steadily contracting cannot be pursued at the expense of patient care.

Policies applied with immediate price cuts including rebates and clawbacks, reduction in reimbursement and increased co-pay have led to reaching the target of pharmaceutical expenditure of 2,88 bn euros for 2012.

The saving achieved may be shifted to a later time in other forms of expenses linked to increasing morbidity (ie hospital and interventional) that could pose a major potentially non manageable challenge to the Health Care System.

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How to Implement a Unified GxP Quality Management System (QMS) in a Pharmaceutical Company

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In the last decade and especially the last 3 years, one can see the increasing requirements regarding the implementation of a Quality Management System. Those requirements are established in the areas of Good Manufacturing Practices[1] and Good Clinical Practices[2] and it is no surprise to see the expansion of these to the area of Pharmacovigilance[3] and very recently of Good Distribution Practices[4].

Have you ever thought of what quality is about? It's about meeting expectations, the so called requirements; Expectations of whom? Of our customers: patients, physicians, regulatory authorities and of course in the company we work in. The system (*organizational structure, resources & responsibilities, processes & procedures*) that a company has to manage Quality is called a Quality Management System. It is a management system to direct, plan and control an organization with regard to Quality. The word "System" is to emphasize that company should manage quality based on Process Management approach, meaning to manage the company as a system of interlinked processes; each process is a set of interrelated activities which transforms inputs into outputs. The outputs of the one process should be the input of the other.

A Quality Management System will support the company to always focus on Continuous Improvement. This objective is only achievable only when Quality is incorporated in a cycle (**Deming Cycle[5]**) consisting of the following elements:

- **Quality planning(PLAN)**: establishing structures and planning integrated and consistent processes
- **Quality control (DO):** carrying out the tasks and responsibilities
- **Quality assurance (CHECK):** monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out
- **Quality improvements (ACT):** correcting and improving the structures and processes and the carrying out of those processes as necessary.

Implementing a Quality Management System in a pharmaceutical company is not an easy task. Factors to take into consideration are the complexity of the processes, the already established culture of the company and of course the budget and resources. An important decision to take at the very first step is related to the "limits" of the Quality Management System. Will this system be only related to the Pharmacovigilance Processes, should include also the Distribution Processes and the Clinical Operations? Why not expand the Quality Management System to all GxPs requirements? The latter seems to be more difficult and more challenging in terms of time, resources and change of mentality but ultimately it is the best solution for a pharmaceutical company. The reason is that going back and reading again the requirements mentioned

in the GxPs that are relevant to QMS, it is easy to recognize that are identical. So, instead of developing four times the same QMS for ensuring compliance with GVPs (Good Vigilance Practices), GCPs (Good Clinical Practices), GMPs (Good Manufacturing Practices) and GDPs (Good Distribution Practices) requirements, the company can develop **one** system capturing all GxPs obligations. This is the so called Unified Centralizing Quality Management System approach. But, how to succeed on it?

The very first step is to get the **endorsement** from the Top Management and the overall commitment in Quality. In the majority of times, these discussions are very challenging as Quality is not depicted in numbers. A successful outcome will be achieved by explaining the risks of non-compliance against requirements and by quantifying the importance of quality towards this cost of noncompliance. Of course, a perceptive and quality driven Top Management makes the decision easier to take and the project smoother run. The project leader should have always in mind that the endorsement itself is not enough. The Top Management commitment should be fully visible into the communication plans and tangible into everyday Top Management behavior, as the Quality Mindset should be promoted best in a top down approach.

Having the Top Management endorsement, the second step is the **establishment of a Quality Management Unit**. The Unit (further referred as Quality Unit) can vary from one person to several ones depending of the length of the company and the structure. The Quality Unit should be the single point of contact for all Quality Related issues and should have the role of Business Partner for quality for all departments of the company. This Unit **must be independent** for operations and ideally should report directly to the General Manager of the company. The role of Quality Unit is to coordinate all activities that constitute the QMS components. This means that the following components of the QMS will be managed **centrally** by this unit: QMS Documentation, Corrective and Preventive Actions (CAPA) management, Archiving, Quality Risk Management (QRM) Activities, Change Management, Deviations Management, Inspections Management and Management of Personnel Records (CVs, Job Descriptions and Training Records).

Analyzing further the QMS components, let's start with the management of the QMS Documentation. The Quality Unit should be the sole responsible unit for deciding on the Documentation Hierarchy, for developing the templates to be used (SOPs, Flowcharts, Forms, and Manuals), for reviewing and approving the documents and finally for controlling the distribution of those to the entire company. It is also under the Quality Unit's responsibility to support the authors of the QMS Documentation in the writing process and to trigger the periodic review of the QMS Documentation and also to assign training requirements to staff together with the author of each QMS document. What is of utmost importance is to ensure that Quality Unit is the single point of contact within the company for any request relevant to QMS Documentation.

The same approach should be used for the other components of the QMS like the CAPA Management, the management of Changes and Deviations. Quality Unit has the responsibility to centralize all the data into one tool/system so to ensure that all staff has access to the latest information regarding CAPAs and Changes/Deviations. In addition, Quality Unit is the sole responsible for monitoring of the CAPA status (by sending periodically reports to the responsible staff on the status of their CAPAs) and for measuring the effectiveness of them.

In addition, Quality Unit, due to its independency, is the accountable unit for

performing internal audits as well as audits to suppliers and service providers of the company. The Quality Unit is also taking part in the management of suppliers/service providers as part of a functional team (procurement department and operations/business are part of the team as well) by compiling the quality questionnaires, by performing pre-capability audits to suppliers/ service Providers and by establishing the monitoring strategy of the selected one.

Regarding Quality Risk Management Activities, Quality Unit due to the experience of the staff on analyzing and evaluating risks, acts as the Quality Risk Assessment (QRA) Facilitator supporting departments to implement the risk management approach to daily decisions. Quality Risk Assessments are performed also during all phases of management of a Supplier/Service Provider (from selection phase till decommissioning phase). Quality Risk Management is a very efficient proactive tool for identifying what could go wrong in company processes. Do not underestimate it!

Finally, during the Quality Management Review meetings lead by Quality with the mandatory participation of Top Management, a systematic periodic review of the Quality Management System of the company is taking place. Inputs of this meeting are the following: Key Performance Indicators Trend Analysis, Audits/Inspections Results, CAPA status reports, QRA results, Quality and other Projects affecting QMS, customer's feedback etc. The productive discussions lead to several outputs like decisions on resources/ structure, requests for new audits or new risk management activities or changes to existing processes etc. The ultimate goal of these meetings is always the improvement of the existing QMS so to meet company's objectives.

In a nutshell, in the very demanding regulatory pharmaceutical environment that even keep up with the changes it seems very challenging, investing in Quality by implementing a Quality Management System is the best way to move forward, as it will help the company to identify gaps in the existing processes and undoubtedly to be in full continuous compliance with all GxPs requirements. Because overall Quality is improvement and improvement means more safe products, more satisfied customers, increased compliance, less uncertainty and less risk.

Key words:

Quality, Quality Management System, Top Management, GxPs, Compliance

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STEP Registry

Studying the Epidemiology of Peripheral Arterial Disease in Greece

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1. Introduction

Peripheral Arterial Disease – PAD is an important manifestation of systemic atherosclerosis / atherothrombosis1, leading to deterioration of quality of life, increased Coronary Heart Disease – CHD or Cerebral Vascular Disease – CVD incidence and cardiovascular mortality. Unfortunately, PAD awareness is relatively low2-3 and the disease is often underestimated by physicians and / or patients, as it doesn't usually give major clinical symptoms (only 10% of PAD patients have the typical symptoms of intermittent claudication and half of them suffer from calf pain, indicating more advanced disease stage4). Therefore, the early detection, diagnosis and further effective treatment of PAD in atherothrombotic patients become very important and crucial in most aspects – clinical, financial and social5.

Data to estimate the PAD prevalence and treatment used in Greek PAD population are limited. Even more, the disease management is currently being performed by physicians of multiple medical specialties, which might increase the discrepancy between local clinical practices and international guidelines.

The Ankle–Brachial Index (ABI) is an inexpensive, non-invasive and simple procedure, which can accurately identify PAD patients and set relevant diagnosis. It has also been proven in scientific literature that ABI could be used in clinical practice as a good predictor of mortality[6-8]. Hence, ABI should be considered as a useful tool for the reliable diagnosis of PAD, while it could further monitor treatment strategies or patients' perspectives through time. In addition to the above, ABI is thought to play decisive role in preventing further evolution of atherothrombosis with its complications [9-11].

The aim of STEP Disease Registry was to provide data relevant to treatment, medication and duration of therapy recommended to each type of participating patients, with the ambition to contribute in increasing awareness of PAD and clinical necessity of extended ABI use in routine practice.

An additional aim was to estimate the prevalence and progress of Peripheral Arterial Disease in Greece, as well as to make essential comparisons between Health Care Professionals' practice in Greece and recommendations of relevant evidence-based guidelines[12-18].

2. Research Design and Methods

STEP Registry was designed as a local observational, non-controlled Disease Registry, aiming to provide data on Peripheral Arterial Disease – PAD prevalence and clinical management in Greece.

Participating physicians – mainly internists, GPs and cardiologists, were planned to recruit 15 consecutive patients each at their private offices and follow them for a period of total 12 months. Along with data on PAD prevalence, registered by performing measurements of Ankle – Brachial Index (ABI), participating physicians would provide information on several aspects of clinical practice and management of PAD patients. The initial plans included 100 office-based physicians in 100 investigational sites and a total number

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of patients of 1.500, classified in three groups: patients with Coronary Heart Disease – CHD, patients with Cerebro-Vascular Disease – CVD and patients with Cardio-Vascular Risk Factors.

As the main objective of the STEP Registry was to identify a "real-life" PAD prevalence rate, which was expected to range between 20% (REACH Study population – local results) and 40% (AGATHA Study results), the inclusion of minimum 1.000 patients would allow estimations of this rate with a precision of 2,5% to 3,0%.

Main diagnostic and disease monitoring tool for this study was ABI measurement, performed using a continuous-wave Doppler device provided to participating physicians along with detailed training on measurement techniques and clinical implications of the method. Dedicated clinical seminars, organised by the Hellenic Vascular Surgery Society in major cities in Greece, offered relevant theoretical and practical guidance to search for, diagnose, manage, monitor and prevent PAD. Participating physicians expressed their written consent to be included in the study after receiving detailed instructions and training.

Finally, due to several administrative and resources reasons, in the current local observational Disease Registry, conducted in Greece between 2008 and 2011, participating physicians were totally 58 in a network of 58 investigational sites, while the total number of recruited patients was 420.

The Primary Objectives of the STEP Registry were to document the prevalence of PAD for each type of patients (with established Coronary Heart Disease or Cerebro-Vascular Disease or only with cardiovascular risk factors) and to register treatments, medications used (by class) and the duration of therapy suggested, in terms of compliance to Clinical Practice Guidelines.

The **Secondary Objectives** were to document the treatment strategies for the management of different types of patients, as well as to estimate the convenience of performing ABI measurements in real life clinical practice of participating physicians.

The **Inclusion Criteria** for patients' recruitment were:

✓ Age > 55 years old, **with** one of the following:

– Documented CHD (History of Stable Angina, Percutaneous Coronary Interventions – PCI, Coronary Artery Bypass Grafting – CABG, Myocardial Infarction – MI)

– Documented CVD (Ischaemic Stroke – IS, Transient Ischaemic Attack – TIA)

– Documented PAD

– One of the Cardio-Vascular Risk Factors (diabetes, arterial hypertension, hypercholesterolaemia, hypertriglyceridaemia, smoking, claudication, waist circumference > 102cm in men or > 82cm in women, Body Mass Index – BMI > 27kg/m^2)

✓ Signed by the patient Informed Consent to participate in the study

On the other hand, **Patients' Exclusion Criteria** included acute medical or surgical illness, requiring hospitalization, presence or history of cancer or any other disease with limited life expectancy, actual or anticipated geographic or social factors, that would limit the subject's participation for the duration of the study and denial to participate in the study or to sign the Informed Consent Form.

The STEP Registry data was collected on paper CRF and recorded by participating physicians, who provide clinical examinations, required

ABI or other measurements and follow-up for a period of 12 months. All information and data registered were further handled with the greatest care and confidentiality in accordance with the Guidelines for Good Pharmacoepidemiology Practice (GPP)19-20. Data quality control was performed on site in minimum 5% of the active sites which have enrolled at least one patient and been randomly selected.

The study protocol was approved by Hospital Scientific Committees and National Medicines Organisation – EOF on December 3rd, 2007.

3. Statistical Considerations

For the implementation of the statistical analysis, **descriptive statistics** was used. Statistical measures used were frequencies and distribution percentages for discrete variables and descriptive measures (mean, median, maximum, minimum, standard deviation) for continuous variables.

Statistical tests among discrete variables were implemented by using the statistical test **Chi- Square**. For statistical tests of discrete variables with two categories each (2x2 tables) the **Fisher Exact Test** was used. Also, the statistical **Student's T-test** was used for the comparison of values of continuous variables between two categories of discrete variables and the statistical **Anova FTest** for the comparison among more than two categories of discrete variables. At the same time, comparisons of quantitative variables between two points in time were made by using the **paired t-test**, whereas for corresponding comparisons in time for two-value variables (0,1) the non-parametric **McNemar test** was used.

Moreover, for studying the parallel correlation among the prognostic factors of the study and PAD diagnosis, a **multivariate logistic regression model** was used. The choice of the optimum model which interprets the study data was made by the forward selection method.

All statistical analyses were implemented at a significance level of $\alpha=0.05$ by using the statistical package SPSS version 16.0

The main criterion is the PAD prevalence, for which a two-sided 95% confidence interval was planned to be calculated. The inclusion of at least 1,000 patients was planned to allow a **precision of 2.5% to 3%** in PAD prevalence rate estimations.

4. Results

A total of 420 patients (N=420) were recruited for the STEP registry within a period **from January 2008 up to August 2010.** Follow-up visits were made every 6 months approximately until completion of a total of 12 months. For 332 patients (**79%**) a second visit was recorded, in the time period between June 2008 and November 2010. The third visit was recorded for 204 patients (**48.6%**), from March 2009 up to November 2010.

Despite initial plan to recruit 1,000 patients, only 420 were finally included in the STEP Registry. The reasons are associated with poor response from the pool of potential STEP investigators, who had been trained on PAD diagnosis and management, as well as with lack of time for combining investigator duties and everyday clinical practice.

Very limited investigator fees in the context of the economic crisis in the country had also influenced the patients' recruitment and follow-up.

Patients' characteristics – 57.1% of the patients participating in the study were males and 42.9% females. Mean patient age was 67.8 years old. At the level of age distribution 42.2% was up to 65 years old and 57.8% more than 65 years old.

Regarding Body Mass Index – BMI, 70.7% of the patients had high values (more than 27). Mean BMI was 29.9 (median: 29.5, min: 17.9, max: 49.1). No significant correlations between BMI and gender or age were observed (***Table 1***).

Moreover, the waist circumference was high (over 102 cm for men and 88 cm for women) for 70.5% of the patients. Women had significantly higher waist deviations from normal values compared to men (83.1% vs 61.7% respectively, p-value<0.001). Overall, 71.2% of the patients have been characterized as obese.

Regarding their relationship with smoking, 43.6% of the patients reported a history of smoking (mean 61 pack-years for current smokers and 46 for former smokers who gave an answer). The smoking history was highly associated with the patients' gender (64.2% among men versus 15.7% among women, p-value<0.001) and their age as well (53.4% among those less than 65 years old versus 36.5% among those over 65 years old, p-value=0.001).

At the same time, 90% of the patients have been diagnosed with hypertension, percentage significantly increased in those older than 65 years (93.4% versus 85.2% for younger than 65 years old, p-value<0.01). Mean heart rate of the patients during the physical examination was 74.5 heartbeats per minute (median 75, min: 45, max: 108) and the mean systolic and diastolic pressure was 138.9 (median 140, min: 85, max: 200) and 82.8 (median 80, min: 50, max: 120) respectively.

28.1% of the patients had a history of cerebrovascular disease and/or recent symptoms. More specifically, 71.2% of those had a history of transient ischemic attack, 33.1% of ischemic attack, 3.4% had undergone carotid angioplasty with stent placement, 0.8% without stent placement and 2.5% had undergone carotid intra-arterial or other carotid surgeries. The presence of CVD history was increased in men rather than in women (32.1% vs 22.5%, p-value=0.04).

Additionally, **29.8% of the patients had a history of Coronary Heart Disease – CHD** or / and recent symptoms. More specifically, 42.4% of those patients had suffered a heart attack, 33.6% had undergone Percutaneous Transluminal Coronary Angioplasty PTCA [or other Percutaneous Coronary Interventions – PCI] with stent placement (and 3.2% without stent), 29.6% was diagnosed with stable angina and 3.2% with unstable angina. At the same time, 25.6% of those patients had undergone Coronary Arterial Bypass Grafting – CABG treatment, while a percentage of 5.6% was diagnosed Congestive Heart Failure. In 330 out of 420 patients (78.6%) an electrocardiogram check was made during their inclusion in the study. 57.0% of those patients had normal ECG versus 43.0% who didn't. From those without normal ECG, 38.0% had conductivity abnormalities, in 19.7% Q-waves were detected, in 12.0% depression of ST-segment and in 7.7% T-wave inversion.

Furthermore, 22.6% of the patients had additional medical conditions or symptoms regarding their medical history. More specifically 20.0% of those had deep vein thrombosis, 6.3% had suffered from pulmonary embolism, 34.7% were diagnosed with superficial thrombophebitis while 49.5% had other diseases (e.g. hypothyroidism, atrial fibrillation, depression etc).

Almost half of the patients participating in the study suffered from type II diabetes (51.0%) without significant differences based on gender and age of patients. Additionally, 15.6% of the patients was diagnosed with intermittent claudication (mainly men 20.0% versus 9.6% women, pvalue= 0.004) and 81.1% were diagnosed with dyslipidaemia (significantly increased in <65 years old 86.9% versus in 65+ 76.8%, p-value=0.01). Out of the patients

diagnosed with dyslipidaemia, 49.4% had increased total cholesterol, 47.1% increased LDL, 31.8% had low values of LDL, 34.7% had increased values of triglycerides and 78.3% were taking hypolipidaemic pills.

The measurement of Ankle-Brachial Index – ABI was used as a basic tool for setting PAD diagnosis. The measurement of systolic pressure has been performed in both sides of the upper and lower extremities. The lowest value of ABI has been used for evaluating PAD. The measurement of ABI was recorded for 419 out of 420 patients of the study (99.8%). **The mean value of ABI was 0.926** with median 0.95, standard deviation 0.178 and min: 0.28, max: 1.52. More specifically, 4 patients (**1.0%**) had **serious PAD** (with ABI values less than 0.4), 164 patients (**39.1%**) had **mild or moderate PAD** (with ABI values between 0.41-0.90), 247 patients had normal PAD values (ABI values between 0.91-1.30) and 4 patients had ABI values over 1.30. Overall, **40.1% of the patients were diagnosed with mild, moderate or serious PAD.**

Over the total **prognostic factors** studied, the following factors showed significant relation with PAD diagnosis (***Table 2***): the history of cerebrovascular disease (p-value<0.001), coronary heart disease (p-value<0.001), smoking (p-value=0.01) and other diseases (p-value<0.001), diagnosis of intermittent claudication (p-value<0.001), dyslipidaemia (p-value=0.04) and in a marginally significant level the gender (p-value=0.06) and diabetes diagnosis (p-value=0.06). All the remaining factors did not show any significant relation with the presence of the disease.

In order to study the parallel effect of the above factors in the presence of PAD, the multivariate logistic regression has been used. The final model chosen based on the simultaneous significance of the factors consisted of three important factors, history of cerebrovascular attack, and history of other diseases and the diagnosis of intermittent claudication. As shown in ***Table 3***, **a patient with history of cerebrovascular incident had 2.2 times higher probability of having PAD rather than a patient without such a history** (95% CI: 1.4-3.6). At the same time, the risk of PAD emergence in a patient with history of other diseases (apart from stroke or coronary disease) compared to a patient without such a history was 2 times higher (95% confidence interval: 1.2-3.3). Finally, a patient diagnosed with intermittent claudication had 6 times higher probability of PAD presence rather than a patient without relative diagnosis (95% confidence interval: 3.1-11.8).

During patient inclusion in the study, **88.8% of the patients received hypertension agents, 78.3% hypolipidaemic agents, 71.2% antiplatelet agents, 44.5% antidiabetic treatments and 23.3% vasodilating agents**[21-29]**.** Detailed results are shown in ***Tables 4 – 17***.

Revisit at 6 months

The second visit was recorded for 332 patients (79%). In order to ascertain how much the subgroup of patients differs from the original sample, a statistical test regarding the basic parameters of the study was conducted. Statistically significant differences were located based on the presence of hypertension (p-value=0.03), coronary disease history (p-value<0.01) and smoking history (p-value=0.02), with patients participating in the second visit having increased percentages in all three parameters. Combined with the above mentioned, patients participating in the second phase had received at a **significantly higher level hypertension treatment** (p-value=0.03), **vasodilator agents** (p-value<0.01), **anti-platelet agents** (p-value<0.001) and **hypolipidaemic treatments** (p-value<0.001) compared to patients not studied in the second visit. It is noted that **there was no significant**

difference in the PAD percentage between the two patient groups (p-value=0.63).

During the second visit, corresponding physical examination measurements of the patients were made, which were not significantly different from the first visit. The percentage of diabetes mellitus was similar between the two measurements (53.8%), as well as the smoking history (46.8%) whereas the obesity percentage was 70.7% versus 73.1% in the first phase. The percentage of dyslipidaemia in the second visit was 84.6% versus 82.8% of the corresponding patients in the first visit.

Regarding new occurrence of cerebrovascular disease observed from the start of the study up to reappraisal, 17.8% of the patients presented with new occurrence (mostly patients already having a disease history). From those patients 66.1% had transient ischemic attack, 32.2% vascular ischemic attack, whereas carotid angioplasty and carotid endarterectomy were observed in less than 5% of the cases. **The mean value of the ankle-brachial index in patients with occurrence after reappraisal in 6 months was significantly lower from those without** (values: 0.84 versus 0.94 respectively, p-value<0.001). Moreover, **23% of the patients showed symptoms of coronary disease during the reappraisal period**, namely: heart attack (31.6%), percutaneous transluminal coronary angioplasty – PTCA with stent placement (28.9%), coronary artery bypass graft (19.7%), stable angina (14.5%), unstable angina (13.2%), congestive heart failure (13.2%), PTCA without stent placement (3.9%). Additionally, **the values of the ankle-brachial index at the start of the study for patients who showed symptoms of coronary disease were significantly lower from those of patients who didn't show any new occurrence** (values: 0.86 versus 0.94 respectively, pvalue< 0.001).

At the same time, 13.6% of the patients showed other symptoms during the time up to reappraisal as follows: superficial thrombophlebitis (33.3%), vein thrombosis (13.3%), pulmonary embolism (4.4%) and other diseases (53.3%). Similarly, the values of the ankle-brachial index at the beginning of the study for patients showing symptoms of another disease were significantly lower compared to the patients who didn't show any new occurrence (values: 0.83 versus 0.94 respectively, p-value<0.001).

Regarding the **second ABI measurement**, the mean value was **0.943** (median 0.95, standard deviation 0.162 and min: 0.37, max: 1.36). The corresponding mean value of the index for patients participating in both measurements was: 0.922 (median 0.95, standard deviation 0.178, min: 0.28, max: 1.52). Based on the statistical paired t-test, **the ABI values were significantly increased between the two time periods (p-value<0.001).** More specifically, during the second visit 64.8% of the patients had normal PAD values versus 59.2% in the respective sample of patients from the first visit.

Regarding therapeutic treatments there were no significant variations in changing the treatment category for hypertension (91.2% from 90.7%), vasodilators (28.5% from 26.5%), antiplatelets (77.3% from 75.3%), hypolipidaemic agents (82.4% from 81.9%) and antidiabetics (45.8% from 45.2%). More specifically, regarding the types of treatment in each therapeutic category, the strategy followed 6 months onwards was maintenance of therapy for hypertension (90%, versus just 4.7% for starting a new therapy or 5.3% for changes), vasodilators (90.4% versus 3.2% starting new therapy and 6.4% changes), antiplatelets (92.2% versus 4.3% start of new therapy and 3.5% changes), hypolipidaemics (90.1% versus 5.1% and 4.8% respectively) and antidiabetic therapies (89.4%, start of new therapy 6.0% and maintenance 4.6%).

Revisit at 12 months

The third visit at 12 months was recorded for 204 patients (48.6%). Moreover, this subgroup of patients showed significant differences from those not participating in this visit regarding the parameters of hypertension (p-value=0.02), coronary disease history (p-value=0.03), diabetes (pvalue= 0.01), as well as initial PAD diagnosis (with those diagnosed initially participating to a greater degree in the third phase, 56.5% of them versus 43.0% of those not diagnosed, pvalue< 0.001). As a result, the corresponding comparisons for the third phase will focus only on those patients participating in all three phases.

The percentage of diabetes mellitus was similar between the last two measurements (59.3%), as well as the smoking history (42.2%) whereas the obesity percentage was lower, at 67.8% versus 72.5% in the second phase. On the contrary, the percentage of dyslipidaemia was comparatively higher at the present phase (85.8% versus 82.4% in the corresponding patients at the 6 month point).

Regarding **new occurrence of cerebrovascular disease observed between the second and the third visit, 14.2% of the patients showed new occurrence**. From those patients 69.0% had transient ischemic attack, 34.5% vascular ischemic attack, whereas carotid angioplasty and carotid intraarterial excision were observed at lower percentages. **The mean ABI value measured at 6 months in patients with a new occurrence was significantly lower from those without** (values: 0.87 versus 0.95 respectively, p-value=0.02).

Moreover, 21.6% of the patients showed symptoms of coronary heart disease during the reappraisal period, as follows: stable angina (25.0%), unstable angina: (9.1%), heart attack (29.5%), PTCA with stent placement (31.8%), without stent placement (4.5%), coronary artery bypass graft (27.3%) and congestive heart failure (6.8%). In addition, the ankle-brachial index values at the second measurement for patients showing symptoms of coronary disease were significantly lower from those of patients without a new occurrence (values: 0.88 versus 0.95 respectively, p-value=0.03).

At the same time, 14.7% of the patients showed other symptoms during the time up to reappraisal, as follows: vein thrombosis (13.3%), pulmonary embolism (6.7%), superficial thrombophlebitis (43.3%) and other diseases (43.3%). Additionally, the ankle-brachial index values at the second measurement for patients showing symptoms of another disease were significantly lower compared to the patients who didn't show any new occurrence (values: 0.81 versus 0.96 respectively, p-value<0.001).

Regarding the ankle-brachial index during the third measurement, the mean value was 0.942 (median 0.96, standard deviation 0.156 and min: 0.46, max: 1.31). The respective mean value of the index for patients measured in all three phases was: 0.934 (median 0.94, standard deviation 0.168, min: 0.40, max: 1.33). **Based on the statistical paired t-test, the values of the ankle-brachial index were marginally higher between the last two time periods** (p-value=0.08). More specifically, during the second visit 67.5% of the patients had normal PAD values versus 63.1% in the corresponding sample of patients participating in all visits. As a result, the increase of the anklebrachial index is stronger in the first 6 months from the original measurement, compared to the next 6 month period.

Regarding therapeutic treatments there were no significant variations in changing the treatment category for hypertension (92.6% from 92.6%), vasodilators (33.3% from 33.3%), antiplatelets (86.3% from 81.9%), hypolipidaemic agents (79.4% from 79.9%) and antidiabetics (54.4% from

53.4%). Regarding the types of treatment in each therapeutic category, the strategy followed 12 months onwards maintained the treatment in hypertension (90%), vasodilators (88.2%), antiplatelets (89.8%), hypolipidaemics (90.7%) and antidiabetic therapies (93.7%).

5. Discussion

Peripheral Arterial Disease – PAD is one of the leading manifestations of **Atherothrombosis**30. Despite the fact that, even when asymptomatic, PAD is strongly associated with an increased risk

of Myocardial Infarction or Stroke, the awareness about PAD in Greece still remains relatively low.

STEP Disease Registry aimed to provide data on PAD prevalence and clinical management by primary care physicians – internists, GPs and cardiologists of the community sector. Participating physicians had received adequate training and developed required skills to diagnose PAD using Ankle-Brachial Index measurements by means of a Doppler device.

In the current discussion, results from 420 patients in 58 centres are reviewed. Patients meeting inclusion criteria were recruited between 2008 and 2011. After initial medical examination and inclusion in the study with registering required data, the patients were followed-up for a period of total of 12 months and visited their treating physicians at least every 6 months.

The mean value of ABI in 419 out of 420 participating patients was found to be normal (0.926). Based on ABI measurements, **40% of patients received a diagnosis of PAD**. Taking into consideration particular limitations of the current study, this percentage provides a rough estimation of the PAD **prevalence** among patients older than 55 years of age with either a history of Coronary Heart Disease – CHD or Cerebro-Vascular Disease – CVD, or with cardiovascular risk factors, who are visiting office based primary care practitioners in Greece.

Diagnosis of PAD was significantly associated with the presence of prognostic factors such as history of CVD or CHD, smoking and dyslipidaemia, while the relation of gender and diabetes mellitus with the diagnosis of PAD was found to be marginally significant.

It is important to highlight that **atherothrombotic patients with a history of stroke or coronary disease had more than twice higher probability to develop PAD compared to nonatherothrombotic people without such history**.

During patients inclusion in STEP Registry, 71.2% of patients were receiving **antiplatelet agents**. Among patients diagnosed with PAD 87.5% received antiplatelet treatment versus 60.2% of patients not diagnosed with PAD. Furthermore, 52.2% of enrolled patients continued receiving Acetyl-Salicylic Acid – ASA and 34.8% of patients continued treatment with clopidogrel. Changes inside the category of antiplatelet agents were limited to 2%.

In the **first follow-up visit at 6 months after inclusion in the study**, there was **no significant difference in the PAD percentage between the two patient groups**. Participating in the second phase patients had received significantly higher levels of hypertension treatment, vasodilators and antiplatelet agents, and hypolipidaemic treatments compared to patients not studied in the second visit. During the second visit, corresponding physical examination measurements of the patients were not significantly different from the first visit.

14.2% of the patients presented with **new occurrence of CVD** (mostly patients already having a disease history) in the second visit, with 66.1%

of them having suffered a Transient Ischaemic Attack – TIA and 32.2% an ischaemic Stroke. Moreover, 23% of the patients showed **symptoms of coronary disease** during the reappraisal period. The mean ABI value in patients with either CVD occurrence or CHD symptoms after reappraisal in 6 months was significantly lower from those without CVD new occurrence or CHD symptoms.

ABI values at the second measurement were significantly increased between the two time periods. During the second visit 64.8% of the patients had normal ABI values versus 59.2% in the respective sample of patients from the first visit.

Therapeutic strategies and **medications prescribed in the second visit** showed no significant variations compared to relevant clinical decisions in the first visit for inclusion in the study.

In the **second follow-up visit at 12 months after inclusion in the study**, the registered ABI values were marginally higher. **The increase of ABI values was found to be stronger in the first 6 months after enrollment compared to the next 6-months period.**

17.8% of the patients presented with **new occurrence of CVD** in the third visit, with 69% of them having suffered a TIA and 34.5% an ischaemic Stroke. Moreover, 21.6% of the patients showed **symptoms of coronary heart disease** during the reappraisal period. The mean ABI value in patients with either CVD occurrence or CHD symptoms after reappraisal in 12 months was significantly lower from those without CVD new occurrence or CHD symptoms.

Therapeutic strategies and **medications prescribed in the third visit** showed no significant variations compared to relevant clinical decisions in the first and second visit.

Limitations of the current study should be taken into consideration when interpreting study data, namely the failure to meet the number of subjects needed for the analysis and the high drop-out rate at visits 2 (21%) and 3 (52%).

6. Conclusions

The estimated prevalence of Peripheral Arterial Disease – PAD among patients with a history of atherothrombotic events or with cardiovascular risk factors is roughly 40%. Documented diagnosis of PAD underlines the increased risk of myocardial infarction or ischaemic stroke31-33 and requires particular therapeutic strategies to be implemented.

Medications prescribed when patients were included in STEP Disease Registry showed no significant variations compared to relevant clinical decisions in the next follow-up visits. **For a period of 12 months after PAD diagnosis, recorded ABI values showed significant increase** – mainly in the first 6 months, which is indicative of **PAD improvement**. Given that basic medication and management strategy remained unchanged for the same period, it is likely that the disease improvement is associated with the progress of atherothrombosis or should be due to study limitations, as well as to chance.

On the other hand, almost 1 in 5 patients with lower ABI values at enrollment or CVD / CHD history suffered cardiovascular events – new occurrence of CVD or symptoms of CHD in the period of 12 months after inclusion in the study. Therefore, **more effort is needed for achieving optical therapeutic management of high cardiovascular risk patients, who are diagnosed with PAD** in Greece.

Full list of investigators

A list of all participating in STEP Registry physicians under the coordination of Professor Dr Christos **Liapis** is following *(Family Names first, in bold letters)*:

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ABI is a useful tool for the diagnosis of PAD in patients with a history of atherothrombosis or with cardiovascular risk factors.

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APPENDIX - TABLES AND GRAPHS

Table 1

Prognostic factor and disease history profile based on the gender and age of the patients (% by column)

Prognostic factors and disease history		Total (%)	Gender (%)		Age (%)	
			Male	Female	<65	65+
BMI	<=27 Kg/m2	29.3	32.5	25.3	30.7	28.2
	>27 Kg/m2	70.7	67.5	74.7	69.3	71.8
p-value:			*0.129*		*0.588*	
Waist breadth	Normal	29.5	38.3	16.9	32.4	27.0
	High	70.5	61.7	83.1	67.6	73.0
p-value:			*<0.001*		*0.233*	
Hypertension	Yes	90.0	91.3	88.2	85.2	93.4
p-value:			*0.327*		*0.008*	
Cerebrovascular disease history	Yes	28.1	32.1	22.5	22.7	31.5
p-value:			*0.036*		*0.06*	
Coronary disease history	Yes	29.8	39.6	16.9	27.3	32.0
p-value:			*<0.001*		*0.331*	
Other history	Yes	22.6	23.3	21.9	20.5	24.1
p-value:			*0.814*		*0.408*	
Diabetes	Yes	51.0	50.0	52.2	56.3	47.3
p-value:			*0.693*		*0.075*	
Obesity	Yes	71.2	67.9	75.3	69.9	71.8
p-value:			*0.104*		*0.743*	
Smoking	Yes	43.6	64.2	15.7	53.4	36.5
p-value:			*<0.001*		*0.001*	
Intermittent Claudication	Yes	15.6	20.0	9.6	16.5	14.5
p-value:			*0.004*		*0.585*	
Dyslipidaemia	Yes	81.1	81.3	80.9	86.9	76.8
p-value:			*1.000*		*0.011*	

Table 2

PAD diagnosis and main prognostic factors (% by row)

Main prognostic factors		PAD diagnosis (%)	
		NO	YES
Total		59.9	40.1
Gender	Males	56.1	43.9
	Females	65.7	34.3
p-value:		0.055	
Cerebrovascular disease history	YES	41.5	58.5
	NO	67.1	32.9
p-value:		*<0.001*	
Coronary disease history	YES	49.6	50.4
	NO	64.3	35.7
p-value:		*<0.001*	
Other disease history	YES	43.2	56.8
	NO	64.8	35.2
p-value:		*<0.001*	
Smoking	YES	53.0	47.0
	NO	65.3	34.7
p-value:		*0.012*	
Intermittent Claudication	YES	20.0	80.0
	NO	67.6	32.4
p-value:		*<0.001*	
Dyslipidaemia	YES	57.5	42.5
	NO	70.0	30.0
p-value:		*0.043*	
Diabetes	YES	55.4	44.6
	NO	64.6	35.4
p-value:		*0.059*	

Table 3

Logistic regression model for the probability of PAD emergence based on relevant prognostic factors

Risk factors	Baseline	Standard Error	Wald	Diffe-rence	Signifi-cance	Expo-sure (B)	95,0% C.I. for EXP(B)	
							Lower	Upper
Presence of cerebrovascular disease history (Yes vs. No)	.794	.243	10.641	1	.001	2.21	1.37	3.57
Presence of other disease history (Yes vs. No)	.697	.260	7.192	1	.007	2.01	1.21	3.34
Presence of intermittent claudication (Yes vs. No)	1.798	.342	27.704	1	.000	6.04	3.09	11.80
Constant	-1.079	.147	54.100	1	.000	.34		

Table 4

Administration of hypertension agents and main prognostic factors (% by row)

Main prognostic factors		Administration of hypertension agents (%)	
		NO	YES
Total		11.2	88.8
Age	<65 years old	15.3	84.7
	66+ years old	8.3	91.7
p-value:		0.028	
BMI	<=27 Kg/m2	17.9	82.1
	>27 Kg/m2	8.4	91.6
p-value:		*0.010*	
Hypertension	YES	1.3	98.7
	NO	100.0	0.0
p-value:		*<0.001*	
Obesity	YES	8.4	91.6
	NO	18.2	81.8
p-value:		*0.006*	
Dyslipidemia	YES	9.4	90.6
	NO	18.8	81.3
p-value:		*0.028*	
Cerebrovascular disease history	YES	3.4	96.6
	NO	14.2	85.8
p-value:		*0.001*	
Coronary disease history	YES	1.6	98.4
	NO	15.3	84.7
p-value:		*<0.001*	

Table 5

Administration profile of hypertension agents and main prognostic factors (% by row)

Main prognostic factors		Treatment Preservation	Treatment Start	Treatment Change
Total		72.7	21.4	5.9
Age	<65 years old	65.1	30.9	4.0
	66+ years old	77.4	15.4	7.2
p-value:		0.001		
Cerebrovascular disease history	YES	63.2	30.7	6.1
	NO	76.8	17.4	5.8
p-value:		*0.014*		
Diabetes	YES	67.4	23.8	8.8
	NO	78.3	18.9	2.8
p-value:		*0.015*		
PAD diagnosis	YES	66.2	25.3	8.4
	NO	77.2	18.7	4.1
p-value:		*0.045*		

Table 6

Administration profile of hypertension agents based on administered hypertension agents (%)

Administered hypertension agents	Treatment preservation	Treatment Start	Treatment Change
Diuretics	46.1	8.0	2.9
Calcium channel blockers	43.2	7.5	2.4
Beta – blockers	34.3	4.8	3.2
Angiotensin Converting Enzyme inhibitors	39.7	3.5	2.7
Angiotensin II Receptor Antagonists	33.5	11.3	2.4
Other	2.9	1.3	0.0

Table 7

Administration of vasodilating agents and main prognostic factors (% by row)

Main prognostic factors		Administration of vasodilating agents (%)	
		NO	YES
Total		76.7	23.3
Gender	Males	72.9	27.1
	Females	81.5	18.5
p-value:		0.047	
Hypertension	YES	75.1	24.9
	NO	90.5	9.5
p-value:		*0.033*	
Diabetes	YES	72.4	27.6
	NO	81.1	18.9
p-value:		*0.038*	
Obesity	YES	73.6	26.4
	NO	84.3	15.7
p-value:		*0.022*	
Intermittent Claudication	YES	47.7	52.3
	NO	81.9	18.1
p-value:		*<0.001*	
Cerebrovascular disease history	YES	60.2	39.8
	NO	83.1	16.9
p-value:		*<0.001*	
Coronary disease history	YES	48.8	51.2
	NO	88.5	11.5
p-value:		*<0.001*	
Other disease history	YES	57.9	42.1
	NO	82.2	17.8
p-value:		*<0.001*	
Smoking	YES	71.0	29.0
	NO	81.0	19.0
p-value:		*0.020*	

Table 8

Administration profile of vasodilating agents and main prognostic factors (% by row)

Main prognostic factors		Treatment preservation	Treatment Start	Treatment Change
Total		71.4	21.4	7.1
Cerebrovascular disease history	YES	59.6	29.8	10.6
	NO	82.4	13.7	3.9
p-value:		*0.044*		
PAD diagnosis	YES	60.6	28.8	10.6
	NO	93.8	6.3	0.0
p-value:		*0.003*		

Table 9

Administration profile of vasodilating agents based on administered vasodilating agents (%)

Administered vasodilating agents	**Treatment preservation**	**Treatment Start**	**Treatment Change**
Coronary vasodilators	53.1	2.0	5.1
Peripheral vasodilators	27.6	17.3	2.0
Cilostazol	1.0	3.1	0.0
Pentoxyfylline	11.2	2.0	0.0
Other	2.0	0.0	0.0

Table 10

Administration of anti-platelet agents and main prognostic factors (% by row)

Main prognostic factors		Administration of anti-platelet agents (%)	
		NO	YES
Total		28.8	71.2
Gender	Males	22.5	77.5
	Females	37.6	62.4
p-value:		*0.001*	
Hypertension	YES	24.3	75.7
	NO	69.0	31.0
p-value:		*<0.001*	
Diabetes	YES	20.6	79.4
	NO	37.4	62.6
p-value:		*<0.001*	
Dyslipidaemia	YES	23.8	76.2
	NO	50.0	50.0
p-value:		*<0.001*	
Intermittent Claudication	YES	7.7	92.3
	NO	32.9	67.1
p-value:		*<0.001*	
Cerebrovascular disease history	YES	5.1	94.9
	NO	38.1	61.9
p-value:		*<0.001*	
Coronary disease history	YES	6.4	93.6
	NO	38.3	61.7
p-value:		*<0.001*	
Other disease history	YES	14.7	85.3
	NO	32.9	67.1
p-value:		*<0.001*	

Table 11

Administration profile of anti-platelet agents and main prognostic factors (% by row)

Main prognostic factors		Treatment preservation	Treatment Start	Treatment Change
Total		68.9	27.8	3.3
Gender	Males	74.7	20.4	4.8
	Females	59.5	39.6	0.9
p-value:		*0.001*		
PAD diagnosis	YES	54.4	40.1	5.4
	NO	82.8	15.9	1.3
p-value:		*<0.001*		

Table 12

Administration profile of anti-platelet agents based on administered anti-platelet agents (%)

Administered anti-platelet agents	Treatment preservation	Treatment Start	Treatment Change
Acetylsalicylic acid	52.2	6.7	2.0
Clopidogrel	34.8	22.1	2.3
Ticlopidine	1.0	0.7	0.0
Dipyramidol	0.7	0.0	0.0
Other	2.7	0.0	0.0

Table 13

Administration of hypolipidaemic agents and main prognostic factors (% by row)

Main prognostic factors		Administration of hypolipidemic agents (%)	
		NO	YES
Total		21.7	78.3
Age	<65 years old	12.5	87.5
	65+ years old	28.2	71.8
p-value:		<0.001	
Cerebrovascular disease history	YES	14.4	85.6
	NO	24.5	75.5
p-value:		*0.025*	
Coronary disease history	YES	5.6	94.4
	NO	28.5	71.5
p-value:		*<0.001*	
Dyslipidaemia	YES	6.2	93.8
	NO	87.5	12.5
p-value:		*<0.001*	

Table 14

Administration profile of hypolipidaemic agents and main prognostic factors (% by row)

Main prognostic factors		Treatment preservation	Treatment Start	Treatment Change
Total		74.5	21.9	3.6
Cerebrovascular disease history	YES	65.3	29.7	5.0
	NO	78.5	18.4	3.1
p-value:		*0.041*		
Diabetes	YES	69.3	25.0	5.7
	NO	80.4	18.3	1.3
p-value:		*0.026*		
PAD	YES	66.9	28.1	5.0
	NO	80.4	16.9	2.6
p-value:		*0.020*		

Table 15

Administration profile of hypolipidemic agents based on administered hypolipidemic agents (%)

Administered hypolipidemic agents	Treatment preservation	Treatment Start	Treatment Change
Statins	77.8	14.6	3.6
Fibrates	2.7	1.8	0.0
Bile acid retention resins	0.0	0.0	0.0
Nicotinic acid	0.3	0.0	0.0
Other	8.5	9.7	0.0

Table 16

Administration of antidiabetic therapy and main prognostic factors (% by row)

Main prognostic factors		Administration of antidiabetic therapy (%)	
		NO	YES
Total		55.5	44.5
Age	<65 years old	48.9	51.1
	65+ years old	60.2	39.8
p-value:		0.028	
Coronary disease history	YES	43.2	56.8
	NO	60.7	39.3
p-value:		*0.001*	

Table 17

Administration profile of anti-diabetic therapy based on administered anti-diabetic therapies (%)

Administered anti-diabetic therapies	Treatment preservation	Treatment Start	Treatment Change
Insulin	15.0	4.3	2.7
Per Os Anti-diabetic Agents	76.5	9.1	4.8

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